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Does Hypothyroidism Promote Gallstone Formation?

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Abstract

Introduction: Gallstone disease is a very common disorder affecting humans, particularly fertile females. Although there are numerous established risk factors in the development of gallstones, hypothyroidism is a commonly associated entity seen in clinical practice, not well established in literature.

Purpose: The aim of this study is to find out the association of hypothyroidism with gallstone formation.

Methods: A total of 124 patients with gallstone disease were included in the study. Thyroid function tests were performed in all of them. The incidence of hypothyroidism was found out and compared with the established incidence of hypothyroidism in adult population. The results were compared statistically.

Results: Of the 124 patients included in the study, 28.5% were found to be hypothyroid. Based on a national study, the prevalence of hypothyroidism in general population was 10.95%. Statistically, hypothyroidism was found to be significantly higher in patients with gallstone disease.

Conclusion: The incidence of hypothyroidism is significantly higher in patients with gallstone disease. Hence, thyroid testing is recommended in these patients as it has anesthetic implications.

Key words: Anesthetic complications, Gallstone disease, Hypothyroidism, Thyroid function tests

INTRODUCTION

Gallstone disease is the most common disorder affecting the biliary system and is a relatively common problem in patients presenting to the outpatient. Through the ages, there have been various risk factors that are associated with gallstone formation such as gender, obesity, pregnancy, dietary factors, Crohn's disease, terminal ileal resection, gastric surgery, hereditary spherocytosis, sickle cell diseases, and thalassemia. In the course of clinical practice, it was observed that a number of patients with gallstones had hypothyroidism in their medical history. Although it appeared to be a constant finding not many previous studies^[1-3] on this particular topic was found, the objective

of this study was to identify the possible relation between diagnosed hypothyroidism and gallstone disease.

MATERIALS AND METHODOLOGY

This is a prospective study done from October 2015 to August 2017. This study included patients, with cholelithiasis or choledocholithiasis diagnosed through radiological studies, who were admitted for the same in the department of general surgery in our hospital. After excluding patients with a history of medical or surgical thyroid intervention, the patients were investigated by analyzing blood samples for thyroid function tests. According to the hospital standard values, patients with thyroid stimulation hormone (TSH) between 0.35 and 4 IU/ml were considered euthyroid, TSH >4 as hypothyroid and TSH <0.35 as hyperthyroid.

Hypothyroidism and Its Association with Cholelithiasis

The pathogenesis of gallstones is a complex process involving mechanisms affecting bile content and bile flow. There are

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various factors that contribute to the formation of gallstones in hypothyroid patients.^[2] Moreover, current investigations fail to differentiate primary from secondary common bile duct stones developing in hypothyroidism. However, hypothyroidism possibly increases the risk of primary as well as gallbladder-originated stones through various mechanisms. In hypothyroidism, the lack of thyroxine

1. Produces a decrease in liver cholesterol metabolism^[4] which results in supersaturation of bile cholesterol. This impairs gallbladder motility,^[5] contractility,^[6] and filling,^[7] thus producing retention of cholesterol crystals and nucleation and growth of gallstones;^[5]
2. Produces impairment of precipitate clearance due to decreased bile secretion from hepatocytes;^[8]
3. Reduces sphincter of Oddi relaxation^[9,10] resulting in delayed bile flow,^[11] and hence, the formation and accumulation of ductal stones.^[12]

RESULTS

Based on the above-mentioned methodology, blood investigations were sent for patients and the results interpreted. A total of 124 patients were tested, 4 were found to be in hyperthyroid state, 85 euthyroid, and 35 hypothyroid were identified. It accounts to 3.2%, 68.5%, and 28.5%, respectively [Figure 1]. A Chi-square test was done with comparison to the epidemiological study in eight cities of India^[13] [Table 1]. It was found to be statistically significant ($P > 0.01$).

T3 studies with a normal parameter of 2.35–4.2 $\mu\text{IU/mL}$ were considered normal, $>4.2 \mu\text{IU/mL}$ high, and $<2.35 \mu\text{IU/mL}$ low serum fT3 levels. Of the 81 patients tested for T3 levels, 11 were found to have low T3, 68 normal, and 2 high levels of serum T3. It accounts to 13.6%, 84%, and 2.5%, respectively. Low serum T4 (level $< 0.8 \mu\text{IU/mL}$) was found in 9.7% of the population.

DISCUSSION

A few studies have been conducted in the past to establish the connection between thyroid function and cholelithiasis.^[1-3] In our study, we analyzed the association of cholelithiasis with hypothyroidism. We then compared it with preexisting prevalence data.

Overall, 143 patients were included in this study, of which 124 thyroid profile was taken and interpreted using standard data analysis.

Of the 124 patients with cholelithiasis in the thyroid study, 28.2% were in hypothyroid, 3.2% in hyperthyroid, and 68.5% in euthyroid states.

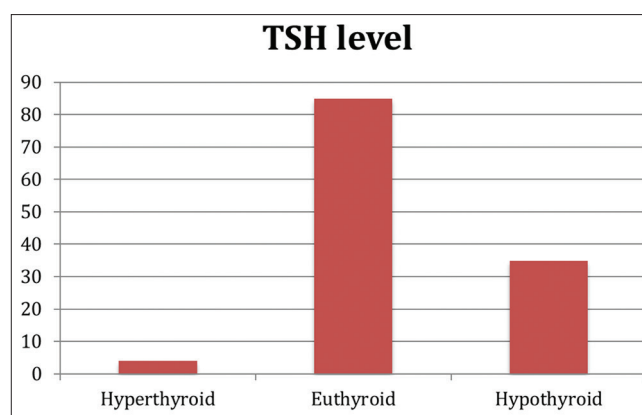


Figure 1: Thyroid stimulating hormone levels

Table 1: Statistical analysis

Thyroid status	TSH in cholelithiasis and general population		
	Observed N	Expected N	
Hypothyroid	35	587	622
	14.06	607.94	
	(31.16)	(0.72)	
Euthyroid	85	4669	4754
	107.49	4646.51	
	(4.71)	(0.11)	
Hyperthyroid	4	104	108
	2.44	105.56	
	(0.99)	(0.02)	
	124	5360	5484

$\chi^2=37.719$ $df=2$ $\chi^2/df=18.86$ $P(\chi^2>37.719)=0.0000$. Expected values are displayed in *italics*. Individual χ^2 values are displayed in parentheses, TSH: Thyroid stimulation hormone

Based on “a study of prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India.”^[13] The national prevalence data were acquired and were compared with our study.

An overall of 5360 patients were studied. The national prevalence of hyperthyroidism was noted to be 1.9%, i.e., 104 patients out of 5380, and 587 patients were found to have hypothyroidism which accounted for 10.95% of the general population.

Whereas, in our study of cholelithiasis patients, it was found to be 28.2% which is statistically significant with $P < 0.01$. This showed a significant association of cholelithiasis with hypothyroidism.

Furthermore, based on the national study,^[13] it was found that thyroid levels in Chennai were 9.77% which is 36 patients out of 5360 as the coastal regions were usually places of less incidence. However, our study showed 28.2% in Chennai, thus showing an even greater significance.

Hypothyroidism reduces oxygen consumption and affects hemodynamic, cardiac, respiratory, and renal functions

because of low metabolism. Myocardial dysfunction reduced ventilatory responses to hypoxia and hypercapnia, abnormal baroreceptor function, and decreased plasma volume, may be present in hypothyroidism and impaired drug metabolism adversely affects anesthesia. Hence, for safe anesthetic management of these patients, hypothyroidism needs to be identified preoperatively.^[14]

Hence, based on the findings of our study, it can be established that hypothyroidism is a risk factor to the formation of gallstones. The need to evaluate the thyroid status in patients with gallstone disease is absolutely essential, as surgery on a hypothyroid patient could lead to complications pertaining to the anesthesia.^[14]

CONCLUSION

There is a definite association between cholelithiasis and hypothyroidism. Thyroid testing in all patients with gallstones is recommended because hypothyroidism may be a predisposing factor for stone formation. Furthermore, early detection and treatment of hypothyroidism can prevent complications during surgery.

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Comparison of Analgesic Efficacy of Peritubal Infiltration of Ropivacaine versus Ropivacaine and Morphine in Percutaneous Nephrolithotomy Under Fluoroscopic Guidance

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Abstract

Background: The root cause of pain in percutaneous nephrolithotomy (PCNL) surgery is dilatation of renal capsule and parenchymal tract which is rich in pain-sensitive nerve fibers. A nephrostomy tube is retained which causes discomfort to the patients postoperatively. Local anaesthetics (LA) infiltrated into nephrostomy tract was done which decreases the pain scores significantly.

Aim: The aim of this study is to compare the efficacy of peritubal infiltration of ropivacaine versus ropivacaine with morphine in PCNL surgeries under fluoroscopic guidance for post-operative analgesia.

Materials and Methods: A prospective randomized, double-blinded study was compared the efficacy of peritubal infiltration of ropivacaine (0.25%) versus ropivacaine with morphine (0.1 mg/kg) under fluoroscopic guidance in 60 patients undergoing PCNL surgeries under general anaesthesia. They were allocated into two groups Group R - injection ropivacaine 0.25% and Group RM - injection ropivacaine 0.25% (10 mg) with morphine (0.1 mg/kg). Hemodynamic parameters, visual analog scale score, and any adverse effects were recorded.

Results: The mean duration of analgesia was more in group RM than the patients in Group R. The mean dose of the analgesic requirement was less in group RM compared to Group R. Other hemodynamic parameters were comparable in both groups.

Conclusion: Addition of morphine (0.1 mg/kg) to ropivacaine (0.25%) in peritubal infiltration offers a significant advantage over plain ropivacaine (0.25%) in terms of duration of analgesia and the need for rescue analgesia.

Key words: Morphine, Percutaneous nephrolithotomy, Ropivacaine, Visual analog scale scores rescue analgesics

INTRODUCTION

Nephrolithiasis or stone formation in the kidney is a common problem around the world. Percutaneous nephrolithotomy (PCNL) is procedure in which cutaneous puncture is done and stones are removed from the kidney and is generally done for larger intrarenal stones

resistant to shock wave lithotripsy, staghorn calculi, and some proximal ureteric calculi.^[1,2] This is relatively safe but associated with certain complications. Open surgeries are more invasive and morbid than PCNL. The root cause of pain in PCNL surgery is dilatation of renal capsule and parenchymal tract which are rich in pain-sensitive nerve fibers.^[3] A nephrostomy tube is retained which causes discomfort to the patients postoperatively. LA infiltrated into nephrostomy tract was done which decreases the pain scores significantly. Tubeless PCNL was done which decreases the post-operative pain but have their own risks like infection. Parenteral drugs such as opioids and NSAIDs will decrease the pain but have their own side effects. Skin infiltration was not very effective as LA infiltrated up to renal capsule. The addition of adjuvants

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to local anaesthetics such as ropivacaine prolongs the effect and decreases the post-operative pain significantly.^[4-6]

Aim

The aim of this is to compare the analgesic efficacy of ropivacaine (0.25%) with 0.5 ml normal saline versus ropivacaine (0.25%) with morphine 11,12, (0.1 mg/kg) by peritubal infiltration on post-operative pain and analgesic requirement for patients undergoing PCNL.

MATERIALS AND METHODS

A prospective comparative study was conducted in Madras Medical College Hospital, Department of Anaesthesiology. The Institutional Ethics Committee approval and written informed consent were obtained. A total of 60 patients aged 18–60 years, ASA physical status 1 and 2 scheduled for elective PCNL surgery under general anaesthesia (GA), were enrolled in this study. Exclusion criteria were as follows: Patient refusal, allergy to LAs, posted for emergency surgery, and patients with more than one nephrostomy tube. Patients were administered GA following routine protocols and toward the end of surgery drugs were infiltrated with the help of 23 G spinal needle along the Amplatz tube reaching the renal capsule under fluoroscopic guidance. The drugs were infiltrated along 6” clock and 12” clock position of the kidney. Patients were randomized into two groups: Group R patients received - injection ropivacaine 20 ml (0.25%) with 0.5ml normal saline and Group RM - injection ropivacaine 20 ml (0.25%) with 0.5 ml of morphine. The study medications were prepared by a different anesthetist and data measurements and recording was carried out by different anesthetists. Post-operative pain score and need for demand analgesia were noted. Intraoperative hemodynamic parameters were monitored. Side effects of opioids such as nausea, vomiting, and sedation were also noted. If visual analog scale (VAS) score was more than

4, patients were given injection tramadol 13,14 1 mg/kg intravenously as rescue analgesia, and the time of rescue analgesia was also noted. Anesthesia time, surgery time, and any adverse events were also recorded. Heart rate (HR), mean arterial blood pressure, oxygen saturation, and VAS scores were recorded in all patients at 15 min interval over 1 h postoperatively.

RESULTS

Both the study groups were comparable in view of demographic data [Table 1]. Patients in group RM had a lower HR on average than those in group R [Figure 1]. There was not much statistically significant variation in mean respiratory rates across intervention groups. The patients in the RM group had a lower respiratory rate on average than those in the Group R. There was no statistically significant difference in the mean systolic and diastolic BP across the intervention groups [Figures 2 and 3]. The systolic BP had less fluctuations, and the diastolic BP was lower on average in group RM patients.

The differences in the VAS scores are compared in table. The patients in RM group had lower VAS scores on an average than those in R group which was statistically significant [Figure 4]

The mean duration of analgesia for both the intervention groups are given. Patients in RM group had the analgesic effect lasting for 4.267 hours more on an average than those in group R which was statistically significant. [Table 2]. The difference in the requirement of a mean dose of analgesic requirement was less in group RM than in group R which was statistically significant [Table 3]. Side effects such as nausea and vomiting were similar in both groups.

DISCUSSION

PCNL is one of the most common urological procedures done in our institution. Pain affects the post-operative quality of patients' life during the recovery period. Pain increases anxiety, decreases respiratory efforts, delays mobilization, and prolongs hospitalization. Due to the better understanding of pain and physiology, the efficacy of LA infiltration has been used to relieve pain and addition

Table 1: Distribution of study patient's characteristics

Parameters	Group RM	Group R
Age	42.4±7.86	36.63±9.89
Male	15	22
Female	15	8
Duration of surgery	1.5±30 min	1.6±35 min

Table 2: Duration of analgesia-comparison across intervention groups

Duration of analgesia in hours	Group RM	Group R	Mean difference±S.E difference	95% CI		P
				Lower bound	Upper bound	
Mean	12.87±1.14	8.6±0.93	4.267±0.268	3.729	4.804	<0.001*

CI: Confidence interval, SE: Standard error

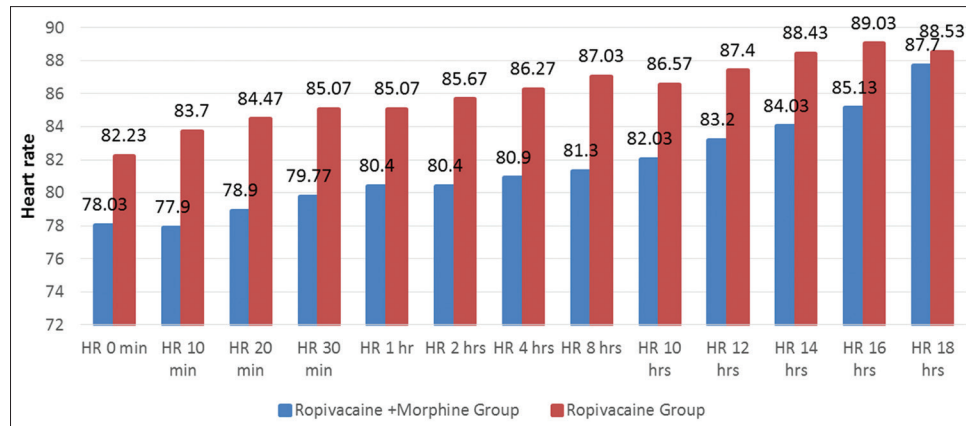


Figure 1: Comparison of heart rate of the study group

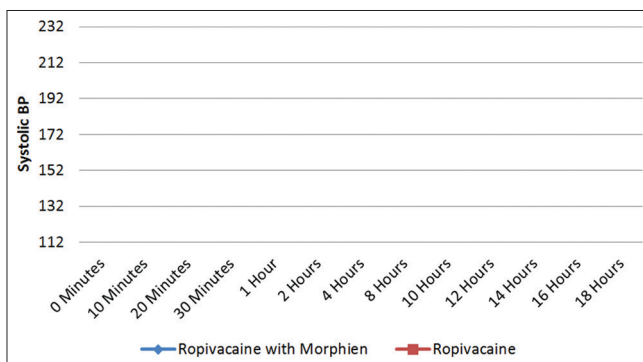


Figure 2: Comparison of systolic blood pressure of the study group

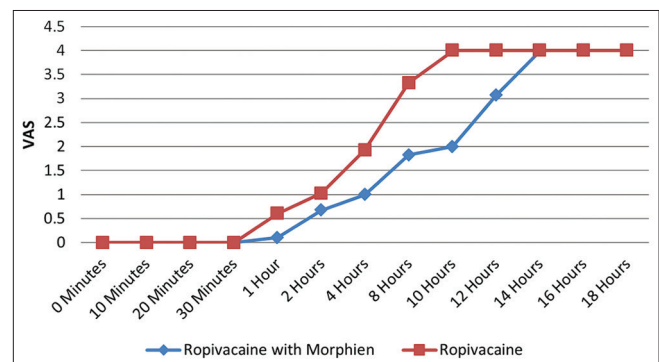


Figure 4: Comparison of visual analog scale of the study group

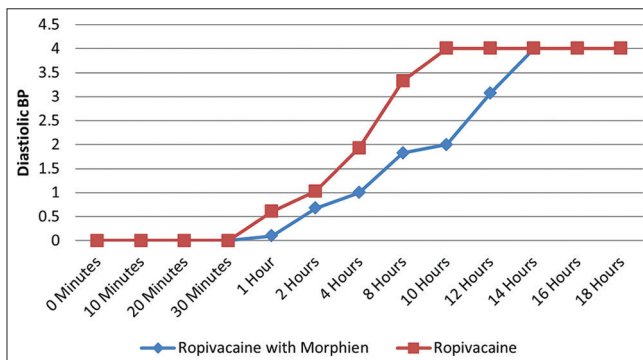


Figure 3: Comparison of diastolic blood pressure of the study group

of opioids which exert their action through peripheral opioid receptors.^[7] A study conducted by Vaddineni *et al.* which compared the effect of various local anaesthetics infiltration under fluoroscopic guidance.^[8] The study group R had more number of males which occurred by chance, and it was insignificant which was similar with the results obtained by Parikh *et al.* There is the statistical difference in VAS scores between R and RM group at 1, 2, 4, 8, and 12 h which has not occurred by chance. Similar results were obtained in a study done by Mehta *et al.* in which buprenorphine was added to LAs for wound

Table 3: Difference in the mean dose required between the groups

Group	n	Mean±SD	Std error mean	P
R	30	135.00±46.60916	8.50963	<0.0001
RM	30	76.665±50.74163	9.26411	

SD: Standard deviation

infiltration. The VAS scores were lower in patients received bupivacaine with buprenorphine. Ugras *et al.* studied the effect of ropivacaine infiltration in PCNL surgeries and showed the lower VAS scores and peak expiratory flow rate were higher in groups who received LA infiltration.^[9] Similarly, Likar *et al.* demonstrated that addition of morphine to LAs for submucosal infiltration in dental surgery prolonged the duration of analgesia.^[10] The patients in RM group had the analgesic effect lasting longer than in patients in group R which is consistent with the study conducted by Parikh *et al.* and Mehta *et al.*^[11,12] The mean number of rescue analgesic doses for group R is 2.7000, whereas for group RM, it is 1.5333. The mean dose of tramadol in group R is 135 mg, whereas for group RM, it is 76.665 mg. These results were similar to the study conducted by Parikh *et al.*^[11] and Mehta *et al.*^[12] Regarding the side effects in both the Groups R and RM 2 patients in

the group, RM experienced nausea compared to 1 patient in group R. Similar results were obtained by Parikh *et al.*^[11]

CONCLUSION

It is concluded that addition of morphine to LA in peritubal infiltration significantly prolonged the duration of analgesia. The need for rescue analgesia is significantly delayed in patients received morphine with ropivacaine. Addition of morphine to ropivacaine in peritubal infiltration offers the significant advantage regarding the duration of analgesia and need for rescue analgesia.

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Pseudoexfoliation Syndrome with Cataract and its Surgical Management

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Abstract

Introduction: Pseudoexfoliation (PXF) syndrome is an age-related disease where fibrillogranular material accumulates in many ocular tissues. Therefore, cataract extraction has increased the risk of zonular dehiscence with poor pupillary dilatation leading to complications.

Purpose: The aim of the study was to study PXF syndrome and its surgical management.

Materials and Methods: A prospective study conducted among 25 patients with PXF. Examination includes visual acuity, anterior segment with slit-lamp biomicroscopy, intraocular pressure, gonioscopy, and dilated fundus examination followed by cataract surgery.

Results: Majority of patients were in the age group between 66 and 75 years (66%). Cataract surgery with implantation of posterior chamber intraocular lens (IOL) was done 20 patients (80%), anterior chamber IOL in 2 patients (8%), scleral-fixated IOL in 1 patient (4%), and aphakia in 2 patients (8%).

Conclusion: PXF presents with cataract and glaucoma which needs pre-operative evaluation and intra-operative care to prevent complications for good surgical outcome.

Key words: Cataract, Glaucoma, Posterior capsular rent, Pseudoexfoliation, Surgery

INTRODUCTION

Pseudoexfoliation (PXF) is an age-related condition characterized by deposition of whitish fibrillogranular material in and around the anterior segment of the eye.

- Anterior capsule of the lens
- Pupillary margins and iris surface
- Corneal endothelium
- Ciliary processes and zonules
- Anterior chamber (AC) angle.

Mean age of onset of this condition ranges from 60s to 70s and the prevalence increases with increasing age.^[1,2]

This exfoliative material gets deposited along the pupillary margin of the iris, vasculature of the iris leading to iris atrophy and poor pupillary dilatation.^[3] Deposition of this material in the angle of the AC leading to the blockage of trabecular meshwork causing a type of glaucoma called pseudoexfoliative glaucoma. Exfoliative material thus alters the anatomy and physiology of the anterior segment posing many challenges to a surgeon. Cataract extraction in PXF has increased the risk of zonular dehiscence^[4] and this combined with poor pupillary dilatation may lead to capsular rupture and vitreous loss, with its early and late complication.

MATERIALS AND METHODS

Type of Study

This was a prospective cross-sectional study.

Study Period

The duration of the study was 6 months from November 2016 to May 2017.

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Place of Study

This study was conducted at Rajarajeswari Medical College and Hospital, Bengaluru.

Sample Size

The sample size was 25 cases.

Source of Data

The study was conducted on all patients who fulfill the inclusion/exclusion criteria attended to our Department of Ophthalmology in Rajarajeswari Medical College and Hospital, Bengaluru.

DISCUSSION

PXF is a condition that mainly affects the elderly patients. Age of presenting with PXF was 50–80 years [Figure 1], of which 14 were male and 11 were female showing almost equal prevalence in both sexes [Figure 2]. PXF is known for its association with raised intraocular pressure (IOP) leading to PXF glaucoma, in the study the mean IOP was 16.7 mm Hg NCT, with no obvious pseudoexfoliative glaucoma.

The most frequent problem encountered during surgery was a poor pupillary dilatation, 44% cases had small size pupil (<6 mm) and 56% cases had good dilatation (7–8 mm) [Figure 3]. When the incidence of the intra-operative complications was compared with the pupil size, it was noted that the incidence was high in patients having

pupil size <6 mm.^[4,5] Pupil size has direct implications on the outcome of the surgery, as with small pupil size adequate capsulorhexis cannot be achieved and the delivery of nucleus becomes difficult leading to posterior capsular tear^[6] and increased manipulation during surgery may lead to increased post-operative inflammation and corneal endothelial damage.^[7]

In the present study where nucleus delivery was difficult, due to small pupils, sphincterotomy was done to facilitate nucleus prolapsed into AC. Other alternatives like iris hooks can be used.

In the presence of weak zonules, this may lead to complications such as lens dislocation, bag dialysis, nucleus drop, and vitreous loss. Intra-operative complications were noted in 5 out of 25 (with posterior chamber [PC] rent, bag dialysis, and vitreous loss).

PC intraocular lens (PCIOL) were placed in 20 eyes [Figure 4]; however, in 2 eyes IOL was placed in sulcus (because of the adequate support), and in 2 cases IOL could not be placed in the bag (as patients had complete bag dialysis and large PC rent).

All patients were studied postoperatively on day 1, after 2 weeks and after 6 weeks for any prolonged post-operative inflammation, any IOL related complication or corneal decompensation. The most common post-operative complication on the immediate post-operative day was corneal haze with increased inflammation due to increased manipulation during the surgery. Out of 25 patients, 12 had

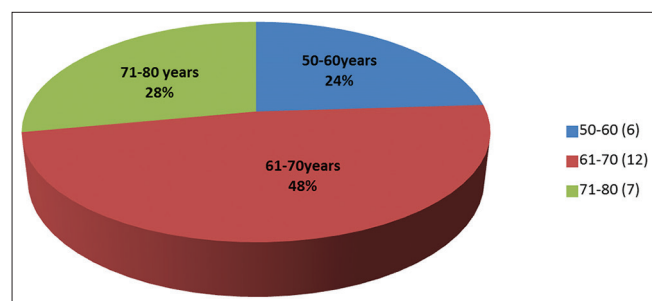


Figure 1: Patients distribution by age

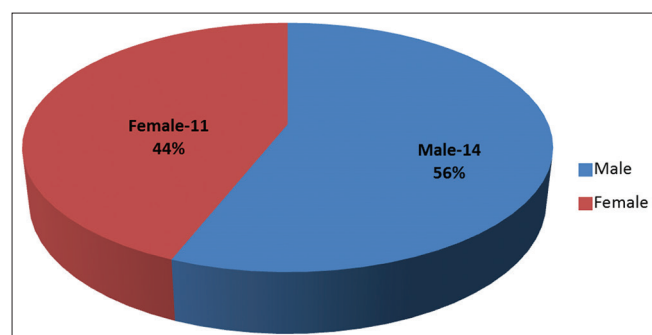


Figure 2: Sex ratio

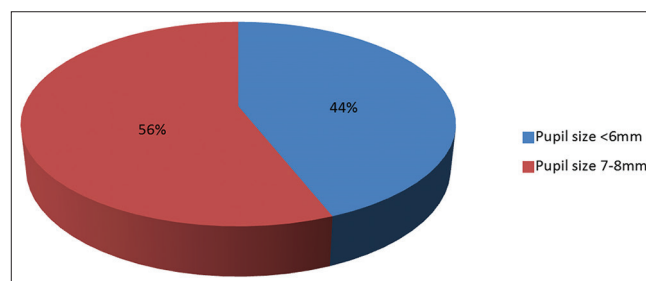


Figure 3: Percentage of patients

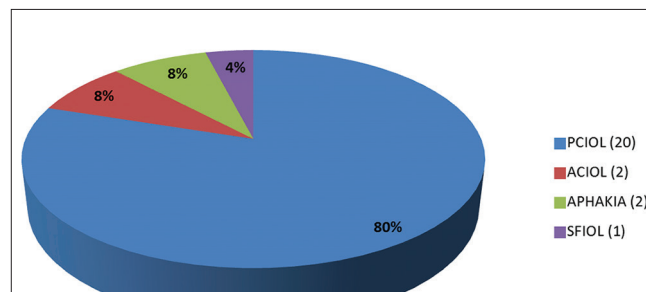


Figure 4: Intraocular lens implantation

hazy cornea on the first post-operative day either in the form of epithelial edema or striate keratopathy, which subsided on treatment. There were no IOL related complications or prolonged inflammation in any of the patients.

The visual outcome of the patients in the study was evaluated at the end of 6 weeks, and glasses were prescribed. 20 cases out of 25 had vision of 6/12–6/9 and 5 cases had vision between 6/24 and 6/36, due to coexistent posterior segment pathology (2 cases had drusen at macula, 1 case of healed macular scar, and 2 cases of disc temporal pallor).

RESULTS

Majority of patients were in the age group between 66 and 75 years (66%). Cataract surgery with implantation of PCIOL was done 20 patients (80%), ACIOL in 2 patients (8%), scleral-fixated IOL in 1 patient (4%), and aphakia in 2 patients (8%).

CONCLUSION

Cataract surgery in eyes with PXF has a higher incidence of intraoperative and post-operative complications. This presents challenges to the surgeon and mandates proper pre-operative planning and post-operative follow-up. A careful slit lamp examination to detect this condition and

to focus for any presence of zonular instability, pupillary dilatation is necessary. Complications correlate directly with intra-operative pupil size and nucleus hardness. Operating PXF cases at early stages of nuclear sclerosis, use of intra-operative highly cohesive viscoelastics, pupil expansion devices and capsule tension rings can increase the margin safety. A careful post-operative follow-up to monitor any rise in IOP, IOL decentration and dislocation is required. Thus with knowledge of possible complications, operating these cases with utmost care, with use of appropriate adjunct devices one can minimize the risk and provide a favorable outcome.

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Study of the Level of Awareness of Diabetic Neuropathy among Diabetic Patients in Al-Ahsa Region, Kingdom of Saudi Arabia: A Cross-sectional Study

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Abstract

Introduction: Diabetic neuropathy (DN) is a prevalent complication of type 2 diabetes mellitus (T2DM) with a major impact on the health of the affected patient. Effective screening and treatment strategies for peripheral neuropathy are lacking. This usually results in delay in the diagnosis of DN till it is well established and more difficult to treat. No study has been done before in the Al-Ahsa region, Saudi Arabia. Making it is important to do such kind of studies.

Purpose: To determine the level of awareness of DN among diabetic patients in Al-Ahsa governorate, Kingdom of Saudi Arabia.

Materials and Methods: A retrospective cross-sectional study was conducted in Al-Ahsa region, Kingdom of Saudi Arabia, from November 2016 to July 2017. 329 participants were selected randomly from Al-Ahsa region, aged from 20 years and above using simple random sampling. Data analysis was done using SPSS program version 24.

Results: Mean age (\pm standard deviation) was 47 ± 7 years. 55% of subjects were female. The minimum age of the participants was 20 and the maximum age was 65. More than half of them are in the age group of 20–50 years. The number of male participants is 146 (44.3%) and females 183 (55.7%). The mean score of the level of awareness was 7.1 ± 3.4 . However, Table 2 shows the number of the participants who know that diabetes mellitus can cause diabetic neuropathy are 173 (56.4%). Furthermore, 82 (27.5%) do not know why this condition occurs in diabetes. 76 (20.4%) of the participants have no idea about diabetic neuropathy. As there is lack of awareness among Saudi diabetic population about this problem, there is a strong need for health and educational intervention programs to increase the knowledge level and awareness about this disease.

Conclusion: DN is common and growing problem worldwide but not adequately recognized problem among diabetic population in Al-Ahsa region, Kingdom of Saudi Arabia. The conclusion of this study is there is extremely needed for health, educational and screening programs because the majority of the Saudi diabetic people have lack of awareness about this disease as well as the necessity of periodic follow-up programs.

Key words: Awareness, Diabetic foot, Diabetic neuropathy, Educational intervention programs, Knowledge, Practice, Screening

INTRODUCTION

According to the International Diabetes Federation, 382 million people worldwide are currently diabetic.^[1] It is estimated that 193 million people are diabetic and undiagnosed which raise the risk of DM complication.

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Hyperglycemia challenges patients with numerous complications; it can affect the heart and blood vessels, eyes, kidneys, and nerves.^[2] Diabetic patient may present with diabetes complication at the time of diagnosis or only a few years of known poor glycemic control.^[3] DN is a prevalent complication of type 2 diabetes mellitus (T2DM) with a major impact on the health of the affected patient.^[4] DN has been defined by the Toronto consensus panel on DN as a “symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure, and cardiovascular risk covariates.”^[5] The exact pathophysiological processes that result in DN remains

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enigmatic, both peripheral and central mechanisms have been implicated and extend from altered channel function in peripheral nerve through enhanced spinal processing and changes in many higher centers.^[6] It is thought to be that the most probable pathophysiology involves biochemical abnormalities causing protein glycation and overproduction of reactive oxygen species, leading to vascular damage and responsive activation of tissue-specific growth/repair systems.^[7] DN encompasses a variety of clinical or subclinical presentations.^[8] Distal symmetrical neuropathy is the most common presentation and accounts for 75% DN. Asymmetrical neuropathies may involve cranial nerves, thoracic or limb nerves are of acute onset resulting from ischemic infarction of vasa nervosa.^[9] In general, DSPN affects the toes and distal foot, but slowly progresses proximally to involve the feet and legs in a “stocking and gloves” distribution. The main clinical consequences of DSPN are foot ulceration and painful neuropathy and result in significant increase in morbidity and mortality.^[10] Interestingly, symptoms cannot be used as indicator of the severity of axonal loss. Often, those with the most severe painful symptoms have minimal or no sensory deficit on examination or electrodiagnostic studies.^[11] Peripheral neuropathy accounts for hospitalization more frequently than other diabetes complications. Peripheral neuropathy recognized as the most frequent cause of non-traumatic amputation.^[12] A major problem with peripheral neuropathy is that this condition usually painless and patients look for medical help only when pain appears. Unfortunately, patients usually presented with well-established foot ulcer and no escape from amputation. Another challenging problem is that current effective screening and treatment strategies for peripheral neuropathy are lacking. This usually results in delay in the diagnosis of DN till it is well established and more difficult to treat.^[13]

MATERIALS AND METHODS

A retrospective cross-sectional study was conducted in Al-Ahsa region, Kingdom of Saudi Arabia, from November 2016 to July 2017. 329 participants were selected randomly from Al-Ahsa region, aged from 20 years and above using simple random sampling to assess the level of awareness toward DN. Data collection was validated by electronic questionnaire. The study population was randomly selected from the population in Al-Ahsa region. The participants were assured that confidentiality would be maintained. After obtaining informed consent, the questionnaire was distributed among the participants. The questionnaire which was prepared consisted of five categories: (1) Sociodemographic data (age, gender, educational level, marital status, daily lifestyle, healthy diet, and regular exercises), (2) early signs and symptoms of the

disease, (3) risk factors, (4) the regular screening, and (5) foot ulcer distributed among diabetic patients in Al-Ahsa region. The questionnaire was pre-tested and translated into Arabic and then back-translated to English to validate the translation.

The level of awareness was assessed on 25 questions about the awareness of the disease. The authors got the approval from Ethical Committee (REC) from King Faisal University. Patients who were diagnosed with diabetes either type 1 or type 2 was included in this study. Patients of age group from 20 to 65 years for both genders (male and female) were included in the study. We excluded the patients who participated from outside the Saudi Arabia. Furthermore, patients of age below 19 or above 65 years were excluded from the study. Data analysis was performed using SPSS (version 24). Chi-square test was run for analyzing qualitative data. *P* values were considered statistically significant if *P* < 0.05.

A total of 329 individuals with diabetes in Al-Hasa city were included in our study. Mean age (\pm standard deviation) was 47 ± 7 years. 55% of subjects were female. The minimum age of the participants was 20 and the maximum age was 65. More than half of them are in the age group of 20–50 years. The number of male participants is 146 (44.3%) and females 183 (55.7%). Average duration of diabetes was ≤ 5 years in 176 (47%), 6–10 years in 98 (28.4%), and ≥ 11 years in 58 (24.6%) individuals.

Primary educational level was found in 15 (2.8%), 53 (17.9%) had secondary, and 261 (79.3%) had academic educational level. The demographic characteristics are shown in Table 1.

The study found that age group (21–50 years) has highest awareness level (22.7%) compared to the other age groups. Another finding in this study was the level of awareness between males and females. 60% of female was aware compared with 40% in male.

In addition, 2.9% was aware in primary educational level compared with 16.8% in secondary school, 56.1% in academic educational level.

Regarding the type of diabetes, type 1 was 21 (6.5%) of the participants. 308 (82.8%) were type 2 diabetic participants. Rest of the participants were not sure about their type. They were 43 (11.6%) patients. The duration of treatment was ≤ 5 years in 189 (53.2%), 6–10 years in 51 (18.6%), and ≥ 11 years in 98 (34.6%) individuals. Most of the participants discovered that they are diabetic in age between 30 and 50 years which equal to 238 (72.5%). The

others were variable, 53 (16.1%) were diabetic ≤ 30 years and 38 (11.4%) discovered the disease ≥ 50 years.

The mean score of the level of awareness was 7.1 ± 3.4 . However, Table 2 summarizes the number of the participants who know that DM can cause DN (173, 56.4%). Furthermore, 82 (27.5%) do not know why this condition occurs in diabetes. 76 (20.4%) of the participants have no idea about DN. The majority of the diabetic patients who are included in this study were found to have inadequate knowledge about nerves complications of diabetes and DN.

Our study shows that only 21 (7.6%) of diabetic patients are aware about the effects of the DM on their nerves. On the other hand, we found that 203 (54.6%) of participants have a low level of awareness about the disease.

DISCUSSION

DM is well known to be a common metabolic disease in Saudi Arabia. DN is a prevalent complication of T2DM with a major impact on the health of the affected patient. Early recognition of DN could prevent its major complications.

The aim of the study was to determine the level of awareness of DN among diabetic patients in Al-Ahsa region, Kingdom of Saudi Arabia.

Table 1: Demographical data (n=329) n (%)

Demographical data (N=329)	N (%)
Age	
36 (5.6)	<20
204 (80.8)	20–50
89 (13.6)	>50
Gender	
146 (44.3)	Male
183 (55.7)	Female
Marital status	
83 (32.7)	Single
231 (62.2)	Married
15 (5.1)	Divorced
Educational level	
15 (2.8)	Primary
53 (17.9)	Secondary
261 (79.3)	Academic

Table 2: Awareness

Knowledge level	Frequency (%)	Valid Percent	Cumulative Percent
Valid			
Not aware	203 (54.6)	54.6	100.0
Aware	105 (38.2)	38.2	75.0
Highly aware	21 (7.2)	7.2	32.5
Total	329 (100.0)	100.0	

In our study, we evaluated the level of awareness among male and female diabetic patients in Al-Ahsa region about DM neuropathy. Our finding is that there is no significant difference between males and females in the level of awareness of DN.

As can be seen, most of the participants in our study were in age group between 21 and 50 years. We attribute that this age group is the active age of the life. Usually, people at this age group are well educated and mindful about their health. However, no significant difference was found between the age groups in the level of awareness.

We find in our study that those participants who have academic educational levels had higher awareness level about the importance and the impact of the educational intervention to diabetic patients about DM neuropathy.

Furthermore, the study showed high discrepancy in the level of knowledge and awareness between those who have been educated about DN by healthcare providers and those who did not. As the Chi-square ($P = 0.001$) showed that patients who have been informed by the physicians have a higher level of awareness level than the others.

As the incidence of diabetic is very high in our population, healthcare providers have to encourage positive attitude toward the disease. We find in our study that the level of knowledge and awareness has to be increased among diabetic patients.

Unfortunately, the majority of diabetic patients in Al-Ahsa region were not appropriately aware about DN, and generally, they are not aware about diabetes complications. Diabetic patients in Saudi Arabia had poor attitude toward their disease. Their knowledge and awareness about diabetes and its complication is not adequate.

A study conducted in Medicine Department of Indus Medical College Tando Muhammad Khan, Pakistan, in February 2016–July 2016 showed that patients had very poor knowledge regarding DN.

Recently, the DN study group of the Korean Diabetes Association conducted a study investigating the awareness of DN on disease burden and quality of life in patients with T2DM showed there is lack of awareness of DN. Although if we compared our study which was done in selected region of Saudi Arabia and limited patients with other studies that conducted widely in different countries such as Pakistan (8.1%) and Korean (12.6%). We found that the knowledge score 7.2% is low.

Table 3: The responses of different statements related to the awareness of DN

Statement	Yes	I do not know	No
DM is a major cause of DN?	173 (56.4)	82 (27.5)	74 (16.1)
Foot ulcers (open sores) take a long time to develop?	83 (11.3)	201 (75.6)	45 (13.1)
Good circulation in the feet means that I will not get foot ulcers (open sores)?	39 (16.9)	276 (71.2)	14 (11.9)
If you have diabetes, has your doctor ever talked to you about your risk for developing DN?	69 (24.9)	207 (55.6)	53 (19.5)
Foot ulcers would be painful?	89 (24.6)	201 (63.1)	39 (12.3)
Do you know what the worst complications of DN?	109 (37.9)	121 (32.5)	99 (29.6)
Do you think there are effective ways to prevent neuropathy?	153 (50.0)	134 (36.0)	42 (24.0)
Do you think you will notice the symptoms of DN?	43 (14.1)	231 (66.8)	55 (19.1)

DN: Diabetic neuropathy, DM: Diabetes mellitus

According to our result, we suggest that diabetic patients have to be well educated about diabetes and all the possible consequences related to their disease. The level of their knowledge and awareness has to be appropriately increased. The responses of different statements related to the awareness of DN are shown in Table 3.

Implementing strategies that target all population “with specific emphasis for diabetics and prediabetic population” require fundamental social changes and may necessitate major public health initiatives.

CONCLUSION

DN is common and growing problem worldwide. The general knowledge level of awareness in Al-Ahsa population about DN and its risk factors are low. Individuals with diabetes/hypertension are not adequately informed regarding their increased risk for developing DN. To reduce the lack of awareness among Saudi diabetic population about this complication, there is a strong need for health and educational intervention programs about the DM as well as the necessity of screening and periodic followup programs. That will lead to increase the knowledge level and awareness about this disease and prevent its major complications.

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Effect of Dialysis on Upper Gastrointestinal Symptoms and Endoscopic Findings Along with Biochemical Parameters in Patients of Chronic Renal Failure: A Cross-sectional Study in Tertiary Care Settings in North India

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Abstract

Introduction: Chronic kidney disease (CKD) is defined as the presence of objective kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m² or less for at least 3 months, irrespective of the underlying etiology of kidney damage. It affects almost every organ of body. GI manifestations of CKD present in as various symptoms and endoscopic findings are mostly inflammatory in nature.

Materials and Methods: The present study Group 1 included 80 patients of chronic renal failure (28 patients of Stage 4 with estimated GFR [eGFR] of 15–29 ml/min/1.73m²) and 52 patients of Stage 5 with eGFR <15 ml/min/1.73 m². Biochemical parameters and upper GI endoscopy were performed in all 80 patients, but 52 patients of Stage 5 were put on the active treatment of hemodialysis for 1–2 times/week for a period of varying from 1 month to as long as 1 year in the nephrology department. After dialysis, patients were subjected to endoscopic re-evaluation.

Result: There were 80 patients Stages 4 and 5 of chronic renal disease. Mean age of patients was 56.73 ± 14.02 with a range of 18–80 years M: F = 1.42 (58.75%):1 (41.25%). There was a significant decrease in GI symptoms such as nausea and vomiting after dialysis ($P < 0.05$). Endoscopic findings when compared before and after dialysis, there was no significant change observed in abnormalities of esophagus, stomach, and duodenum on endoscope. However, biochemical analysis revealed that after dialysis, there was a significant improvement in the mean serum levels of urea, creatinine, potassium, calcium, phosphorus, and magnesium ($P = 0.05$).

Conclusion: GI symptoms are common in CKD patients and constitute an important cause of morbidity and mortality. There was an improvement in few of upper GI symptoms/biochemical profile but no significant change in endoscopic findings following the hemodialysis therapy.

Key words: Biochemical profile, Chronic kidney disease, Endoscopic findings, Hemodialysis

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INTRODUCTION

Chronic kidney disease (CKD) is a silent epidemic of the 21st century. Surveys have suggested that as many as 16% of adult population have CKD. Its occurrence is not confined to developed countries, but it is universal. Every year, over 1 lakh people in India are diagnosed with CKD necessitating a kidney transplant or continual dialysis.^[1,2]

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Prevalence of gastrointestinal (GI) symptoms in patients of CKD ranges from 70% to 79% CKD.^[3] Chronic renal disease (CKD) leads to disturbance in virtually in every organ of body and GI complications include anorexia, nausea, vomiting, hiccups, stomatitis, esophagitis (with/without fungal/viral infection) and abnormalities in esophageal motility, gastritis, duodenitis, peptic ulcer, hiatus hernia, colonic diseases in the form of angiodysplasia, perforation, obstruction/pseudo-obstruction, diverticulitis, idiopathic ascites, and peritonitis.^[4] Patients with CKD also suffer from recurrent GI bleeding episodes with superficial mucosal inflammatory lesions as the underlying cause along with effects of uremia on the GI mucosa, platelet adhesiveness and effect of heparin used in dialysis.^[5] Bleeding can originate from upper or lower tract, with a predominance of gastritis from upper tract and angiodysplasia and diverticula from the lower; in every case, the bleeding is favored by uremic hemostatic defects.^[6] The etiology of upper GI disorders is multifactorial and include hypergastremia, helicobacter pylori infection, psychological stress, effects of uremia on GI mucosa, endocrine disturbances of CKD, gastroparesis, and miscellaneous causes such as acidosis, hypocalcaemia/hypercalcemia, hypokalemia/hyperkalemia, and hyperparathyroidism (Kang *et al.*, 1998, Muto *et al.*, 1985 and Monnikes *et al.*, 2001).^[6-9]

GI disorders contribute to malnutrition and latter is associated with high morbidity and mortality in CKD patients (Spiegel *et al.*, 1993, Marcén *et al.*, 1997, Price and Mitch 1994, Nespor and Holley, 1992, Hammer *et al.*, 1998, and Van Velm *et al.*, 2000).^[10-15] Most of GI symptoms are reversed by hemodialysis (Zelnick and Goyal).^[16] The aim of the present study was to evaluate upper GI disorders in patients and observe the effects of hemodialysis on symptomatology/abnormalities of upper GI tract and biochemical profile.

MATERIALS AND METHODS

The present study was conducted in the Departments of General Medicine and Nephrology, Government Medical College, and Associated Hospitals, a Tertiary Care Hospital in Jammu (Jammu and Kashmir), North India, for a period of 1 year (2014-2015). It was approved by Institute Ethics Committee.

After the informed consent, 80 patients fulfilling inclusion and exclusion criteria reporting to indoor/outdoor Departments of General Medicine and Nephrology were included in the study. Patients aged above 18 years, diagnosed as CKD (Stages 4 and 5) and with symptoms of nausea, vomiting, anorexia, heartburn, indigestion, melena, and epigastric pain were taken in the study.

Patients (1) with encephalopathy, (2) very poor health, (3) with significant cardiac/pulmonary/hepatic disease, (4) alcoholism, (5) H/o intake of steroids, nonsteroidal anti-inflammatory drugs, and H2 blockers were excluded from the study.

CKD was diagnosed as per National Kidney Foundation (2002), i.e., Stage 4 (estimated glomerular filtration rate [eGFR] 15–29/min/1.73 m² and Stage 5 - eGFR <15/min/1.73 m²) and diabetes mellitus (DM) as per the WHO criteria. Hypertension was defined as blood pressure (BP) >140/90 or controlled BP with medication.

Profile of patients in the individual group as below:

1. Group 1: Included 80 patients of CKD Stages 4 and 5 on conservative management.

The group was further subdivided on the basis of eGFR into two subgroups.

- a. Subgroup 1a (eGFR <15) - 52
 - b. Subgroup 1b (eGFR 15–29) – 28.
2. Group 2: Included 52 patients of CKD on maintenance hemodialysis.

All relevant investigations were carried out and upper endoscopy all 80 patients was performed with FUJINON EG265 WR gastroscope using system –2200 processor and disinfected with 2% glutaraldehyde. Results of endoscopies were recorded in the performance.

All 52 (Group 2) patients were underwent active treatment of hemodialysis. After dialysis patients were subjected to endoscopic re-evaluation had undertaken dialysis treatment for 1–2 times/week for a period of varying from 1 month to as long as 1 year in the nephrology department.

Statistical Analysis

Data were compiled and entered into Microsoft Excel 2007 and analysis of results was performed using SPSS 20. The quantitative variables were described as mean and standard deviation (SD) while qualitative data were expressed as proportions. The differences in categorical variables were compared using a Chi-square test. Paired *t*-test was used to compare the mean values. *P* < 0.05 was considered to be statistically significant.

RESULTS

A total of 80 patients of CKD Stages 4 and 5 were registered for study purpose, among whom 28 patients were in Stage 4 (eGFR 15–29) and 52 in Stage 5 (eGFR <15). About one-third of patients in the study were in the age group of 51–60 years (30%), followed by 61–70 years (23.75%). Mean age ± SD of patients was 56.73 ± 14.02 with a range of 18–80 years. Male to female ratio among

the patients was 1.42:1, with male constituting 58.75% and female 41.25% of the study population. 98.75% (79) of patients had a history of hypertension while the history of DM was present in 67 (83.75%) patients.

52 patients of Stage 5 CKD were put on maintenance hemodialysis, and review endoscopy was done after they had undergone active treatment with hemodialysis and symptoms were reviewed again.

Table 1 shows that in pre-dialysis stage, all the 52 patients were symptomatic while after dialysis only 28 patients remained symptomatic. Applying Chi-square test, it was observed that there was a significant decrease in symptoms such as nausea and vomiting in a post-dialysis group of patients.

Table 2 shows that endoscopic findings when compared before and after dialysis, there was no significant change in abnormalities of esophagus, stomach, and duodenum.

Table 3 depicts that after dialysis, there was a significant improvement in the mean serum levels of urea, creatinine, potassium, calcium, phosphorus, and magnesium ($P < 0.05$).

Table 1: Effect of dialysis on the upper GI symptoms in patients with chronic renal failure

GI symptoms	Pre-dialysis n=52 (%)	Post-dialysis n=52 (%)	Statistical interpretation
Nausea	29 (55.76)	10 (19.23)	$P < 0.001$: HS
Vomiting	24 (46.15)	8 (15.38)	$P < 0.001$: HS
Indigestion	18 (34.61)	13 (25.00)	$P > 0.05$: NS
Heartburn	2 (3.84)	1 (1.92)	$P > 0.05$: NS
Loss of appetite	17 (32.69)	14 (26.92)	$P > 0.05$: NS
Epigastric pain	4 (7.69)	2 (3.84)	$P > 0.05$: NS
Malena	2 (3.84)	0 (0)	—

HS: Highly significant, NS: Non-significant, GI: Gastrointestinal

Table 2: Effect of dialysis on endoscopic findings in patients with chronic renal failure

Endoscopic findings	Pre-dialysis n=52 (%)	Post-dialysis n=52 (%)	Statistical interpretation
Esophageal			
Hiatus hernia	3 (5.76)	3 (5.76)	$P > 0.05$: NS
Gastric			
Antral gastritis	9 (17.30)	9 (17.30)	$P > 0.05$: NS
Fundal gastritis	0	2 (3.84)	—
Antral gastritis and fundal gastritis	6 (11.53)	0	—
Pan gastritis	2 (3.84)	0	—
Hiatus hernia and antral gastritis	1 (1.92)	1 (1.92)	$P > 0.05$: NS
Snakeskin appearance of gastric mucosa	3 (5.76)	0	—
Snakeskin appearance of gastric mucosa GAVE	1 (1.92)	0	—
Antral erosions	0	0	—
Fundal erosions	0	0	—
Fundal and antral erosions	1 (1.92)	0	—
GAVE	2 (3.84)	3 (5.76)	$P > 0.05$: NS
Duodenal			
Duodenitis	3 (5.76)	2 (3.84)	$P > 0.05$: NS

NS: Non-significant, GAVE: Gastric antral vascular ectasias

DISCUSSION

The chronic renal disease is associated with several diseases including gastrointestinal alterations which are characterized by multiple symptoms. Further, these alterations are confirmed by endoscopy that shows a large range of pathological pictures. In the present study, besides baseline evaluation of GI symptoms and endoscopic findings, the effect of hemodialysis on these symptoms, and endoscopic findings in patients with chronic renal disease was also studied.

In the current study, in pre-dialysis stage, all the 52 patients were symptomatic and after dialysis 28 patients remained symptomatic. Nausea, vomiting, indigestion, and anorexia were the most common symptoms in both pre- and post-dialyzed patients. Similar observations have been reported by Farasakh *et al.* and Sivinovic *et al.*^[17,18].

In the pre-dialysis period, patients presented with nausea (55.76%), vomiting (46.15%), indigestion (34.61%), loss of appetite (32.69%), epigastric pain (7.69%), and melena (3.84%). In the post-dialysis period, the prevalence of all symptoms reduced with a significant reduction in nausea and vomiting ($P < 0.05$). Similar findings were reported by Nand *et al.*^[19] Improvement in symptoms of upper GI tract disease after active treatment with hemodialysis was also observed in a study by Goenka *et al.*^[20]

In our study, esophageal involvement in the form of hiatus hernia was seen in 3 out of 52 patient comprising 5.76% in both pre-dialysis and post-dialysis group. Farsakh *et al.*^[17] observed hiatus hernia to be present in 27 out of 92 patients on hemodialysis. Gastric involvement in

Table 3: Comparison of mean serum levels in pre- and post-dialysis patients with chronic renal failure using paired t-test

Parameter	Pre-dialysis (n=52) mean±SD	Post-dialysis (n=52) mean±SD	t-test	P (statistical interpretation)
Serum urea (mg/dl)	155.94±67.72	110.10±28.91	7.993	0.000 (HS)
Serum creatinine (mg/dl)	8.54±3.64	6.89±2.06	2.918	0.005 (HS)
Creatinine clearance (ml/min)	8.87±4.00	10.02±3.05	-1.729	0.09 (NS)
Serum sodium (mEq/L)	134.27±4.45	134.48±3.57	-0.300	0.766 (NS)
Serum potassium (mEq/L)	4.80±0.57	4.47±0.66	2.773	0.008 (HS)
Serum calcium (mg/dL)	7.73±0.85	8.21±0.89	-3.264	0.002 (HS)
Serum phosphorus (mg/dL)	5.51±1.66	4.61±1.46	3.066	0.003 (HS)
Serum magnesium (mg/dL)	2.04±0.59	2.27±0.49	-2.205	0.032 (Sig)
Serum uric acid (mg/dL)	5.15±1.34	5.59±1.17	-1.552	0.127 (NS)
Serum Alk. phosphate (U/L)	96.42±30.15	94.59±21.47	0.384	0.702 (NS)

SD: Standard deviation, HS: Highly significant, NS: Non-significant

the form of antral gastritis was seen in 17.30% patients in both pre- and post-dialysis group. Both hiatus hernia and antral gastritis were seen in 1.92% in pre-dialysis and none in post-dialysis group. However, no case of peptic ulcer was found in this study. Similarly, in two prospective studies, Morgalis *et al.*, and a recent study from Chennai on dialysis patients, did not find any case of peptic ulcer.^[21,22] Duodenitis was present in 5.76% in pre-dialysis and 3.84% in post-dialysis patients.

Mean values of serum urea, creatinine, potassium, calcium, phosphorus, and magnesium when compared in patients before and after dialysis, a statistically significant improvement was observed in the present study ($P < 0.05$). These findings are in collaboration with other studies.^[23-25]

CONCLUSION

Patients with CKD frequently develop different GI symptoms and lesions and an important cause of morbidity and mortality. GI symptoms tend to worsen with increasing uremia and more common in Stage 5 CKD than Stage 4. Early diagnosis and management of upper GI disorders can reduce morbidity and prevent fatal complications like massive upper GI bleed. Endoscopic examination is a useful investigation for their diagnosis.

There was an improvement in few of upper GI symptoms/biochemical profile but no significant change in endoscopic findings following adequate hemodialysis therapy.

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Comparison of Upper Lip Bite Test, Ratio of Height to Thyromental Distance, and Maxillopharyngeal Angle to Predict Difficult Laryngoscopy

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Abstract

Introduction: The incidence of “difficult” intubation is approximately 1–4%, whereas the most dreadful incidence of “cannot ventilate by mask, cannot intubate” is around 0.0001–0.02%.

Materials and Methods: A total of 556 patients aged between 18 and 65 years of ASA I and II scheduled for elective general anesthesia with intubation were analyzed preoperatively for upper lip bite test (ULBT), ratio of height to thyromental distance (RHTMD), and maxillopharyngeal angle (MPA). Cormack-Lehane (CL) grading was noted in them by an experienced anesthesiologist who was unaware of the pre-operative findings.

Results: The incidence of difficult laryngoscopy was 12.8%. ULBT had a high positive predictive value (42.11%) and stood second in terms of sensitivity, specificity, negative predictive value (NPV), and accuracy (90.93%, 45.07%, 91.88%, and 81.07%), respectively. RHTMD had high sensitivity (71.83%) and NPV (93.49%). MPA had highest specificity and diagnostic accuracy (94.43% and 85.79%).

Conclusion: Each of the three parameters significantly correlated with CL grading. However, each test scored differently in terms of their sensitivity, specificity, accuracy, and predictive tests when compared to each other. Hence, it will be safer to use a combination of tests which assess different aspects of patient's airway.

Key words: Cormack-Lehane grading, Maxillopharyngeal angle, Ratio of height to thyromental distance, Upper lip bite test

INTRODUCTION

The incidence of “difficult” intubation is approximately 1–4%, whereas the most dreadful incidence of “cannot ventilate by mask, cannot intubate” is around 0.0001–0.02%.^[1] No single anatomical factor determines the ease of direct laryngoscopy, and therefore, no single test to assess anatomical factor can be used to predict a difficult laryngoscopy.^[2]

Upper lip bite test (ULBT) is a representation of the temporomandibular joint movement.^[3] Ratio of height to thyromental distance (RHTMD) will assess the submental space.^[4] Maxillopharyngeal angle (MPA) will assess the occipito-atlantal joint movement. This angle <90° suggests difficult direct laryngoscopy.^[5]

The sensitivity, specificity, positive predictive value, negative predictive value (NPV), and diagnostic accuracy were calculated for each variable.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethical Committee and taking consent from patient, 556 patients between 18 and 65 years of ASA I and II were assessed pre-operatively on the day before surgery by the same

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anesthesiologist in all patients to avoid interobserver error.

Three parameters were examined in each patient:

- ULBT,
- RHTMD, and
- MPA.

The end point of the study was Cormack-Lehane (CL) grading score.

ULBT

ULBT was done by asking the patient to bite their upper lip with lower incisor.

- Class I: Lower incisors can bite the upper lip above the vermilion line.
- Class II: Lower incisors can bite the upper lip below the vermilion line.
- Class III: Lower incisors cannot bite the upper lip.

Class III predicts difficult laryngoscopy [Figure 1].

RHTMD

Thyromental distance was measured from the bony point of the mentum to thyroid notch, while head was fully extended and mouth closed with the help of a flexible measuring tape. Height of the patient was measured in centimeters from vertex to heel with the patient standing and was rounded to the nearest 1 cm.

The RHTMD was calculated as follows:

$$\text{RHTMD} = \text{Height (in cm)} / \text{TMD (in cm)}$$

<23.5 predicts easy laryngoscopy.

≥ 23.5 predicts difficult laryngoscopy.

MPA

A lateral cervical radiograph was taken in erect posture of patient with the neutral position of head and jaw closed in the natural occlusive position. The radiograph was taken at the end of expiration. Anatomical landmarks were identified and connected for the purpose of angle measurements.

The maxillary angle (MA) and pharyngeal angle (PA) are the line parallel to the hard palate and the line passing through the anterior portion of the first cervical vertebra (atlas) and second cervical vertebra, respectively. The angle between the MA and PA was defined as the MPA [Figure 2].

$\text{MPA} \geq 90^\circ$ predicts easy laryngoscopy.

$\text{MPA} < 90^\circ$ predicts difficult laryngoscopy.

Inside OT

After connecting all standard monitors and inducing the patient with propofol (2 mg/kg), atracurium (0.6 mg/kg) IV was given to facilitate endotracheal intubation. Laryngoscopy was performed with the patient's head in the sniffing position with a Macintosh #3 laryngoscope blade by an anesthesiologist (of at least 2 years' experience) who was blinded to the results of pre-operative airway assessment.

Glottic visualization was assessed using CL scale, without any external laryngeal manipulation.

CL scale

- Grade 1: Vocal cords visible.
- Grade 2: Only posterior commissure and arytenoids visible.
- Grade 3: Only epiglottis visible.
- Grade 4: None of the above visible.

Easy visualization was described as Classes 1 and 2 classifications.

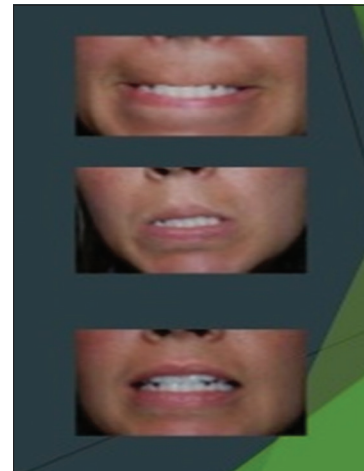


Figure 1: ULBT demonstration

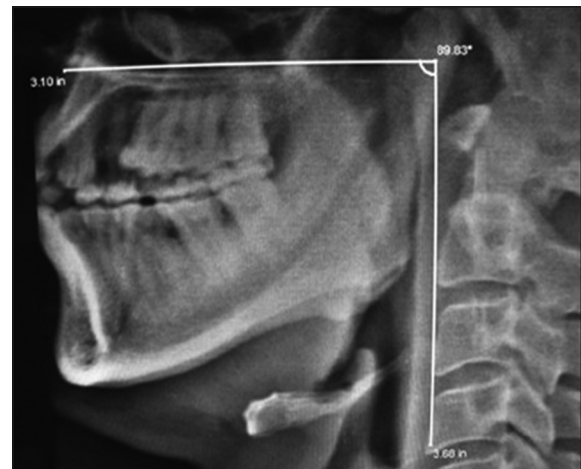


Figure 2: Radiographic measurement of MP angle

Difficult visualization was described as Grades 3 and 4 classifications.

After evaluation, if needed, external laryngeal pressure was permitted for endotracheal tube insertion. Surgery followed under standard anesthesia.

RESULTS

Sensitivity:

RHTMD > ULBT > MPA
71.83 45.07 26.76

Specificity:

MPA > ULBT > RHTMD
94.43 90.93 59.18

Positive predictive value:

ULBT > MPA > RHTMD
42.11 41.30 20.48

Negative predictive value:

RHTMD > ULBT > MPA
93.49 91.88 89.80

Accuracy:

MPA > ULBT > RHTMD
85.79 85.07 60.79

DISCUSSION

Anesthesiologists are recognized as airway management specialist in most aspect of modern practice and to some extent it's primary clinical skill that defines anaesthetists. Difficulty in managing the airway is the single most important cause of anesthesia-related morbidity and mortality.^[6,7]

Successful management of a difficult airway begins with recognition of the potential problem. Many variables have been proposed for pre-operative identification of patients with difficult intubation. Unfortunately, no single test reliably predicts difficult airway. Lassic predictor criteria are mainly dependent on surface anatomy and tend to have poor sensitivity and low PPV.

The present study attempted to estimate diagnostic value of ULBT, RHTMD, and MPA in predicting CL III and CL IV of laryngoscopy.

In the present study, 556 cases studied. The age group was selected between 18 and 65 years and we observed age group between 18 and 27 years had significant

easy laryngoscopy while between 48 and 57 years was significantly associated with difficult laryngoscopy. A study done by Prakash *et al.* pointed that difficult laryngoscopy increased with age due to osteoarthritic changes and poor dentition.^[8] However, in the present study, age between 58 and 65 years did not show any significant relation to difficult laryngoscopy. There are studies done by Savva^[9] and Patel *et al.*,^[10] which do not show age-related changes to difficult laryngoscopy. The present study reflects two different results for age-related conclusions. This could be because the volume of cases in 48–57 years was 84 cases, and in 58–65 years, it was 28 cases which could have altered the proportion of patients with difficult laryngoscopy.

However, no gender or body mass index -related difference in difficult laryngoscopy was observed in our study [Table 1]. The American Society of Anesthesiologists physical status classification was not found to be independent risk factors of difficult laryngoscopy according to the study by Lundström *et al.*^[11]

In the present study, the ASA II patients had a greater degree of difficult laryngoscopy than ASA I. "This difference could be due to associated controlled comorbidities patient can have for which they are categorized in ASA II status."^[12]

The incidence of difficult laryngoscopy in our study was found to be 12.8% which coincides with the incidence reported by other studies.^[8,13-16] Any difference in incidence of difficult laryngoscopy in the present study might have been due to factors such as different anthropometric features, unavailability of uniform grading in description of laryngeal views, application of cricoid pressure, position of head, and the degree of muscle relaxation.

A perfect predictor is characterized by high sensitivity, specificity, and diagnostic accuracy, to identify almost every patient at risk with minimal false-positive predictions. In clinical practice, we are mostly concerned for the unanticipated difficult airway (false-negative predictions). However, false-positive predictions, although distressing and inconvenient, have no life-threatening sequelae. The most significant clinical problem is the false-negative predictions when intubations predicted to be easy, proved to be difficult later. Sensitivity and NPV are statistical measures of a test performance incorporating the false-negative predictions in their calculation formula. Among the tests studied, the above-mentioned characteristics apply best to RHTMD as a single predictor of difficult laryngoscopy.

ULBT in the present study showed to have a sensitivity of 45.07% which is between the sensitivities of 76.5% found by Khan *et al.*^[3] and 28.9% by Zadeh *et al.*^[17] Jain *et al.* compared ULBT and RHTMD and found a specificity of 91.53%,^[2] as compared to 88.7% found in the present study. The accuracy of this study was similar to the study by Eberhart *et al.* and he did not recommend ULBT as the sole predictor for difficult laryngoscopy.^[18]

ULBT is a simple bedside test to perform; however, it is highly operator dependent and we may experience change in class in the same individuals if patient does not understand the maneuver. A clear explanation and demonstration to the patient may limit the error. In the present study, 13.7% of patients belonged to Class III ULBT, and this could have affected the sensitivity of ULBT in our study [Figure 3].

The present study highlights that ULBT with the highest PPV and second highest sensitivity, specificity, NPV, and diagnostic accuracy has total power in predicting CL grading when compared to the other tests in spite of low sensitivity [Table 2].

The present study with a RHTMD “cut off” value of 23.5 got the highest sensitivity of 71.83% [Table 2]. Although this is comparable to the studies by Jain *et al.* (76.4% with the same cutoff), ULBT ranked first in their study.^[2] RHTMD also stood first in terms of NPV of 93.49%. The results are in accordance with Safavi *et al.* 98.4% who found higher NPV than ULBT.^[13] Krobbaaban *et al.*^[4] and Krishna *et al.*^[19] assumed RHTMD ≥ 23.5 cm as risk factor showed high sensitivity, specificity, and NPV and observed variable results. RHTMD is based on precise measurement of patient’s TMD and height, and thereby, interobserver variations are highly unlikely as shown by Srinivasa *et al.*,^[20] and consistency is maintained.

It is crucial that RHTMD is interpreted in terms of its cutoff value. Ratios as high as 29.5 have been used in westerners. However, anthropological assays in India derive a range of 17.1–23.5. This is a vital issue influencing its accuracy.^[13,16,19,21]

Thus, in this study, RHTMD had the highest NPV and sensitivity which means that it misses the least number of difficult laryngoscopies which reduces life-threatening events. However, it stands last compared to other two tests in terms of specificity, PPV, and accuracy. This may unnecessarily subject the patients to receive follow-up diagnostic procedures which can be invasive or expensive and they may be subjected to difficult airway algorithm. Thus, it would be prudent to combine with other tests to strengthen its diagnostic value.

There are not many studies which have focused on MPA. A study done by Gupta and Gupta emphasized the importance of this angle by correlating it with modified Mallampati test, thyromental distance, and atlanto-occipital extension. They found that MPA $<90^\circ$ reflects difficult

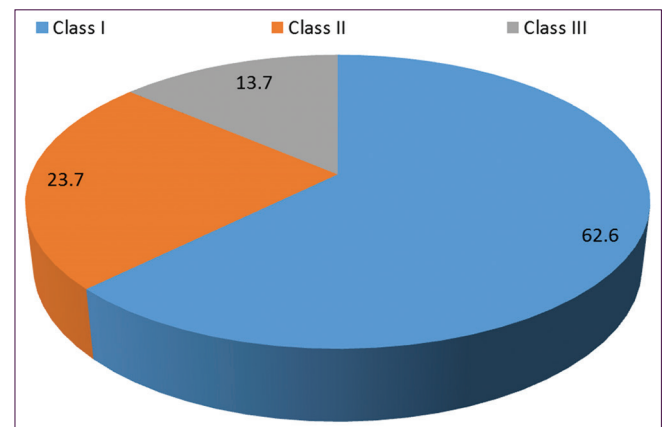


Figure 3: Distribution of cases according to upper lip bite test class

Table 1: Distribution of cases studied according age, sex, BMI, ASA class, and difficult airway

Parameters	Difficult n (%)	Easy n (%)	Total n (%)	P
Age group (years)				
18.0–27.0	47 (37.6)	78 (62.4)	125 (100.0)	0.001***
28.0–37.0	90 (48.9)	94 (51.1)	184 (100.0)	0.590 NS
38.0–47.0	69 (51.1)	66 (48.9)	135 (100.0)	0.879 NS
48.0–57.0	59 (70.2)	25 (29.8)	84 (100.0)	0.001***
58.0–65.0	16 (57.1)	12 (42.9)	28 (100.0)	0.473 NS
Sex				
Male	149 (52.7)	134 (47.3)	283 (100.0)	0.311 NS
Female	132 (48.4)	141 (51.6)	273 (100.0)	
BMI (kg/m ²)				
Normal (18.50–24.99)	163 (51.6)	153 (48.4)	316 (100.0)	0.573NS
Overweight (25.00–29.99)	118 (49.2)	122 (50.8)	240 (100.0)	
ASA class				
Class I	159 (45.2)	193 (54.8)	352 (100.0)	0.001***
Class II	122 (59.8)	82 (40.2)	204 (100.0)	

Values are n (% of cases). P value by Chi-square test, P=0.001***, NS: Statistically non-significant. BMI: Body mass index

Table 2: Diagnostic efficiency of ULBT, RHTMD and MP angle against CL grading

Statistical measure	ULBT (%)	RHTMD (%)	MPA (%)
Sensitivity	45.07	71.83	26.76
Specificity	90.93	59.18	94.43
PPV	42.11	20.48	41.30
NPV	91.88	93.49	89.80
Diagnostic accuracy	85.07	60.79	85.79

PPV: Positive predictive value, NPV: Negative predictive value, MPA: Maxillopharyngeal angle, ULPT: Upper lip bite test, RHTMD: Ratio of height to thyromental distance

laryngoscopy in approximately 80% of patients and is a very simple, non-invasive test. She also found that Grade III and IV CL which correlated with MPA $<90^\circ$ also correlated with A-O angle $<30^\circ$ and TM distance <6.5 cm.^[5]

In this study, MPA ranked first in specificity and diagnostic accuracy, and this shows its value in recognizing easy laryngoscopy [Table 2]. Its values were similar to ULBT in all parameters except a low sensitivity. MPA has to be combined with other tests to increase the recognition of difficult airway which is essential as it has a low sensitivity.^[22]

The present study analyzed individual parameters and each one was correlated to CL; however, results may have differed if analyzed in combination. In addition, a study would be more conclusive if we would have considered odds ratio, Kappa coefficient, and likelihood ratio to measure its clinical significance.

To summarize [Table 2], ULBT had a high specificity, PPV, and diagnostic accuracy while it stood second in sensitivity and NPV. RHTMD was more sensitive with a high NPV by which it can identify difficult laryngoscopy more effectively. MPA with high specificity and diagnostic accuracy is comparable to ULBT and can be used as an objective test in addition to bedside tests to predict difficult laryngoscopy as it is least susceptible to measurement errors. However, each test has its own drawbacks as it scores differently in terms of their sensitivity, specificity, accuracy, and predictive tests when compared to each other. Hence, it will be safer to use a combination of tests which assess different aspects of patient's airway.

CONCLUSION

The ULBT is an acceptable alternative test to predict difficult tracheal intubation and can be used in combination with other bedside tests in pre-operative airway evaluation.

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Gender Differences in Presenting Symptoms and Outcome in Myocardial Infarction

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Abstract

Introduction: Cardiovascular disease is the leading cause of death among women, regardless of race or ethnicity, accounting for deaths of 1 in 3 women. Mortality rates for coronary heart disease have fallen for both men and women, but the rate of fall is much less in women than men.

Aim: The aim of the study was to compare the presentation and outcome of acute myocardial infarction (AMI) in men versus women.

Materials and Methods: All patients satisfying the diagnosis of myocardial infarction were included in the study. All acute myocardial infarction cases were divided into men and women. A detailed evaluation of patients presenting with AMI was done. Clinical presentations, risk factors, vitals, and killip functional classification, electrocardiography were recorded.

Results: Diabetes mellitus found to be 46% in women and 38% in men. Out of 100 females, 60 had precordial chest pain, and 33 had retrosternal chest pain. Evidence of left ventricular failure was more common in women. Thrombolysis was done in 20% of women, where 60% of men undergone thrombolysis. AMI leading to death was reported high in women (9%) followed by men (6%).

Conclusion: Coronary artery diseases in women continue to be a major public health problem that represents a leading cause of death and disability. Better understanding of gender differences in manifestation and detection of myocardial ischemia is a critical initial step to improve outcomes for women.

Key words: Coronary artery disease, Gender bias, Women health

INTRODUCTION

Acute myocardial infarction (AMI) is continuous to be a major public health problem in developing country like India. Coronary care practice is nowadays better equipped than other fields of cardiovascular medicines to reduce the morbidity and mortality.^[1] In comparison with the people of European ancestry, cardiovascular disease (CVD) affects Indians at least a decade earlier and in their most productive midlife years.^[2,3] For example, in Western populations only 23% of CVD deaths occur before the age of 70 years;

in India, this number is 52%.^[4] In addition, case fatality attributable to CVD in low-income countries, including India, appears to be much higher than in the middle- and high-income countries.^[4,5] Although CVD risk factors are widely prevalent in India, there are significant variations between and within different regions. Diabetes mellitus (DM) appears to be more prevalent in the southern states of India, whereas hypertension (HTN) appears to be higher in the northeastern states. Although this heterogeneity can be attributed to diversity in culture (leading to differences in dietary practices, tobacco use, and physical activity patterns) and variations in economic development between and within different states in India, it is important to understand the social determinants.^[6] The cardiovascular anatomy and physiology of women differ from men in many ways. Women have comparatively smaller chests, hearts and different body structure and fat distribution. The life expectancy of women and men varies. Due to their underlying survival advantage, female patients may

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appear to have a similar or even good long-term outcome after MI than men do, even if the disease has a greater impact on women's survival than on men's. Consequently, failure to account for gender differences in the absence of MI may lead to underestimation of the burden of MI on women's mortality.^[7]

Aim

The aim of the study was to compare the presentation and outcome of AMI in men versus women.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of Medicine at Tirunelveli Medical College. All patients satisfying the diagnosis of MI were included in the study. All acute myocardial infarction cases were divided into men and women. A detailed evaluation of patients presenting with AMI was done. Clinical presentations, risk factors, vitals, and killip functional classification, electrocardiography (ECG) were recorded. Serial ECG, routine biochemical analysis and required other lab procedures were done.

RESULTS

A total of 300 patients were included in this study, 100 females and 200 males. The most common symptom is typical chest pain. Duration of chest pain to hospitalization varies between 2 and 72 h. AMI was found to be more common in men than women. DM found to be 46% in women and 38% in men [Table 1]. Among women, 42%

Table 1: Distribution of site of MI

Site	Female	Male
Anterior wall	50	94
Inferior wall	29	67
Anteroseptal	20	33
Lat wall	1	6

MI: Myocardial infarction

Table 2: Distribution of risk factors

Risk factors	Female	Male
DM	46	76
HTN	35	57
Smoking	Nil	85
Hyperlipidemia	42	72
Obesity	27	49

HTN: Hypertension, DM: Diabetes mellitus

Table 3: Distribution of complication

Complication	Female	Male
LV failure	33	51
Death	9	12

had elevated total cholesterol followed by men 36%. 35% of women were found hypertensive, where 28.5% of men found hypertensive in this study [Table 2]. Out of 100 females, 60 had precordial chest pain, and 33 had retrosternal chest pain. The most common infarction is anterior wall MI which is very common in male patients also. Next common site in inferior wall MI. Evidence of LVF was more common in women [Table 3]. Thrombolysis was done in 20% of women, where 60% of men undergone thrombolysis. AMI leading to death was reported high in women (9%) followed by men (6%).

DISCUSSION

The American heart association reports the signs and symptoms of MI with no distinction between women and men. These are uncomfortable pressure, fullness, squeezing, or pain in the center of the chest, pain that spreads to shoulders neck or arms, chest discomfort with lightheadedness, fainting, sweating, nausea, or shortness of breath.^[8] McCance and Huether describe the common symptoms of MI as chest pain that is heavy or crushing, chest pain with nausea and/or vomiting, diaphoresis, shortness of breath, or radiation to neck, jaw, back, or left-arm.^[9] Patients may complain of a feeling of weakness, severe indigestion, shortness of breath, or chest discomfort.^[10]

Sex differences in the cardiovascular system are as a result of differences in gene expression from the sex chromosomes, which may be further modified by sex differences in hormones, resulting in sex-unique gene expression and function. These differences result in variations in prevalence and presentation of cardiovascular conditions, including those associated with autonomic regulation, HTN, DM, and vascular and cardiac remodeling. In contrast, gender differences are unique to the human and arise from sociocultural practices (behaviors, environment, lifestyle, and nutrition).

The increasing prevalence of Type 2 DM is concerning because it is a potent risk factor for atherosclerotic CVD and has long been recognized to confer greater risk for atherosclerotic CVD death in women compared with men.^[11] The impact of obesity on the development of coronary artery disease (CAD) seems to be greater in women than in men. In the Framingham Heart Study, obesity increased the relative risk of CAD by 64% in women, as opposed to 46% in men.^[12]

CONCLUSION

CVD research has focused primarily on men, thus leading to an underappreciation of sex differences from an

etiologic, diagnostic, and therapeutic perspective. The incidence of AMI among women was less when compared to men. The prevalence of risk factors such as DM, HTN, and obesity was high among women when compared to men. Most of the women presented with characteristics features of AMI. The common presenting symptom was chest pain. Left ventricular failure at presentation was more common in women than men.

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Evaluation of Soft Tissue Cephalometric Norms for Maharashtrian Population Using Holdaway Analysis

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Abstract

Aim: Based on Holdaway analysis, the present study aims to evaluate soft tissue cephalometric norms for the Maharashtrian population.

Materials and Methods: The digital lateral cephalograms of 60 subjects with Maharashtrian ethnicity within the age range of 18–30 years with normal occlusion were obtained. Holdaway analysis was carried out using Dolphin Software. The obtained values were statistically analyzed to evaluate soft tissue norms for the Maharashtrian population.

Results: Statistically significant differences were observed in soft tissue norms between Maharashtrian population and Caucasian norms.

Conclusion: Ethnic differences exist between Maharashtrian population and Caucasian population which should be considered when formulating an orthodontic treatment plan.

Key words: Caucasians, Ethnic group, Holdaway, Soft tissue, Cephalometrics

INTRODUCTION

Facial esthetics in dentistry has gained great attention in recent times. The success of orthodontic treatment is frequently related to the improvement gained in patient's facial appearance, which includes soft tissue profile and since there is a considerable variations in soft tissue covering, misleading conclusions can be produced if diagnosis and treatment planning is based on dental and skeletal measurements alone; therefore, analysis of soft tissue profile is mandatory.^[1]

Various cephalometric analysis for orthodontic treatment has been designed, but these cephalometric norms were specific to 1 ethnic group-white subjects of European American ancestry. Cephalometric norms derived for Caucasian population are routinely used for investigations. As these norms show a great degree of variation when applied to different ethnic groups, it becomes necessary to establish the norms for every ethnic group with a standard method for effective orthodontic treatment.^[2-8]

One of the commonly used soft tissue analysis is Holdaway analysis given by Holdaway.^[1] Since India is a subcontinent with a large number of racial subgroups and several religious and interracial mixtures, it was proposed, therefore, to study only the individuals derived from Maharashtra origin using Holdaway analysis.^[2]

Thus, the present study was designed to derive norms for the Maharashtrian population, which would be comparable

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in diagnosis and treatment planning to the Holdaway cephalometric analysis.

Aim

The aim of the study is as follows:

1. To evaluate the mean cephalometric norms for Holdaway analysis in the Maharashtrian population.

Objective

The objective of the study is as follows:

1. To evaluate the mean cephalometric norms for Holdaway analysis in the Maharashtrian population.
2. To compare standards derived with the earlier established norms for other population.

MATERIALS AND METHODS

Source of Data

The sample of 60 subjects was selected. 30 males and 30 females were included. The sample was selected based on age, sex, and straight pleasing profile. A signed informed consent form was taken in Marathi and English language.

Selection Criteria for Subjects

Inclusion criteria

The following criteria were included in this study:

1. Subject should be Maharashtrian origin traced back to two generations.
2. The age range of 18–30 years.
3. Permanent dentition.
4. Class I molar relation.
5. Class I skeletal jaw bases.
6. Normal overjet and overbite.

Exclusion criteria

The following criteria were excluded from the study:

1. Previous or current orthodontic treatment.
2. Severe crowding.
3. Missing tooth other than the third molar.
4. Obvious periodontal disease.
5. Evidence of previous trauma/surgery.
6. Facial asymmetry or deformity.
7. Presence of deciduous/retained teeth.
8. Presence of any pathological conditions.
9. Presence of deciduous or over retained teeth.

Initially, each subject was thoroughly examined clinically according to inclusion and exclusion criteria. A digital lateral cephalometric radiograph was taken of all subjects. Holdaway soft tissue cephalometric analysis was performed and studied.

Radiographic Unit Detail

The Pax-I (PCH2500), Vatech Global, digital radiographic unit from the Department of Oral Medicine and Dental

Radiology, Bharati Vidyapeeth Dental College and Hospital, Sangli, was used to take the lateral digital cephalometric radiographs of the subjects involved in the study [Figure 1].

Cephalometric Tracing

The digital radiographs obtained from Pax-I machine were then transferred to Dolphin Imaging 11.9 Software (Dolphin Imaging and Management Solutions, Chatsworth, Calif.). In our study, Holdaway soft tissue cephalometric analysis was performed and studied [Figures 2 and 3].

Statistical Analysis

- The measurements were statistically analyzed by calculating their means and standard deviations.
- Then, the means of the Maharashtrian population were compared with means of the Caucasian population with the help of unpaired *t*-test.
- A comparison was also made between males and females within the present study.

RESULTS

Descriptive statistics for the variables included in this study is provided from Tables 1-3. Table 1 compares boys versus Caucasian. Table 2 compares girls versus caucasians while Table 3 compares all subjects versus caucasian population. Mean and Standard deviation has been tabulated and based on P value following results have been drawn.

Convexity at Point A

In our study, the mean value for convexity at point A was 1.38 ± 2.44 mm while in Caucasian population it was 0.1 mm. The mean difference between two groups was 1.28 mm which was statistically significant ($P \leq 0.001$).



Figure 1: Patient position for lateral cephalogram

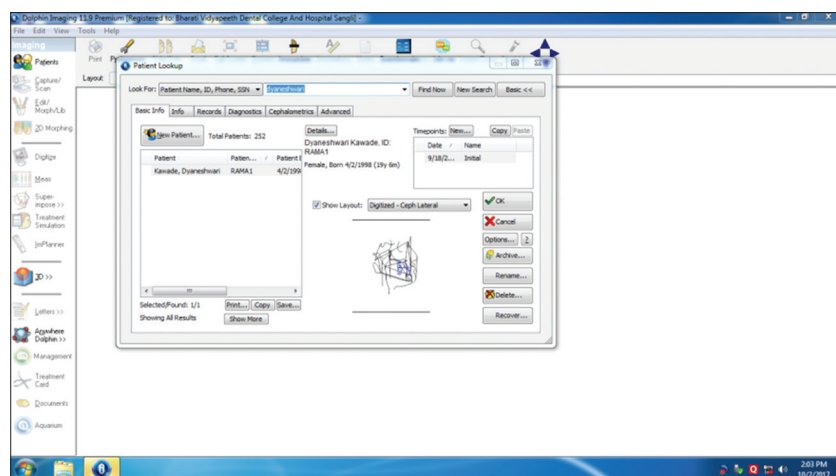


Figure 2: Dolphin imaging 11.9 software

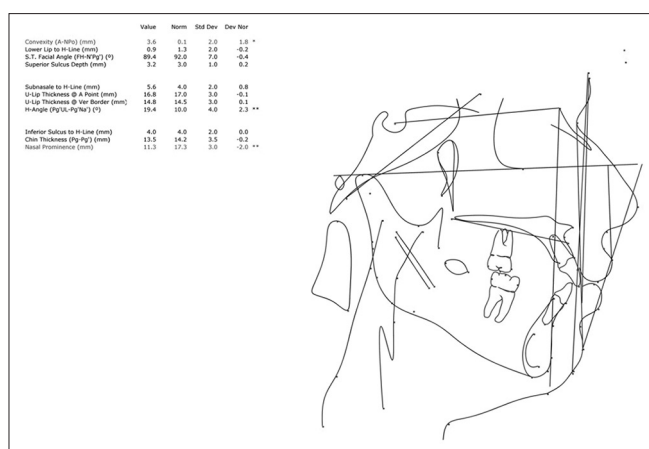


Figure 3: Holdaway analysis tracing

Superior Sulcus Depth

In our study, the mean value for superior sulcus depth was 2.42 ± 1.07 mm while in Caucasian population it was 3 mm. The mean difference between two groups was 0.57 mm which was statistically significant ($P \leq 0.001$).

Nasal Prominence

In our study, the mean value for nasal prominence was 12.14 ± 2.56 mm while in Caucasian population it was 17.3 mm. The mean difference between two groups was 5.15 mm which was statistically significant ($P \leq 0.001$).

Upper Lip Thickness

In our study, the mean value for upper lip thickness was 14.43 ± 2.45 mm while in Caucasian population it was 17 mm. The mean difference between two groups was 2.56 mm which was statistically significant ($P \leq 0.001$).

Upper Lip Thickness at Vermilion

In our study, the mean value for upper lip thickness at vermilion was 10.89 ± 2.01 mm while in Caucasian population it was 14.5 mm. The mean difference between

two groups was 3.60 mm which was statistically significant ($P \leq 0.001$).

H Angle

In our study, the mean value for H angle was $17.25^\circ \pm 3.58^\circ$ while in Caucasian population it was 10° . The mean difference between two groups was 5.72° which was statistically significant ($P \leq 0.001$).

Chin Thickness

In our study, the mean value for chin thickness was 11.74 ± 2.29 mm while in Caucasian population it was 14.2 mm. The mean difference between two groups was 2.45 mm which was statistically significant ($P \leq 0.001$).

Lower Lip to H Line

In our study, the mean value for lower lip to H line was 1.21 ± 1.22 mm while in Caucasian population it was 1.3 mm. The mean difference between two groups was 0.081 mm which was not statistically significant ($P = 0.603$).

Facial Angle

In our study, the mean value for facial angle was $90.36^\circ \pm 12.41^\circ$ while in Caucasian population it was 92° . The mean difference between two groups was 1.63° which was not statistically significant ($P = 0.309$).

Subnasale to H Line

In our study, the mean value for subnasale to H line was 3.57 ± 2.08 mm while in Caucasian population it was 4 mm. The mean difference between two groups was 0.427 mm which was not statistically significant ($P = 0.114$).

Inferior Sulcus to H Line

In our study, the mean value for inferior sulcus to H line was 3.91 ± 1.29 mm while in Caucasian population it was 4 mm. The mean difference between two groups was 0.086 mm which was not statistically significant ($P = 0.602$).

Table 1: Comparison of boys versus Caucasian

Parameter	Number of subjects	Mean±SD	Caucasian norms	Mean difference	t value	P value
Convexity at point A	30	1.33±2.54	0.1	1.23	2.527	0.018*
Lowe lip to H line	30	1.24±1.36	1.3	-0.059	-0.225	0.823
Facial angle	30	88.11±18.31	92	-3.88	-1.103	0.280
Superior sulcus depth	30	2.60±0.85	3	-0.3926	-2.399	0.024*
Sn-H line	30	3.98±1.72	4	-0.011	-0.033	0.974
Upper lip thickness	30	15.47±2.54	17	-1.52	-3.110	0.005*
Upper lip thickness at vermillion	30	12.01±2.29	14.5	-2.485	-5.632	0.001*
H angle	30	16.65±3.76	10	6.65	9.182	0.001*
Inferior sulcus to H line	30	4.25±1.56	4	0.259	0.858	0.398
Chin thickness	30	12.41±2.39	14.2	-1.78	-3.877	0.001*
Nasal prominence	30	12.15±2.25	17.3	-5.14	-11.86	0.001*

One sample t test. SD: Standard deviations

Table 2: Comparison of girls versus Caucasian

Parameter	Number of subjects	Mean±SD	Caucasian norms	Mean difference	t value	P value
Convexity at point A	30	1.424±2.395	0.1	1.323	3.222	0.003*
Lowe lip to H line	30	1.200±1.123	1.3	-0.100	-0.519	0.607
Facial angle	30	92.15±2.949	92	0.1588	0.314	0.756
Superior sulcus depth	30	2.27±1.214	3	-0.726	-3.487	0.001*
Sn-H line	30	3.241±2.300	4	-0.7588	-1.923	0.063
Upper lip thickness	30	13.60±2.072	17	-3.3912	-9.543	0.001*
Upper lip thickness at vermillion	30	10.006±1.175	14.5	-4.49	-22.29	0.001*
H angle	30	14.97±3.304	10	4.9765	8.781	0.001*
Inferior sulcus to H line	30	3.638±0.964	4	-0.3618	-2.188	0.036*
Chin thickness	30	11.218±2.097	14.2	-2.9824	-8.289	0.001*
Nasal prominence	30	12.126±2.82	17.3	-5.17	-10.66	0.001*

One sample t test. SD: Standard deviations

Table 3: Comparison of all subjects' versus Caucasian

Parameter	Number of subjects	Mean±SD	Caucasian norms	Mean difference	t value	P value
Convexity at point A	60	1.38±2.44	0.1	1.28	4.112	0.001*
Lowe lip to H line	60	1.21±1.22	1.3	-0.081	-0.522	0.603
Facial angle	60	90.36±12.41	92	-1.63	-1.026	0.309
Superior sulcus depth	60	2.42±1.07	3	-0.57	-0.421	0.001*
Sn-H line	60	3.57±2.08	4	-0.427	-1.604	0.114
Upper lip thickness	60	14.43±2.45	17	-2.56	-8.146	0.001*
Upper lip thickness at vermillion	60	10.89±2.01	14.5	-3.60	-13.99	0.001*
H angle	60	17.25±3.58	10	5.72	12.455	0.001*
Inferior sulcus to H line	60	3.91±1.29	4	-0.086	-0.524	0.602
Chin thickness	60	11.74±2.29	14.2	-2.45	-8.352	0.001*
Nasal prominence	60	12.14±2.56	17.3	-5.15	-15.68	0.001*

One sample t test. SD: Standard deviations

DISCUSSION

Lifestyle of today's era demands the high esthetic perception. Macro-esthetics, mini-esthetics, and micro-esthetics have been emphasized, and orthodontic ethics has been linked to improving the nose, lip, and chin balance.^[9] Soft tissue analysis has been used by orthodontist and surgeon as an aid in diagnosis and treatment planning.^[10] The nature of the soft tissue profile is affected by many factors, including ethnicity, cultural origin, gender difference, and age;^[7] for this reason, facial characteristics have been studied in various ethnic groups. The thickness of soft tissues is

different in different populations, so it becomes mandatory to study soft tissue analysis along with hard tissue analysis for optimizing treatment results.

Different soft tissue analysis has been introduced by many authors such as Arnett analysis,^[10] Bergman analysis,^[11] and Holdaway analysis.^[1] In our study, we used Holdaway analysis for analyzing soft tissues of the Maharashtrian group.

In our study, we found a statistically significant increase in the value of skeletal convexity at point A than Caucasians. Increase in this value indicates more convex profile and

protrusive upper lips when compared with Caucasians. This is in accordance with a study done by Celebi *et al.* on Turkish population^[4] and Javadpour and Khanemasjedi on Iranian population.^[6]

Decreased nasal prominence increased upper lip strain reveal labial proclination of upper incisors when compared with the Caucasian group. This is in accordance with a study done by Atit *et al.* on Maratha ethnic group.^[5]

H angle value increased in Maharashtrian population shows protrusive upper lips. This is in accordance with a study done by Patel and Goyal on Rajasthani population.^[3]

Upper lip thickness and soft tissue chin thickness values are less when compared to the Caucasian group. This showed thin soft tissue drape covering the facial skeleton. Thin soft tissue immediately alters accordingly to underlying dentoalveolar and skeletal changes during orthodontic changes than thick soft tissue curtain.^[1]

No significant difference found for lower lip to H line, facial angle, Sn-H line, and inferior sulcus depth to H line indicate lower jaw positioned within normal range to cranial base when compared to the Caucasian group.

CONCLUSION

1. According to Holdaway analysis carried out in this study, Maharashtrian adults had more protruded upper lip position and more convex profile along with thin soft tissue drape than Caucasian population.

2. Females had a thin upper lip and soft tissue chin thickness than males.
3. It is legitimate and important for those undertaking orthodontic treatment for patients of the Maharashtrian population to use cephalometric norms for the Maharashtrian population.

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Comparison of Cyclosporine with Systemic Corticosteroid in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis - A Pilot Study

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Abstract

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening dermatological emergencies. Many immunosuppressive modalities have been tried with variable results.

Aims: This study aims to determine the efficacy of cyclosporine in cases of SJS and TEN and compare the efficacy with systemic corticosteroid in the same condition.

Materials and Methods: The study was conducted at a tertiary hospital from January 2015 to December 2017. SCORTEN was assessed at the time of admission. Total body surface area assessment was like any burn patients. Cyclosporine was administered in the dose of 4 mg/kg body weight in two divided dosage for 7 days and then tapered over another 7 days. Data were compared to a similar control series of SJS/TEN patients, managed by systemic steroids in the same time period.

Results: A total of 19 consecutive patients with a mean age of 32.09 and standard deviation ([SD] 16.17) were enrolled into cyclosporine group, which were compared to 19 patients with a mean age of 27.87 (SD 13.97) years in the corticosteroid group. The mean duration of reepithelialization was 14.54 (SD 4.08) and 23 days (SD 6.68) in cyclosporine and corticosteroid group, respectively. Mean hospital stay was 18.09 (SD 5.02) and 26 (SD 6.48) days in cyclosporine and corticosteroid group, respectively. Total mortality was 9. A total of 3 patients died in the cyclosporine group with 2 male and 1 female, compared to 6 deaths occurred in corticosteroid group 4 female, 2 male.

Conclusion: This study definitely suggests that cyclosporine has encouraging role in the management of uncomplicated cases of SJS, SJS-TEN overlap, or TEN, but randomized control trials are needed for further confirmation.

Key words: Cyclosporine, Dexamethasone, Drug reaction, Scorten, Stevens Johnsons syndrome, Toxic epidermolysis necrosis

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening dermatological emergencies mainly due to drugs characterized by peeling of skin along with hemorrhagic crusting of lips and erosions of oral and genital mucosa.^[1] Worldwide, the

average annual incidence of TEN is 0.4–1.3 cases per million populations. The mortality rate of SJS and TEN is high, approximately 5% for SJS and 30% for TEN.^[2] Now, SJS, SJS-TEN overlap, and TEN are considered a spectrum of the same condition having common risk factors and causes, differentiated only by the extent of the body surface area (BSA) involved. Patients with epidermal detachment involving <10% of BSA are classified as having SJS, more than 30% BSA as TEN, and 10–30% as SJS/TEN overlap.

Apoptosis is believed to be the primary mechanism responsible for keratinocyte death in SJS/TEN. Two pathways have been proposed to support this theory. The first theory proposes that cytotoxic T-cells are activated by an inciting drug, which leads to the release of granzyme B

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and perforin, thereby activating the caspase cascade that ultimately results in keratinocyte apoptosis. The second theory proposes that Fas-Fas ligand binding activates caspase 8, which results in nuclease activation and the widespread skin blistering characteristic of this severe drug reaction.

A prognostic score called SCORTEN has been validated to demonstrate its ability to specifically predict patient outcome in SJS and TEN.^[3] Even though some uncertainty still persists on effector mechanisms of TEN, the resemblance to graft rejection provided a rationale for using the immunomodulating agents. There are several studies illustrating variable results in the management of SJS/TEN. These included corticosteroids, plasmapheresis, cyclophosphamide,^[4] and thalidomide. Fas-Fas ligand and cytotoxic T-cell which play a key role in the pathogenesis of SJS/TEN are, respectively, blocked by intravenous immunoglobulin (IVIG) and cyclosporine.^[5] Thus, theoretically making, IVIG and cyclosporine effective drugs in the management of SJS/TEN.^[6-8] Several case reports have suggested encouraging results with IVIG in management of SJS/TEN. However, a study by Bachot *et al.*^[9] did not show any improvement with IVIG. In Indian subcontinent, managing SJS/TEN by IVIG is not cost-effective. In addition, there is no double-blinded controlled trial, which suggests IVIG superior than other modalities. Several case reports and case series revealed encouraging result of the use of cyclosporine in stopping disease progression and to prevent the mortality.^[8,10] In Indian subcontinent, systemic steroids have traditionally been used to manage this condition due to its experience of use, easy availability, and cost-effectiveness despite having multiple complications.^[11] This study was designed to evaluate the efficacy of cyclosporine and compare the results with patients who were managed by systemic steroids in tertiary healthcare setting.

MATERIALS AND METHODS

This was an open, pilot, and uncontrolled study. The study was conducted at Baba Raghav Das Medical College, Gorakhpur, from January 1, 2015, to December 30, 2017. A total of 38 patients were enrolled in the study during this period. All cases fulfilling clinical diagnoses of SJS, SJS-TEN overlap, and TEN, Figures 1-3 were included into the study. Exclusion criteria were prior treatment with any other immunosuppressive drugs, history of intolerance to cyclosporine, uncontrolled diabetes mellitus, human immunodeficiency virus (HIV) positivity, and cases of multiorgan failure and sepsis. It was decided in protocol that cyclosporine will be stopped if there is the development of high blood pressure with a diastolic

pressure >110 mmHg and creatinine $\geq 150\%$ of initial value. Irrespective of the clinical spectrum of disease (SJS/SJS-TEN overlap/TEN) cyclosporine was administered in solution form in the dose of 4 mg/kg body weight in two divided dosage for 7 days, then 2 mg/kg body weight in two divided dosage for another 7 days. If there was no requirement of cyclosporine, it was to be stopped after 7 days of therapy. No other immunosuppressant was administered. Cases of SJS, SJS-TEN overlap, and TEN were managed in the general ward of the Department of Dermatology. It was proposed in the protocol that if there is clinical deterioration in the cases of SJS/SJS-TEN overlap, those would be managed in the burn center having intensive care facility. Barrier nursing, ambient temperature of 30°C, fluid and electrolyte balance, and high calorie-containing diets were considered in each patient. Injectable antibiotics were considered in strongly suspected or evident sepsis mostly managed on azithromycin or linezolid.



Figure 1: (a) Typical hemorrhagic crusting on lips in a patient with toxic epidermolytic necrosis (b) bullous eruptions and erythema on trunk in a patient with Stevens-Johnson syndrome



Figure 2: Detached skin of the hand in a patient with toxic epidermal necrolysis



Figure 3: Involvement of the face in a patient of toxic epidermal necrolysis

The patients were evaluated clinically daily for the entire period of hospitalization. Data were filled as per predesigned pro forma. Efficacy of cyclosporine was assessed by the average number of days in stabilization of disease progress, rate of reepithelization of skin, duration of hospitalization, tolerance to treatment, and rate of mortality at 1 month in comparison with the predicted death estimated by the SCORTEN at the time of admission. The actual death rates were compared to the predicted rates by standardized mortality ratio analysis (sum of observed deaths/sum of expected deaths) $\times 100$. The SCORTEN calculation was as per the study of Bastuji-Garin *et al.*^[3] Stabilization of disease was defined when new lesions cease to appear. Progression of disease was evaluated by any increase in erosions, blistering, and positive Nikolsky's sign. Reepithelization was defined as complete healing of the skin without any erosion. Total BSA (TBSA) assessment was like any burn patients, following rule of nine. Monitoring of patients was like well-established Intensive Care Unit protocol. We compared the data with a side-by-side study with the patients admitted to our hospital during the same period who were managed with systemic steroids in similar setup. The inclusion and exclusion criteria remained the same as it was considered for the cyclosporine therapy except the fact these patients were managed by systemic steroid. These patients were treated with injectable dexamethasone 2 ml twice a day for 2 consecutive days tapered to 2 ml once in morning and 1 ml once in evening for 2 days, followed by 1 ml twice a day for 2 days then stopped by giving to 1 ml once in morning.

RESULTS

A total of 19 cases of SJS/TEN were seen from January 1, 2015, to December 30, 2017, who were treated by cyclosporine. No patient was dropped out from the study because of adverse effects of cyclosporine. A total of 19 consecutive patients (12 men and 7 women) were enrolled;

they were aged 32.09 ± 16.17 years (mean \pm standard deviation [SD]) M: F (12:7). Mean \pm SD delay between onset and admission was 2.63 ± 0.67 days (range 1–4). There was no intolerance to cyclosporine. Five cases of SJS were given cyclosporine only for 7 days due to marked improvement in the clinical condition. Rest in other cases, full 14 days course, as proposed in the protocol, was given three patients died (2 male and 1 female); however, there was no long-term complication in patients who survived the episode.

There were a total of 19 cases of SJS, SJS-TEN overlap, and TEN from January 1, 2015, and December 30, 2017, who were treated by corticosteroid. Mean delay between the onset of the disease and admission was 2.16 (SD 0.75) days. 6 patients died under this treatment regimen (4 female and 2 male). Only one case developed long-term complication that is corneal ulcer with symblepharon.

Based on the SCORTEN system, 7.39 patients were expected to die in patients treated by cyclosporine. While in patients treated by corticosteroid, 8.8 patients were expected to die. The comparison of mortality rate along with SCORTEN is depicted in Table 1.

The age and initial TBSA, which might have interfered with the clinical outcome, were also analyzed. There were no statistically significant differences ($P > 0.05$). The time from the onset of the disease to admission was also not significantly different ($P > 0.05$). However, cyclosporine had significantly reduced the time to the arrest of progression of SJS/TEN ($P = 0.04282$), the total reepithelization time ($P = 0.009956$), and hospitalization stay ($P = 0.02597$) in comparison to corticosteroid. Those, who survived the disease, both drugs were tolerated well by the patients. Only one patient treated by cyclosporine developed corneal ulceration with symblepharon, which was statistically insignificant ($P > 0.05$).

DISCUSSION

The Cochrane review on intervention for TEN revealed only one randomized controlled trial. This trial compared the effectiveness of thalidomide with placebo. The only trial available used thalidomide, but this trial did not show any benefit from treatment compared against placebo but highlighted increased chances of dying from the treatment. Role of steroids in the management of TEN has been controversial. Several studies had shown possible benefit of corticosteroids. However, of late, most of the studies criticized the use of corticosteroids stating it not only prolongs the hospital stay but also makes patients susceptible for complications. A retrospective analysis of 289 patients from the EuroSCAR study found no benefit from corticosteroids or IVIG compared to supportive care alone.^[12] Even the combination therapy of IVIG and

Table 1: Data of mortality of patients of SJS/TEN managed by cyclosporine and corticosteroid

SCORTEN	Expected mortality %	Cyclosporine group			Corticosteroid group		
		Number of patients	Number of death		Number of patients	Number of death	
			Predicted	Actual		Predicted	Actual
0-1	3.2	5	0.16	0	3	0.96	0
2	12.3	4	0.50	0	5	0.61	0
3	35.3	3	1.0	0	4	1.41	0
4	58.3	5	2.93	1	4	2.3	2
5-7	90	3	2.8	2	4	3.6	4
TOTAL	19	19	7.39	3	19	8.8	6

TEN: Toxic epidermal necrolysis, SJS: Stevens-Johnson syndrome

corticosteroid did not find any significant decrease in the mortality rate. In the paucity of data on effective drug for SJS/TEN, prompt withdrawal of causative drugs should be a priority when managing such cases. Garcia-Doval *et al.* have shown that the earlier the causative drug is withdrawn, the better the prognosis and that patients exposed to causative drugs with long half-lives have an increased risk of dying. To identify the culprit drug(s), it is important to consider the chronology of administration of the drug and the reported ability of the drug to induce SJS/TEN. The reported ability or likelihood of a drug being the cause of SJS/TEN can be found in PubMed/MedLine or other appropriate sources such as the Litt's drug eruption reference manual. SJS/TEN is a life-threatening condition, and therefore, supportive care should be an essential part of the management strategy.

Our study was distinct in the way; it had evaluated the efficacy of cyclosporine and compared historically to corticosteroids. It highlighted few important results. Cyclosporine was well tolerated by all the patients. There were three deaths in the patients managed by cyclosporine while there were five deaths in the corticosteroid group. All these results were statistically significant with $P < 0.05$. The only complication noted was a corneal ulceration and symblepharon formation. High survival in cyclosporine group could be explained by probable mechanism of action of this drug, which targets cytotoxic T-cell, which plays an important role in the apoptosis of keratinocytes. Other probable explanation could be better patient selection by excluding patients of multiorgan failure, sepsis, and HIV, which are the groups who succumb to death very fast when they develop SJS/TEN.

Recently, Valeyrie-Allanore *et al.*^[12,13] conducted an open, phase II trial to determine the safety and possible benefit of cyclosporine. A total of 29 patients were included in the trial (10 SJS, 12 SJS-TEN overlap, and 7 TEN), and 26 completed the treatment with cyclosporine administered orally (3 mg/kg/d for 10 days) and tapered over a month. The prognostic score predicted 2.75 deaths and none occurred ($P = 0.1$). There was no comparison with any

historical group of corticosteroid. This study suggested that both the death rate and the progression of detachment seemed lower than expected, suggesting a possible usefulness of cyclosporine in SJS and TEN.

A case series reported by Arevalo *et al.*^[14] in which 11 patients treated enterally with cyclosporine 3 mg/kg daily observed a rapid epithelialization with no significant toxicity in comparison with patients treated with cyclophosphamide and corticosteroids combined. Similar findings were noted by Reese *et al.* in four patients with SJS/TEN who were managed by cyclosporine.

This study provided an excellent result with cyclosporine; however, comment on its efficacy cannot be made due to inherent constraint of the study design. An open, uncontrolled study with very small sample size in each group and selection of uncomplicated cases is obvious limitations of this study, which may have favored the better outcome of cyclosporine. A large, double-blind, placebo-controlled, randomized trial would be more appropriate to confirm its efficacy, which is not only impractical but also unethical. Like most of the recent studies, our study also finds the use of corticosteroid in the management of SJS/TEN cause prolong hospital stay and increase in the mortality rate. This study definitely suggests that cyclosporine has encouraging role in the management of uncomplicated cases of SJS and SJS-TEN.

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A Correlative Study on Clinical, Pathological and Computed Tomography Scan Findings of Cervical Nodal Metastases in Head and Neck Malignancies

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Abstract

Background: Presence or absence of metastatic disease in the neck determines the prognosis and survival period of patients with malignant tumors of head and neck. The year survival rate is reduced to half if the palpable nodes are present at the time of diagnosis. Unfortunately, medical opinion is divided into various aspects of metastatic neck disease. Controversies remain in the assessment of neck disease, the prophylactic treatment of metastatic nodes, and place of radical neck dissection as opposed to modified radical neck dissection and the role of radiotherapy. Potential benefits of clinical examination far outweigh other investigative methods in the assessment of regional lymph nodes metastases.

Aim of the Study: The aim of the study was to study the pattern of cervical lymph node metastasis in various head and neck malignancies and to compare the accuracy between clinical examination, pathological study, and contrast enhanced computed tomography (CT) scans.

Materials and Methods: A total of 181 patients with head and neck malignancies attending the department of ear nose and throat were analyzed by clinical examination, pathological examination, and CT scan findings of the neck for the accuracy of their diagnosis. The sensitivity, specificity and positive and negative predicted values of the methods used in their diagnosis were calculated using crosscheck tables.

Observations and Results: A total of 181 patients with squamous cell carcinoma of the head and neck region were included; 33 patients underwent neck dissection. Maximum numbers of cases were carcinoma hypopharynx 26% followed by carcinoma of larynx 24.3%. Clinical examination had sensitivity, specificity, positive predictive value, and negative predictive value as 66.7%, 75%, 82.4%, and 56.3%, respectively (kappa significance 0.389, $P = 0.021$). The CT examination had sensitivity, specificity, positive predictive value, and negative predictive value as 85.7%, 41.7%, 72%, and 62.5%, respectively, k value 0.389; $P = 0.021$.

Conclusions: Higher incidence of head and neck squamous cell carcinoma was observed among the 61–70 years group. Males were more commonly affected. The most common head and neck malignancy with nodal metastasis were observed to be the hypopharyngeal malignancy, followed by carcinoma oropharynx. The occurrence of nodal metastasis was more common in carcinoma oropharynx. Bilateral nodal metastasis was observed to be high from carcinoma of base of tongue, followed by pyriform fossa malignancy and carcinoma supraglottis. Level I lymph node was observed to be the most common lymph node involved in the oral cavity and paranasal sinus malignancy.

Key words: Computed tomography scan, Head and neck tumors, Histopathology of malignant tumors, Malignancies, Undifferentiated carcinoma

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INTRODUCTION

Since its first description by George Washington Crile in 1906,^[1] classical radical neck dissection has undergone an increasing number of modifications. It has now come to selective neck dissection in which only those lymph node groups are removed that are more likely to

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contain metastatic deposits from the concerned primary. Feinmesser *et al.*^[2] found computerized tomography to have no advantage over physical examination in the detection of metastatic neck disease in their earlier study. Borges *et al.*^[3] retrospectively analyzed various histological parameters in surgically treated patients with carcinoma of the anterior tongue and buccal mucosa to evaluate their role in prognosis and treatment. Their main findings were a strong correlation between high tumor grade, infiltrative tumor margins, perineural invasions, size >2 cm, and lymph node metastasis at presentation for both groups of patients. Shah^[4] in a retrospective study to predict the pattern of cervical lymph node metastasis from squamous cell carcinoma of the oral cavity found the sensitivity, specificity, and overall accuracy of clinical examination for neck nodes to be 70%, 65%, and 68%, respectively. The false negative rate of clinical examination for neck metastasis in the study was 30%. Shah^[5] in an attempt to predict the pattern of cervical lymph node metastasis from squamous cell carcinomas of the upper aerodigestive tract concluded that supraomohyoid dissection would have removed the majority of lymph nodes harboring occult metastasis in no patients. However, if Level I, II, and III were grossly positive at the time of surgery Level IV and V also should be dissected. Friedman^[6] reported on the effectiveness of computerized tomography in staging head and neck cancer and advocated that the concept of elective dissection should be studied in the light of the improved ability to detect the nodal disease with computerized tomography. Van den Brekel *et al.*^[7] performed a prospective study of the value of ultrasonography (US) and US-guided fine needle aspiration cytology (FNAC) for assessment of N₀ lesions in the neck and found it an unreliable method for detecting occult lymph node metastasis. Masahiro^[8] found that computed tomography (CT) or magnetic resonance imaging (MRI) was not conclusive in detecting the extent of metastasis with 15 of the 60 patients exhibiting more extensive neck disease than what was evaluated preoperatively. Dhawan *et al.*^[9] reviewed the histopathological findings in 57 surgical specimens of T₃ and T₄ buccal mucosa cancer, and clinical N+ group of patient's metastatic disease was histologically demonstrated in 17.5% at Level I and 14% at Level II. In clinically N₀ group it was only 11.7% and 9%, respectively. Borges *et al.*^[3] reported 20% false negative rate of clinical examination of the neck in malignancies of oral cavity patients. They also found that CT scan and US can detect 60 to 70% of occult metastatic neck disease in clinically N₀ patients. The present study is a humble attempt to study the pattern of lymph node metastasis from various head and neck malignancies and to determine the sensitivity and specificity of clinical examination and contrast enhanced computed tomography in determining neck metastasis. An attempt has also been made to determine the role of selective neck dissection.

Type of Study

A prospective cross-sectional hospital based open study.

Institute of Study

This study was conducted at the Department of Ear Nose and Throat (ENT), Government Medical College, Kozhikode, Kerala.

Study Period

This study was from December 2010 to October 2012.

MATERIALS AND METHODS

A total of 181 patients with head and neck.

Malignancies attending the department of ENT were included in the study. An Ethical Committee Clearance from the institute was obtained. An ethical committee cleared consent letter was used in the study. These patients were undergoing either therapeutic neck dissection or prophylactic neck dissection for the secondaries in cervical lymph nodes. Both the methods were considered for the comparison of accuracy between clinical examinations and reports of contrasts enhanced CT scans of the neck. The number of patients undergoing either therapeutic neck dissection or prophylactic neck dissection was 33 patients.

Inclusion Criteria

1. Patients with diagnosed newly cases of squamous cell carcinoma of head and neck region were included.
2. Patients undergoing either therapeutic or prophylactic neck dissection were included study group.

Exclusion Criteria

1. Patients with malignancies other than squamous cell carcinoma.
2. Patients with recurrence/post radiotherapy/post-chemotherapy.
3. Cervical lymph node metastasis with occult primary.

Experimental Methodology

All patients in the study population were evaluated by proper history, clinical examination of the primary lesion and detailed neck examination. CT with contrast was done in all cases. MRI was done in indicated cases. FNAC was done for palpable nodes. After neck dissection, the specimen was divided according to the level of lymph nodes. The specimens were fixed in 10% formalin and were sent for histopathological examination. Tissue sections were stained with H&E. Lymph nodes were studied for the presence or absence of metastasis. Results were tabulated and analyzed. The cases were divided

intocarcinoma of oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, and nose and paranasal sinus (PNS). Lymph nodes were assessed as Level I, II, III, IV, V, and VI. The incidence of lymph node metastasis in each group, the lymph node groups involved and the distribution of cases according to the subsite in node-positive cases were studied, and the results were expressed as a percentage.

Comparison between Clinical Examination and Contrast Enhanced CT

The cases undergoing neck dissection were evaluated in detail by clinical examination and contrast enhanced CT preoperatively for the level of the lymph nodes involved. This was compared with the histopathology report. The sensitivity and specificity of the clinical examination and the contrast enhanced CT was determined, and comparison between the two was done.

Analysis

The sensitivity, specificity, and the predictive values are calculated using the following formulae.

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive} + \text{false negative}} \times 100$$

$$\text{Specificity} = \frac{\text{True negative}}{\text{True negative} + \text{false positive}} \times 100$$

$$\text{Positive predictive value} = \frac{\text{True positive}}{\text{True positive} + \text{False positive}} \times 100$$

$$\text{Negative predictive value} = \frac{\text{True negative}}{\text{True negative} + \text{False negative}} \times 100$$

Measure of agreement used was kappa, $P < 0.05$ was considered as significant.

OBSERVATIONS AND RESULTS

There were totally 181 newly diagnosed patients with squamous cell carcinoma of the head and neck region. Among the 181 patients, 33 patients underwent neck dissection. All these patients were considered for comparison between clinical assessment and radiological assessment of neck nodes. Maximum numbers of cases were carcinoma hypopharynx which contributed to 26% of the cases, followed by carcinoma of larynx (24.3%). The distribution of malignant tumors in different sites was tabulated [Table 1 and Figure 1].

The study of the age distribution of cases revealed that maximum incidence was in the age group of 61–70 (37%), followed by 51–60 age group (27%). The youngest patient was 15 years which were a case of nasopharyngeal carcinoma [Table 2 and Figure 2].

Analysis of the incidence of malignant tumors depending on the sex revealed a male preponderance and the male to female ratio was 6:1 [Table 3].

Nodal Metastasis

A total of 117 cases (64.64%) were found to have positive nodal metastasis, of which 20 cases presented with bilateral nodes (17.09%)

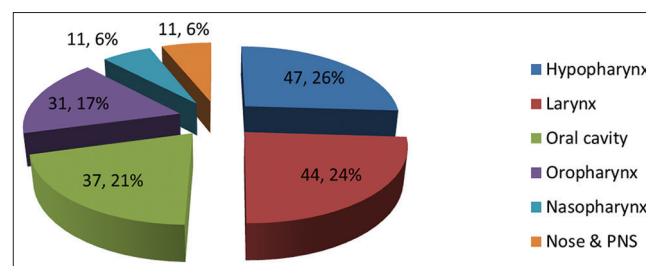


Figure 1: The pie chart of distribution of malignant tumors (n = 181)

Table 1: Site distribution (n=181)

Site	n (%)
Hypopharynx	47 (26)
Larynx	44 (24.3)
Oral cavity	37 (20.4)
Oropharynx	31 (17.1)
Nasopharynx	11 (6.1)
Nose and PNS	11 (6.1)

PNS: Paranasal sinus

Table 2: The age incidence in the study group (n=181)

Age	n (%)
0–10	0 (0)
11–20	1 (0.55)
21–30	0 (0)
31–40	8 (4)
41–50	21 (11.6)
51–60	49 (27)
61–70	67 (37)
71–80	29 (16)
81–90	6 (3)
91–100	0 (0)

Table 3: Sex distribution (n=181)

Sex	n (%)
Male	156 (86)
Female	25 (14)

Primary Tumor Site Distribution in Patients with Bilateral Nodal Metastasis

Total cases with bilateral nodal metastasis were 20, out of which most common was from carcinoma of the base of tongue 7/20 (35%), followed by pyriform fossa 6/20 (30%), [Table 4].

Site Distribution in Nodal Positive Cases

In this study population, the number of cases with nodal metastasis was 34/117 (29.05%), with the primary in hypopharynx 34/117 (29.05%), followed by 25/117 (21.36%) patients with primary in oropharynx [Table 5].

Analysis of each Site: Oral cavity (24/37)

Total cases of oral cavity malignancies were 37, of which 24 cases (64.86%) showed nodal metastasis. Tongue was the most common subsite with nodal metastasis in 11 patients (45.83%) [Table 6 and Figure 3].

The lymph node group most commonly involved in oral cavity malignancy was found to be Level I in 11 patients (45.83%), [Table 7 and Figure 4].

Oropharynx (25/31)

A total of 25 cases out of 31 (80.64%) showed lymph node metastasis in oropharyngeal malignancy, indicating high chances of nodal metastasis. Secondaries from oropharynx base of the tongue were found in 10 patients and were the most common subsite (40%) [Table 8 and Figure 5].

Oropharyngeal malignancies with Level II nodes were found in 23/25 of the malignancies (92%), Level III in 1 patient (4%) [Table 9 and Figure 6].

Table 4: Cases with bilateral nodal metastasis (n=20)

Site	n (%)
Base of tongue	7 (35)
Pyriform fossa	6 (30)
Aryepiglottic fold	3 (15)
Posterior pharyngeal wall	2 (10)
Floor of mouth	1 (5)
Hard palate	1 (5)

Table 5: The patients with positive cervical lymph nodes (n=117)

Site	n (%)
Hypopharynx	34 (29.05)
Oropharynx	25 (21.36)
Oral cavity	24 (20.51)
Larynx	20 (17.54)
Nasopharynx	8 (6.83)
Nose and PNS	6 (5.12)

PNS: Paranasal sinus

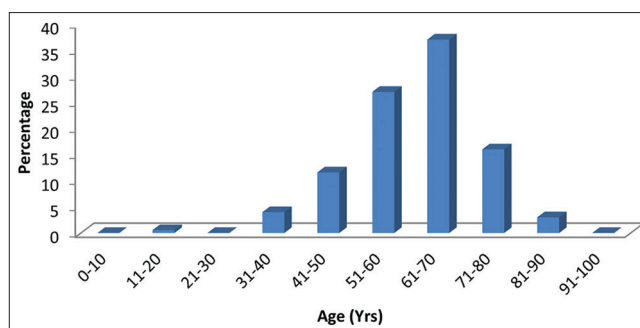


Figure 2: The bar chart of incidence among the various age groups (n = 181)

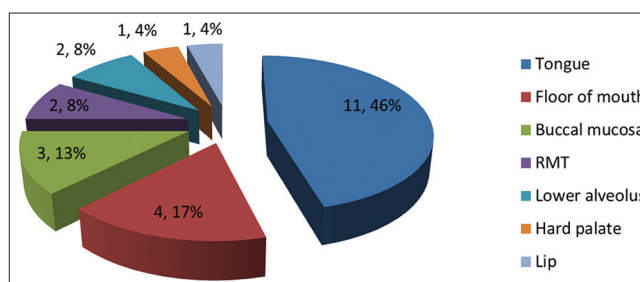


Figure 3: Pie chart the distribution of sites of oral cavity malignancies (n = 24)

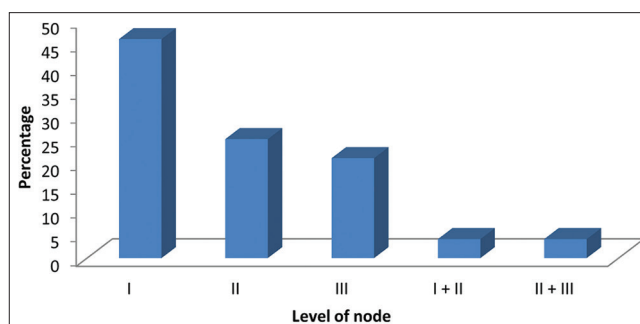


Figure 4: The bar chart depicting the levels of nodal involvement in oral cavity malignancies

Table 6: Oral cavity – subsites (n=24)

Subsite	n (%)
Tongue	11 (45.83)
Floor of mouth	4 (16.66)
Buccal mucosa	3 (12.5)
Retromolar trigone	2 (8.33)
Lower alveolus	2 (8.33)
Hard palate	1 (4.16)
Lip	1 (4.16)

Table 7: Incidence oral cavity malignancy with positive lymph nodes (n=24)

Level of node	n (%)
I	11 (45.83)
II	6 (25)
III	5 (20.83)
I+II	1 (4.16)
II+III	1 (4.16)

Hypopharynx (34/47)

Total nodal positive cases were 34/47 (72.34%). Most common subsite was found to be pyriform fossa in 26/34 (76.47%) [Table 10].

Among the cervical metastases in hypopharyngeal malignancies, Level II lymph nodes were most commonly involved in (58.82%), followed by Level III 4/34 (11.76%), [Table 11 and Figure 7].

Larynx (20/44)

Total cases of Ca larynx were observed in 44 patients, of these 20 (44.44%) showed nodal metastasis. This incidence was found to be low compared to hypopharynx and oropharynx. Carcinoma supraglottis was observed in 15 (75%) and found to be maximum incidence of lymph node metastasis [Table 12]. Among the supraglottis,

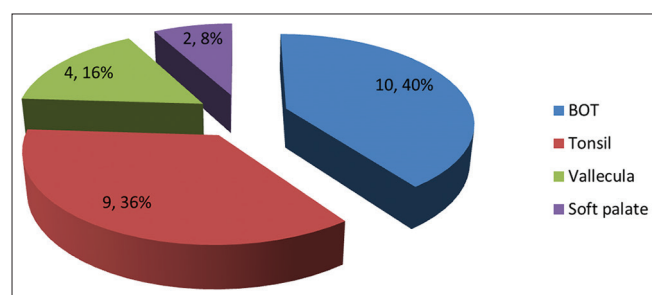


Figure 5: The subsites of oropharynx malignancies with nodal metastases (n = 25)

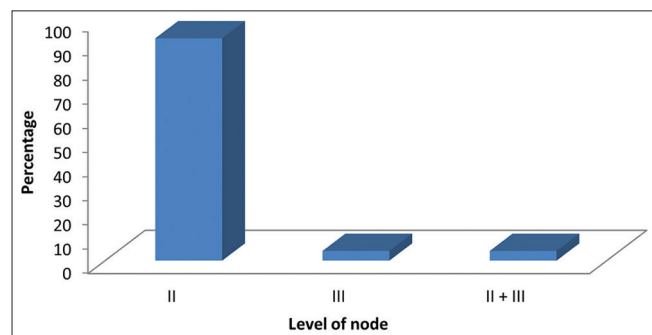


Figure 6: The levels of lymph nodes in oropharyngeal malignancies (n = 23)

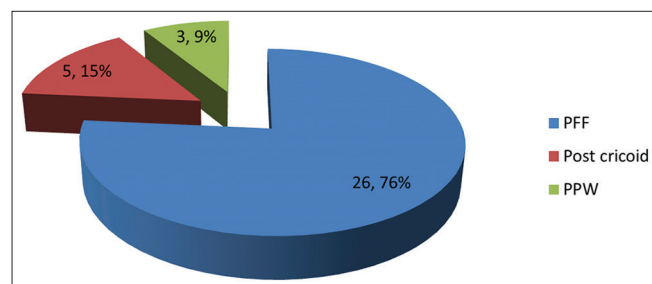


Figure 7: The subsites of hypopharyngeal malignancies with cervical secondaries (n = 34).

aryepiglottic fold showed the maximum incidence of lymph node metastasis.

Most common level of lymph node involved in carcinoma Larynx was Level II (60%) [Table 11].

Nasopharynx (8/11)

There were 11 patients presenting with carcinoma nasopharynx and 8 out of 11 cases (72.72%) showed nodal metastasis. Most common level affected was Level II (50%), followed by Level II + Level V (37%) [Table 14].

Nose and PNS (6/11)

There were 11 patients presenting with carcinoma nose and PNS and 6 out of 11 cases (54.54%) showed metastasis

Table 8: The nodal metastases in malignancies of oropharynx (n=25)

Subsite	n (%)
Base of tongue	10 (40)
Tonsil	9 (36)
Vallecula	4 (16)
Soft palate	2 (8)

Table 9: Oropharynx – lymph nodes

Level of LN	n (%)
II	23 (92)
III	1 (4)
II+III	1 (4)

Table 10: Hypopharynx – subsites

Subsites	n (%)
Pyriform fossa	26 (76)
Post cricoid	5 (15)
Posterior pharyngeal wall	3 (9)

Table 11: Hypopharynx – lymph nodes

Level of LN	n (%)
II	20 (58.82)
II+III	5 (14)
III	4 (12)
II+V	2 (6)
II+III+IV	2 (6)
IV	1 (3)

Table 12: Malignant tumors of larynx with nodal involvement and their subsites (n=20)

Subsites	n (%)
Glottis	5 (25)
Epiglottis	2 (10)
Aryepiglottic fold	8 (40)
Arytenoid	2 (10)
Vestibular band	3 (15)

in lymph nodes. Most common level affected was Level I (50%), followed by Level II (34%). All the node positive cases were from carcinoma maxilla (100%) [Table 15].

Comparison of Accuracy between Clinical Assessment and Radiological Assessment was Done in this Study

A total number of patients who underwent neck dissection was 33/181 (18.23%). The distribution of different primary sites among the 33 patients was shown tabulated in Table 16.

The cellular differentiation on histopathological examination was tabulated in Table 17.

The study showed that maximum incidence of lymph node metastasis occurred from the poorly differentiated tumors 9/21 (42.85%) [Table 17].

Clinical Assessment of Neck Nodes

A cross-check was made between the clinical nodal staging and histopathological staging and tabulated in Table 18.

Table 13: The levels of nodal involvement in carcinoma larynx (n=20)

Levels of metastases	n (%)
II	12 (60)
III	4 (20)
II+III	4 (20)

Table 14: Nasopharynx – lymph nodes (n=8)

Level of LN	n (%)
II	4 (50)
II+V	3 (38)
V	1 (12)

Table 15: Nose and PNS – level of lymph nodes (n=6)

Level of LN	n (%)
I	3 (50)
II	2 (33.33)
I+II	1 (16.66)

PNS: Paranasal sinus

Table 16: Site distribution of cases

Site	n (%)
Ca pyriform fossa	8 (24.2)
Ca larynx	6 (18.2)
Ca tongue	5 (15.2)
Ca alveolus	4 (12.1)
Ca floor of mouth	2 (6.1)
Ca maxilla	2 (6.1)
Ca retromolar trigone	2 (6.1)
Ca tonsil	2 (6.1)
Ca base of tongue	1 (3)
Ca nasal cavity	1 (3)

Out of the 16 clinically N_0 cases, 7 cases (43.8%) were proved to be pathologically positive, demonstrating the possibility of occult metastasis which justifies the role of prophylactic neck dissection in high-risk cases, even if the nodal status is N_0 . From Table 19, it is clear that by clinical assessment of the neck node metastasis; there is a 40–60% chance of downstaging of the nodal status [Table 19].

CT Assessment of Neck Nodes

A similar cross-check was done between CT scan nodal staging and histopathological nodal staging, and the results were tabulated in Table 20.

Out of the 8 CT negative cases (N_0), 37.5% were proved to be pathologically positive, which again justifies that there is a role for neck dissection in cases with a high chance of occult metastasis even if the CT assessment is N_0 . In about 40–58% of the cases, there is a chance for overestimation of the nodal stage by CT assessment [Table 21].

Sensitivity and Specificity of Clinical Examination and Contrast enhanced CT

A cross-check was made between the clinical examination and CT scan enhanced with contrast and tabulated in Table 22; the κ value was 0.295; $P = 0.077$.

Overall, the clinical examination of lymph node has sensitivity, specificity, positive predictive value, and negative predictive value as 66.7%, 75%, 82.4%, and 56.3%, respectively (kappa significance 0.389, $P = 0.021$). The CT examination has sensitivity, specificity, positive predictive value, and negative predictive value as 85.7%, 41.7%, 72%, and 62.5%, respectively, κ value 0.389; $P = 0.021$ [Table 23].

DISCUSSION

More than one-third of all cancers in India occur in the head and neck region (Incidence rate 2, 11, 200/year), compared to <10% in the Western world and 4% in the USA.^[10] The primary reason for this unusually high incidence of head and neck cancer in India may be the indiscriminate use of tobacco in its various forms. Undetected nodal metastasis is the most common cause of treatment failure in head and neck cancer. Hence, regional lymph node metastasis is an important factor in predicting the clinical course and outcome of the patient with head and neck malignancy.^[11] Palpable nodes at presentation reduce the survival by about half, and this is due to the aggressive primary tumor and its ability to metastasize not only loco-regionally but also to distant sites.^[1] In the present study, we had a total of 181 newly diagnosed cases of squamous cell carcinoma in the head and neck region, of which 117 cases (64%) were found to have nodal metastasis and 20 cases presented with bilateral neck nodes.

Table 17: Lymph node metastasis and differentiation of the primary tumor (n=21)

Differentiation	n (%)
Well-differentiated	5 (23.80)
Moderately differentiated	7 (33.33)
Poorly differentiated	9 (42.85)

Table 18: The cross-check between clinical and pathological accuracies

Clinical Nodal staging	Pathological N stage				Total (%)
	0 (%)	1 (%)	2a (%)	2b (%)	
0	9 (75)	3 (60)	3 (21.4)	1 (50)	16 (48.5)
1	1 (8.3)	0	3 (21.4)	0	4 (12.1)
2a	1 (8.3)	0	7 (50)	0	8 (24.2)
2b	1 (8.3)	2 (40)	1 (7.1)	1 (50)	5 (15.2)
Total	12 (100)	5 (100)	14 (100)	2 (100)	33 (100)

Table 19: The result of cross-check between the clinical and pathological staging.

Pathological N stage	Clinical N stage		
	Under estimation (%)	Same (%)	Over estimation (%)
N0		75	25
N1	60	0	40
N2a	42.8	50	7.1
N2b	50	50	-

Table 20: Cross tab (CT vs. Pathological)

CT Nodal stage	Pathological N stage				Total (%)
	0 (%)	1 (%)	2a (%)	2b (%)	
0	5 (41.7)	3 (60)	0	0	8 (24.2)
1	5 (41.7)	0	0	1 (50)	6 (18.2)
2a	1 (8.3)	0	7 (50)	0	8 (24.2)
2b	1 (8.3)	2 (40)	6 (42.9)	1 (50)	10 (30.3)
3	0	0	1 (7.1)	0	1 (3)
Total	12 (100)	5 (100)	14 (100)	2 (100)	33 (100)

CT: Computed tomography

Site Distribution of the Cases

Laryngeal carcinoma is the most common head and neck cancer worldwide, contributing to 25% of all head and neck malignancies.^[1] A recent epidemiological study conducted in India found that most common head and neck malignancy in India is oropharynx (28.6%), followed by carcinoma esophagus (19.4%), oral cavity (16.3%), hypopharynx (14.1%), and larynx (11.8%).^[12] In the present study, conducted in our department maximum number of cases were carcinoma hypopharynx (26%), followed by carcinoma larynx (24.3%), oral cavity (20.4%), and oropharynx (17.1%), which indicates a high incidence of carcinoma hypopharynx and larynx in our study population. The less number of carcinoma esophagus may be attributed

Table 21: The results of cross-check between CT scan and pathological nodal staging

Pathological N stage	CT N stage		
	Under estimation (%)	Same (%)	Over estimation (%)
N0		41.7	58.3
N1	60	0	40
N2a		50	50
N2b	50	50	

CT: Computed tomography

Table 22: Comparison between clinical result and contrast enhanced CT scan results

Clinical	Histopathology		Total
	Yes	No	
Yes			
Number	14	3	17
% within clinical	82.4	17.6	100
% within HPR	66.7	25	51.5
No			
Number	7	9	16
% within clinical	43.8	56.3	100
% within HPR	33.3	75	48.5
Total			
Number	21	12	33
% within clinical	63.6	36.4	100
% within HPR	100	100	100

CT: Computed tomography, HPR: Histopathological report

Table 23: Comparison between histopathological result and CT examination

CT	Histopathology		Total
	Yes	No	
Yes			
Number	18	7	25
% within CT	72	28	100
% within HPR	85.7	58.3	75.8
No			
Number	3	5	8
% within CT	37.5	62.5	100
% within HPR	14.3	41.7	24.2
Total			
Number	21	12	33
% within CT	63.6	36.4	100
% within HPR	100	100	100

CT: Computed tomography, HPR: Histopathological report

to the fact that many of the patients may be attending other departments who were not included in our study.

Age

There is a progressive increase in the incidence of cancer with age, especially after 50 years. Although most patients are between 50 and 70 years of age, younger patients can develop head and neck cancer, especially in smokers and human papillomavirus associated cancers.^[13] The present study also reflects the same pattern with maximum cases

in the seventh decade (37%) followed by sixth decade (27%). The results are comparable with the study by Mehrotra *et al.*^[14] in India. They found that prevalence of head and neck cancer was highest in patients belonging to 50–69 years age group.

Sex

As evident from the table, the incidence of head and neck cancer in this study is more common in males with male:female ratio of 6:1. Literature reviews showed that M:F ratio of head and neck cancer being 3:1;^[15] a study by Ridge *et al.*^[15] also showed a M:F ratio of 3:1. Study by Mehrotra *et al.*^[14] showed that M:F ratio in Indian population was 3.8:1. The low prevalence of addictions in females in our area may be the cause for the low incidence of head and neck carcinoma in our study population.

Nodal Metastasis

In our study, 117 cases (64%) were found to have neck nodes at the time of presentation, and 20 cases had bilateral neck diseases (11%). Percentage of nodal metastasis at presentation was more in our study population compared to the study by Ridge *et al.*,^[15] which showed nodal metastasis in 43% of the cases. Another study by Hussey *et al.*^[16] also showed the risk of clinically positive cervical lymph node metastasis ranging from 2% to 45% at the time of presentation with a chance of bilateral nodes in 5–15%. In our study population, maximum cases with nodal metastasis were from carcinoma hypopharynx (29%), followed by oropharynx (21%) which indicates a high incidence of hypopharyngeal malignancy in our area and increased the chance of lymph node metastasis from carcinoma hypopharynx. Bilateral nodal metastasis was most commonly from carcinoma of the base of tongue (35%), followed by pyriform fossa malignancy (30%) and carcinoma supraglottis (aryepiglottic fold) (15%). Literature reviews also showed that the common primary sites with bilateral neck disease are tongue base, supraglottic larynx, and hypopharynx.^[1]

Oral Cavity

The oral cavity has a wide area of drainage. The most common subsites of oral cavity involved by tumor are tongue (35%) and floor of mouth (30%). Incidence of lymph node metastasis in tongue malignancy is 50%.^[17] In the present study, total cases of oral cavity malignancy were 37, out of which 24 cases (65%) showed nodal metastasis. Tongue was found to be the most common subsite with secondary nodes (46%). The occurrence of nodal metastasis in tongue malignancy was found to be 78.6%. Literature reviews showed that the metastatic rates from oral cavity cancers to various levels of lymph nodes are Level I (58%) followed by Level II (51%).^[1] Study by Shah^[4] showed that Level I, II, and III lymph nodes were

at high risk for metastasis from oral cavity malignancy. The present study also showed the similar pattern, and the lymph nodes most commonly involved were Level I (46%) followed by Level II (25%). There were no cases with involvement of Level IV or Level V nodes, which justifies the role of supraomohyoid neck dissection in case of oral cavity malignancy.

Oropharynx

A recent study has shown that carcinoma oropharynx is the most common head and neck malignancy in India^[12] and it comes in the second position among our node positive cases. Lin *et al.*^[18] have shown that 45–78% of patients with oropharyngeal primary may present with secondary nodes. Lymph node metastasis mostly involves Level II, III, and IV. Almost 20% patients with base of tongue malignancy will have bilateral nodal metastasis. Vartanian *et al.*^[19] showed that 73% of patients with oropharyngeal malignancy had lymph node metastasis. Most common Level of lymph node affected was Level II. The present study also showed the same pattern. 80% had nodal metastasis. Base of the tongue was found to be the most common subsite (40%), and Level II lymph nodes were found to be involved most commonly (92%) followed by Level III. The occurrence of bilateral nodal metastasis in the base of tongue malignancy was found to be 70%, which is very high compared to the available literature reviews.

Hypopharynx

We had a total of 47 cases of carcinoma hypopharynx, out of which 72% showed nodal metastasis indicating high incidence of nodal involvement. Most common subsite with nodal metastasis was pyriform fossa (76%). 22% of the carcinoma pyriform fossa showed bilateral nodal metastasis, indicating the need for addressing both sides of the neck while considering treatment. Lin *et al.*^[18] showed that 25% of the patients with hypopharyngeal cancer present with symptoms of neck mass and 70% will have palpable adenopathy on initial presentation. The present study is comparable with the above study by Lin *et al.*^[18] Another literature review showed that 70–80% of patients with pyriform fossa cancer will have lymph node metastasis at the time of diagnosis and <10% of the cases are associated with bilateral nodes.^[20] In our study, the most common level of lymph node involved was Level II (58%), followed by Level III. 2 cases showed the involvement of Level II + V, which indicates that Level V nodes should be cleared in the clinically N+ neck.

Larynx

Larynx includes supraglottis, glottis, and subglottis. No cases of carcinoma subglottic carcinoma were reported in our study. We had a total of 44 cases of carcinoma larynx, of which 20 (45%) showed nodal metastasis. Of these,

75% cases were contributed by supraglottis, aryepiglottic fold was found to be the most common subsite with lymph node metastasis. Occurrence of lymph node metastasis in carcinoma glottis was found to be low (21.7%) indicating the sparse lymphatic drainage of vocal cords. Waldfahrer *et al.*^[21] found the incidence of a clinically positive node in glottic carcinoma was 8.6%. Dikshit *et al.*^[12] reported that Level II, III, and IV were at highest risk for metastasis in carcinoma larynx and hypopharynx. The present study also agrees with this observation, with maximum incidence of metastasis in Level II (60%), followed by Level III (20%). No cases were presented with Level I or Level V nodes, suggesting that an anterolateral neck dissection clearing Level II, III, IV, and VI may be adequate for carcinoma larynx. In our study, the incidence of bilateral nodal metastasis in supraglottic carcinoma was found to be 19% indicating that both sides of the neck may have to be addressed especially in late-stage tumors.

Nasopharynx

Number of cases of carcinoma nasopharynx in the present study was 11, of which 72% showed nodal metastasis which was slightly lower than the meta-analysis by Ho *et al.*^[22] which showed an incidence of 85% and the most common lymph node involved was Level II. The present study also showed that most common lymph node involved in nasopharyngeal carcinoma was Level II (50%) followed by Level II + V.

Nose and PNS

We had a total of 11 cases of carcinoma nose and PNS. 54% showed metastasis to cervical lymph nodes. Most common level of lymph node affected was Level I (50%), followed by Level II (34%). All were from carcinoma maxilla. Literature reviews showed that the incidence of lymph node metastasis in PNS malignancy is 10%.^[22] The wide disparity of neck node involvement in our series may be due to the less number of cases and the advanced stage of the available cases (4 out of 6 cases were stage T4b).

Occult Metastasis

A total of 33 cases underwent neck dissection and were evaluated for the presence of occult metastasis in the lymph nodes and the comparison between clinical examination of the lymph node and lymph node assessment with contrast enhanced CT. In the present study, out of the 16 clinically N₀ cases, 7 cases (43.8%) proved to be pathologically positive. Moreover, out of the 8 CT N₀ cases 3 cases (37.5%) proved to have metastasis by pathological examination, which indicates that there is fairly high chance of occult metastasis to lymph nodes in head and neck malignancies, justifying the role of selective neck dissection in cases with high chance of node metastasis, even if the CT assessment is N₀. The results are comparable with the study

by O'Brien *et al.* (2000)^[27] who found that the incidence of occult metastasis in selective neck dissections was 30%. Waseem Jerjes *et al.*^[23] noted that the incidence of occult lymph node metastasis in early oral cavity carcinoma was 27-40%. Alvi and Johnson^[24] found that neck dissection in N₀ neck showed 34% occult metastasis and extracapsular spread in 49%. In our study, the maximum lymph node metastasis occurred from poorly differentiated tumors (42.9%). Lymph node metastasis always followed the expected pattern. There were no cases of skip metastasis. Another observation in our study was that in the clinical examination, there is more chance of underestimation of the nodal status and in CT assessment, there is more chance of overestimation of the nodal status.

Sensitivity and Specificity of Clinical Examination and Contrast Enhanced CT

In our study, the sensitivity of clinical examination was found to be low 66.7% and specificity was found to be high 75%. The positive predictive value and the negative predictive value were 82.4% and 56.3%, respectively. CT examination was found to have high sensitivity (85.7%) but low specificity (41.7%). The positive predictive value and negative predictive value were 72% and 62.5%, respectively. The results are comparable with the observation of Haberal *et al.* (2004)^[25] who observed that clinical examination has a sensitivity and specificity of 64% and 85%, respectively, and that for CT examination was 81% and 96% specificity for CT examination in our series was too low compared to this study. Another study by Rottey *et al.*^[26] found that sensitivity and specificity were 48.7% and 95.5% for palpation and 52.5% and 83.6% for CT examination, respectively. To conclude, even though the node detection is more with CT, it has a low specificity, and there is more chance of false positives. Hence, the clinical examination can be considered to be a better cost effective test for the basic evaluation of lymph node metastasis.

CONCLUSIONS

Higher incidence of head and neck squamous cell carcinoma was observed among the 61–70 years group. Males were more commonly affected. The most common head and neck malignancy with nodal metastasis was observed to be the hypopharyngeal malignancy, followed by carcinoma oropharynx. The occurrence of nodal metastasis was more common in carcinoma oropharynx. Bilateral nodal metastasis was observed to be high from carcinoma of base of tongue, followed by pyriform fossa malignancy and carcinoma supraglottis. Level I lymph node was observed to be the most common lymph node involved in oral cavity and PNS malignancy. All other head and neck malignancy showed maximum occurrence of metastasis

to Level II lymph nodes. Occult metastasis in CT N₀ neck was found to be 37.5%. Poorly differentiated carcinomas were observed to be associated with an increased risk of nodal metastasis. The sensitivity and specificity of clinical examination was found to be 66.7% and 75%, respectively. The sensitivity and specificity of contrast enhanced CT was found to be 85.7% and 41.7%, respectively. Clinical examination can be considered as a better cost-effective test for the diagnosis of metastatic lymph nodes, but it should be always supported by appropriate radiological imaging and pathological evaluation.

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A Comparative Evaluation of Effects of Micro-osteoperforations on Canine Retraction Using Finite Element Analysis: An *In Vitro* Study

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Abstract

Objective: The aim of this study is to evaluate the effects of modified corticotomy procedures on canine retraction and compare it with the conventional method using finite element analysis.

Materials and Methods: Three-dimensional finite element method was used to simulate canine retraction after modified corticotomy procedures in sliding mechanics after first premolar extraction. Retractive force of 200 g was applied, and the amount of canine retraction was measured in both micro-osteoperforation and vertical groove model and compared with the conventional model.

Result: Vertical groove model shows the maximum amount of canine retraction followed by micro-osteoperforation model and least with the conventional model.

Conclusion: Modified corticotomy procedures have been proven to be an efficient way of accelerating orthodontic tooth movement as it reduces cortical bone resistance.

Key words: Conventional model, Micro-osteoperforations model, Vertical groove model

INTRODUCTION

Lifestyle of today's era demands a time-valued perception of everything which is also applicable in orthodontics. Patient compliance is the driving force to accomplish the treatment at its finest. Patient's demands for shorter orthodontic treatment duration are on the rise. Orthodontists have been under constant pressure to explore various methods of accelerating tooth movement. One of the most common tooth movements in orthodontic treatment is a canine retraction. At present, conventional fixed orthodontic

treatment requires about 1–2 years.^[1] More time is required for extraction cases, such as for adult patients, which is a great concern and poses a high risk of caries,^[2] external root resorption.^[3,4] Thus, accelerating orthodontic tooth movement and the resulting shortening of the treatment duration would be beneficial. Many researchers have utilized different biochemical methods involving medications to improve the speed and quality of orthodontic treatment, but the systemic influence on the body's metabolism makes this difficult to apply in orthodontics. Recently, investigators have begun studying local techniques for stimulating better orthodontic tooth movement. Surgically aided rapid tooth movement has become one of the novel techniques for accelerating canine retraction. Systemic review by Long *et al.*, concluded that among various methods used for accelerating orthodontic tooth movements, corticotomy surgical method was safe, efficient and time reducing procedure. The original corticotomy technique described by Kole included a combined interradicular corticotomy and supra-apical

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osteotomy. Biologic tooth movement^[5] can be achieved with conventional orthodontic treatment techniques, but the canine retraction phase usually lasts for 6–8 months.

Until now, these research modalities and techniques for accelerating canine retraction have been applied in animal experiments and clinical case reports. Finite element analysis has become a powerful tool for dental biomechanical research due to its increased availability, capacity and ease of use of computer software in biologic modeling. It can be considerably effective and most importantly, non-invasive way and helps us for simulating complicated procedures which ultimately gives right path in treatment planning.^[6]

Among the various ways of accelerating canine retraction, corticotomy procedures recently gaining popularity.^[7] Conventional corticotomy contained the raising of the flap after which vertical grooves or a number of perforations were made on the buccal as well as the palatal aspects followed by bone grafting. This current study gives more emphasis on a modified version of corticotomy for accelerating the canine movements with a reduction in micro-osteoperforations to only three in number in one finite element method (FEM) model and vertical groove on second FEM model which is then compared with conventional FEM model.

Aims and Objectives

Aim

The aim of the study was to evaluate the effects of modified corticotomy on canine retraction and compare it with the conventional method using finite element analysis.

Objective

1. To measure the amount of canine retraction following micro-osteoperforations (3 circular perforations) and compare it with the conventional method using finite element analysis.
2. To measure the amount of canine retraction following micro-osteoperforations (vertical groove) and compare it with the conventional method by finite element analysis.

MATERIALS AND METHODS

Three-dimensional (3D) finite element model was constructed, including maxillary teeth, periodontal ligament (PDL), alveolar bone, brackets, wire, and bands in which first premolars were extracted.

Although PDL thicknesses differ according to age, position, and individual variations, the thickness of the PDL was considered to be consistently 0.25 mm. The 3D finite element models of the alveolar bone were fabricated to fit the teeth and the PDL, and the thickness of cortical bone was considered to be 2 mm.^[6-9]

In this study, the orthodontic force was applied to three FEM models (ANSYS R14.5) which simulated the canine retraction. The forces were applied to the surfaces of the teeth, mesiodistally, as in normal clinical practice. In this study, we defined conventional canine retraction model as model 1. The numbers of nodes and elements of the initial model are shown in Table 1. Construction of second and third model was same as like model 1 to compare the amount of canine retraction. On model 2, three micro-osteoperforations were made distal to canine in extraction space at the level of canine root apex, 2 mm apical to the marginal alveolar bone and in between these two perforations.^[10] In model 3, the vertical groove was made along the long axis of canine root in the extraction space [Figures 1-4]. After removing the barrier of cortical bone which was around 2 mm deep and 1.5 mm, wide immediate orthodontic force was applied.^[8] Optimal force for canine retraction is 200 g which has proven sufficient amount of force to maximize the rate of canine retraction without any ill effects on tooth itself and surrounding structures too.^[11] After application of force amount of canine retraction was measured on all three models. Results are shown in Table 2.

RESULTS

Immediately after loading of the retraction forces of 200 g between the crown of the first molar and the canine, the initial displacement of the canine was highly concentrated in the distal area of the crown in all three models.

The results of this study, which showed stress distribution along the root, PDL, and alveolar bone, provided insight into clinical observations.^[6] Compared with the conventional method of canine retraction, we found that model 3 (vertical

Table 1: Number of nodes and elements generated for initial model

Models	Number of nodes	Number of elements
Cancellous bone	69.897	41.814
Cortical bone	118.762	68.648
Canine	7.293	4.181
Second premolar	3.933	2.241
First molar	5.961	3.497
PDL of canine	17.383	8.584
PDL of second premolar	11.482	5.645
PDL of first molar	18.873	9.306

PDL: Periodontal ligament

Table 2: Deformation in the canine with various arrangements during retraction

Method	Deformation (mm)
Conventional method	0.303
With Micro-osteoperforations	0.382
With groove	0.443

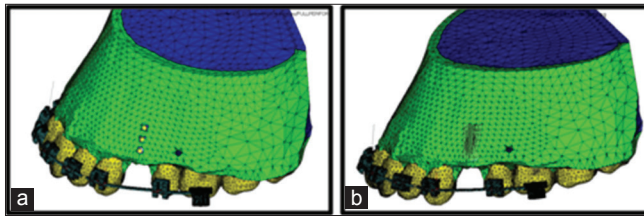


Figure 1: (a) Model 2 showing micro-osteoperforations, (b) Model 3 showing vertical groove

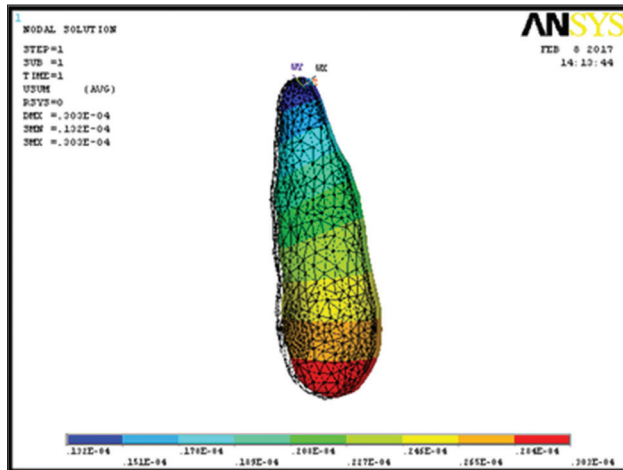


Figure 2: Deformation plot for intact teeth of conventional model (model 1)

groove) showing the maximum amount of canine retraction followed by model 2 (3 micro-osteoperforations).

DISCUSSION

Orthodontic tooth movement is a biological process characterized by sequential reactions of periodontal tissue against a biomechanical force system. It is also a process in which the application of a mechanical force induces alveolar bone resorption on the pressure side and alveolar bone deposition on the tension side.^[12] The orthodontic force system is a complicated three-dimensional system which is difficult to evaluate in clinical conditions, and orthodontic force plays an important role in the entire biomechanical process during tooth movement. In our study, it was found that the effects of force application would be changed when the force-loading environment was changed. For accelerating canine retraction speed, periodontal tissue, especially hard tissue such as alveolar bone around the canine, is the most important source of resistance.^[6]

In this study, the orthodontic force was applied to three FEM models which simulated two different surgical interventions and one conventional treatment for canine retraction. Stress distribution and deformation on the root, PDL, and cortical bone were evaluated.^[6]

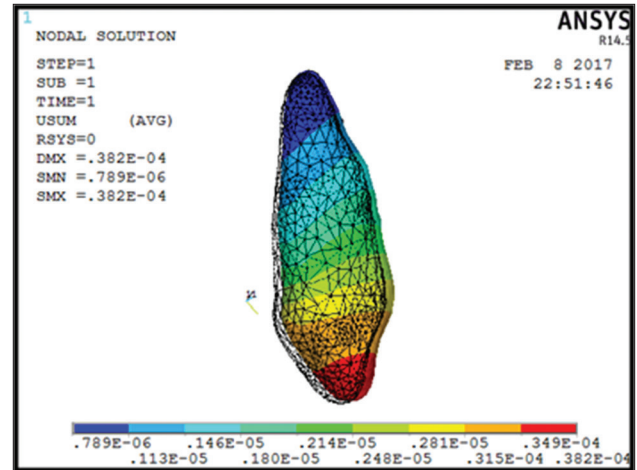


Figure 3: Deformation plot of micro-osteoperforations, model 2 (maximum deformation: 0.0000382 mm)

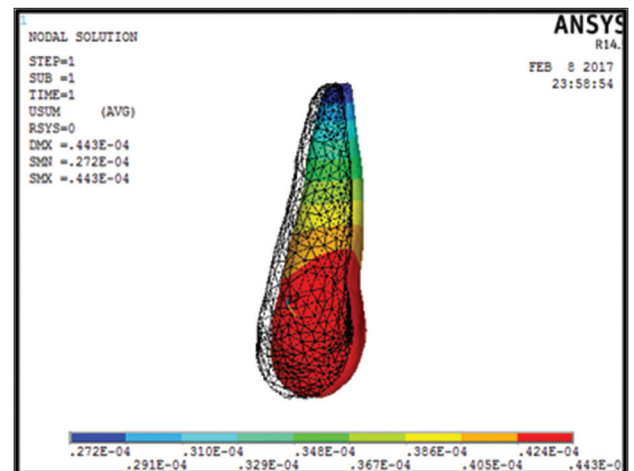


Figure 4: Maximum deformation with grooved configuration: (0.0000443 mm), model 3

On the basis of previous studies, resistance to tooth movement is increased when the roots are torqued lingual or buccal. This principle was used by Rickets^[13] and is called cortical anchorage. In general, cortical bone offers more resistance to resorption. The cortical bone could also block tooth movement in most cases in orthodontic treatment. In this study, we observed the distribution of stress on the buccal side of cortical bone around the canine root, which implied that the cortical bone on the buccal side of the canine was also the source of resistance to canine movement. That explained the principle of surgical procedures of corticotomy which is intentional cutting of cortical bone leaving intact medullary vessels results in osteopenia which is temporary but reversal loss in bone density. Taking advantage of osteopenia tooth movement is accelerated. However, based on our results, modified corticotomy with vertical groove shows faster canine retraction. This procedure would minimize surgical injury and reduce complications for patients. Furthermore, canine retraction with only 3 micro-osteoperforations shows faster

tooth movement when compared to conventional method of canine retraction which is also suggestive of reduced resistance of cortical bone.

Anchorage control should be considered when accelerated tooth movement is necessary. An obvious strategy for anchorage control would be to concentrate the force needed to produce tooth movement where it was desired and then to dissipate the retraction force in the PDL of anchor teeth as much as possible. In this study, the value of maximum equivalent (von Mises) stress in the PDL of the first molar in two models was a surgical reduction of resistance to a level lower than in the canine. Further, the value of total deformation of the first molar in models 2 and 3 was far below that of the canine at the initial stage of force loading.

This indicated that reducing resistance by modified corticotomy procedures to accelerate canine retraction was a safe way to protect anchorage and would not reduce anchorage during canine retraction which may ultimately shorten orthodontic treatment duration.

This study and others have demonstrated that FEM provides a solid, workable foundation for modeling a system of orthodontic tooth movement¹. The chief advantage of FEM is that it can be magnified nearly infinitely, in terms of both the actual volumetric construction itself and the mathematical variability of its material parameters. However, as with any theoretical model of a biological system, there are limitations. The mechanical behavior of the materials was assumed to be linear elastic (homogeneous and isotropic), and the value of each material was inferred from previous reports. Cortical bone thickness and cancellous bone quality were not incorporated into the analysis, to prevent bone stress from being dominated by the bone quality and potentially confounding the outcomes related to other relevant factors. In addition, the stress analysis of soft tissues was not considered in this study. The soft tissues, such as gingival and facial muscles, are also sources of resistance for blocking rapid tooth movement. Regardless of these limitations, we integrated a finite element approach with variable analysis to investigate the comparative influences of resistance source, the pathway of canine movement, and different types of surgeries for rapid canine retraction by reducing resistance.^[14-16]

CONCLUSION

This study was aimed toward evaluating the effects of modified corticotomy procedures on canine retraction

and compare it with the conventional method of canine retraction with FEM study.

In this study, compared with dentoalveolar distraction osteogenesis, periodontal distraction aided by the surgical undermining of the interseptal bone would reduce the resistance in the pathway of canine movement more effectively to accelerate canine retraction speed in rapid canine movement during orthodontic treatment. The results indicated that rapid canine retraction aided by the surgical reduction of resistance might create side effect: (1) It might lead to canine rotation during distalization.

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Chronic Obstructive Pulmonary Disease and Cardiac Comorbidities

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is a global health issue with cigarette smoking being an important risk factor. COPD, defined by global initiative for chronic obstructive lung disease (GOLD) as a preventable and treatable disease with some significant extrapulmonary effects, is a very common clinical entity in clinical practice. COPD is associated with significant extrapulmonary (systemic) effects among which cardiac manifestations are most common. COPD affects pulmonary blood vessels, right ventricle, as well as left ventricle leading to the development of pulmonary hypertension (PH), cor pulmonale (COR-P), right and left ventricular dysfunction. Echocardiography provides a rapid, non-invasive, portable, and accurate method to evaluate cardiac functions, and early diagnoses and intervention for cardiac comorbidities would reduce mortalities. Hence, the present study was undertaken with the following aims and objectives: (1) To assess the cardiac changes secondary to COPD by echocardiography and (2) to find the correlation between echocardiography findings and the severity of COPD using GOLD guidelines.

Materials and Methods: A prospective study was conducted at the Department of Pulmonary Medicine, SVS Medical College, Mahabubnagar. A total of 45 patients of COPD according to GOLD guidelines were taken into the study; all patients underwent investigations such as chest X-ray posteroanterior view, electrocardiography, and spirometry followed by 2D echo.

Results: We investigated 42 male and 3 female patients ranging from 50 to 75 years of age, of these cases, 2 among Category D had left ventricular diastolic dysfunction changes, 3 from Category C and 10 from Category D were diagnosed with PH, and 4 from Category D had changes of COR-P.

Conclusion: Our study puts emphasis on early cardiac screening of all COPD patients which will be helpful in the assessment of the prognosis and will further assist in identifying the individual likely to suffer increased morbidity and mortality.

Key words: 2D echo, Chronic obstructive pulmonary disease, Cor pulmonale

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a global health issue with smoking being the most important risk factor. By 2020, it will be the third most leading cause of mortality and fifth leading cause of morbidity in the world.^[1,2] There is a crude estimate of about 30 million people in India suffering from COPD, and the death rate

is among the highest in the world, and data suggest that about 556,000, i.e., >20% of total 2,748,000 die in India annually.^[3]

Cardiovascular disease (CVD) is a major comorbidity in COPD. General population studies and studies in patients with COPD indicate that COPD is an important risk factor for ischemic heart disease and sudden cardiac death. There is evidence of an association between COPD and CVD, and although COPD and CVD clearly share common risk factors such as smoking, COPD has been described as an independent risk factor for the development of CVD.

COPD affects pulmonary blood vessels, right ventricle, as well as left ventricle leading to the development of pulmonary hypertension (PH), cor pulmonale (COR-P),

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right ventricular dysfunction, and left ventricular dysfunction. Ischemic heart disease is one of the main causes of mortality in COPD.^[4] The observed association between COPD and CVD may be explained due to the coexistence of shared risk factors such as smoking, age, sex, and inactivity. Coexistence of both diseases is very common and has diagnostic, therapeutic, and prognostic implications.^[5,6] Chronic bronchitis alone increases the risk of coronary deaths by 50%. Reduced ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity is also an independent risk factor for coronary events, increasing the risk by 30%. With every 10% decrease in FEV1, all-cause mortality increases by 14% and an increase in cardiovascular mortality by 28%.^[7] In more advanced COPD, CVDs account for 20–25% of all deaths.^[8]

Left ventricular diastolic dysfunction (LVDD) is defined as the inability of the ventricle to fill to a normal end-diastolic volume, both during exercise as well as at rest, while left atrial pressure does not exceed 12 mmHg.^[9-11] LVDD is a common phenomenon in COPD.^[12-14] Abnormal left ventricular function is seen in COPD due to many factors such as hypoxia, acidosis, ventricular interdependence, lung hyperinflation, and distension.

Left ventricular systolic dysfunction is a disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and end-diastolic volume.

PH is an increase of blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries, together known as the lung vasculature.

PH is defined as systolic pulmonary artery pressure (sPAP) >30 mmHg, and it is classified into mild, moderate, and severe grades as sPAP 30–50 mmHg, sPAP 50–70 mmHg, and sPAP >70 mmHg, respectively.^[15]

COR-P is defined as an alteration in the structure and function of the right ventricle caused by a primary disorder of the respiratory system. PH is the common link between lung dysfunction and the heart in COR-P. COR-P can develop due to various cardiopulmonary diseases. COR-P usually has a slow and chronic progression, but acute onset and life-threatening complications can occur.^[16]

Echocardiography provides a rapid, non-invasive portable, and almost accurate method to evaluate the right ventricle function, right ventricular filling pressure, tricuspid regurgitation, left ventricular function, and valvular functions.^[17] It has been studied that echocardiography measured pulmonary arterial pressure closely correlates with pressure measured by right heart catheterization.^[18,19]

This study was undertaken to evaluate cardiac function with echocardiography in COPD patients which may further help to assess the prognosis and assist in identifying the individuals likely to suffer increased morbidity and mortality.

MATERIALS AND METHODS

A prospective study was done at Tertiary Care Hospital, Mahabubnagar, Telangana. 45 patients were diagnosed COPD according to Global Initiative for Chronic Obstructive Lung Disease guideline. The subject included between the age of 50 and 75 years with informed and written consent.

The patients with pneumonia, tuberculosis, bronchial asthma, interstitial lung disease, carcinoma lungs, and other lung pathologies were excluded from the study.

The other category of patients who were excluded had a history of cardiac diseases such as ischemic heart disease, rheumatic heart disease, valvular heart diseases, congenital heart disease, and others.

All the patients were asked for the detailed history of respiratory as well as cardiovascular symptoms and were clinically examined for the signs of biventricular hypertrophy, cardiomegaly, PH, and heart failure.

Patients were investigated for routine investigations such as complete blood profile, renal function test, random blood sugar, electrocardiography, sputum for Gram stain, chest X-ray, and 2D echo.

Statistical Analysis

The statistical analysis of data has been done. The age and sex distribution of all patients, their body mass index (BMI), severity of COPD, echocardiography findings, the frequency of COR-P, and its relation to COPD have been represented graphically.

Correlation between the cardiac parameters on echocardiography findings and pulmonary parameters on spirometry findings has been done to find the relation and to estimate the risk of morbidity.

The mean and standard deviation (SD) of FEV1 and PH of all the patients has been calculated along with Pearson correlation value.

RESULTS

We investigated 42 male and 3 female patients in the age group of 50–75 years. Mean BMI was 19.59 kg/m². Of

45 patients, 24 (48%) patients were underweight. The mean pack years for smoking were 31.33. Mean \pm SD calculated for FEV1 was 49.05 ± 14.61 .

The most common finding on echocardiography was PH 13/45 (28.8%), next to which was LVDD 2/45 (4.5%). The study showed 28/45 (62%) of normal cases.

Of 13 patients of PH, there were 6 (46.15%), 3 (23.07%), and 4 (30.76%) patients of mild, moderate, and severe, respectively. Mean \pm SD calculated for PH ($n = 45$) was 35.59 ± 15.47 .

Of 2 patients with LVDD, 0 (0%) were of Grade 1, 1 (50.0%) of Grade 2, and 1 (50.0%) of Grade 3.

The severity of PH, COR-P, and LVDD was increasing with increasing severity of COPD [Figure 1].

DISCUSSION

There are various cardiac changes seen in the patients suffering from COPD. Right-sided cardiac dysfunction and PH are one of the main established complications described in many studies done worldwide. Cigarette smoking and other exposure factors lead to inflammatory changes which disrupt the vascular pulmonary endothelium, and on the other hand, changes of chronic bronchitis and emphysema lead to chronic hypoxic conditions which result into pulmonary artery remodeling and vasoconstriction. The other mechanism leading to the damage is the change in intrinsic pulmonary vasodilator substances such as prostacyclin synthase, decrease in endothelial nitric oxide synthase, and increase in endothelial 1. As a result, we see remodeling, changes in respiratory mechanics, and also, increase in blood viscosity. All these factors lead to PH. PH increases the afterload of the right ventricle and increase of the right ventricular work as well. If we summarize the whole mechanism of COPD, hypoxic vasoconstriction, and PH will result in right ventricular hypertrophy and even its dilatation giving a clinical presentation of the right heart failure [Table 1].

There are no exact data of PH prevalence in COPD; pulmonary artery pressures were seen elevated in about 20–90% of patients when measured by right heart catheterization, with evidence of changing severity in pulmonary hemodynamics with the severity in airflow obstruction. Two studies have shown an abnormal increase in MPAP (PPA) in COPD of 0.4–0.6 mmHg per year. These studies illustrate that PH in COPD progresses slowly and occur in mild as well as severe forms of disease.^[21,22]

Several studies have demonstrated the prognostic value of PH in COPD patients. Severe the PH, more poor is the prognosis, even in patients of COPD receiving long-term oxygen therapy. In one of the studies, showing the 5-year survival rate was 50% in patients with mild PH (20–30 mmHg), 30% in those with moderate and severe PH (30–50 mmHg), and 0% in small group of patients suffering from severe PH (>50 mmHg).

Comparison between Severity of COPD and Cardiac Changes

In our study, there is a direct linear correlation seen between PH and severity of COPD (FEV1).

COR-P was present in 8.8% of patients in our study. Approximately, about 25% of patients of COPD develop COR-P. One of the autopsy studies showed that 40% of patients of COPD had COR-P. In comparison, the results are matching to our study. The cause of LVDD in COPD patients could be due to chronic hypoxemia leading to the changes in myocardial relaxation, distension, and lung hyperinflation making the parietal pleura stiff and similarly the walls of cardiac fossa adding the load to the walls of the ventricle and also due to ventricular interdependence. In our study, LVDD was present in ~5% of patients as compared to 47.5% seen in the study done by Gupta *et al.*^[20]

Table 1: Whole mechanism

Findings	Category				Total	P
	A	B	C	D		
Normal	10	11	2	3	26	<0.0001
PAH	0	0	3	10	13	
COR-P	0	0	0	4	4	
LVDD	0	0	0	2	2	
LVSD	0	0	0	0	0	
LVH	0	0	0	0	0	
Total	10	11	5	19	45	

COR-P: Cor pulmonale, LVDD: Left ventricular diastolic dysfunction, LVSD: Left ventricular systolic dysfunction, LVH: Left ventricular hypertrophy

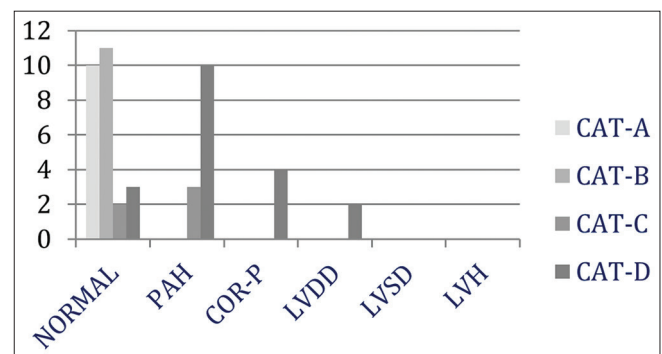


Figure 1: Simple bar diagram showing the presence of various cardiac morbidities in different categories. PH: Pulmonary hypertension, COR-P: Cor pulmonale, LVDD: Left ventricular diastolic dysfunction, LVSD: Left ventricular systolic dysfunction, LVH: Left ventricular hypertrophy

One of the limitations of our study was a small size, the other factors being not able to perform the right-sided heart catheterization or employ transesophageal echocardiography. Further, well-designed cohort studies and the use of future three-dimensional echocardiography with optimal sample size will be helpful in defining the role of echocardiography in COPD patients.

CONCLUSION

The study shows a high prevalence of cardiac comorbidities such as PH, COR-P, and LV dysfunction in COPD patients. The severity of complications increases with severity of COPD and makes a linear relation. This relation was also seen in Grade 2 and 3 LV dysfunctions and was not seen in Grade 1.

Hence, our study puts emphasis on cardiac screening of all COPD patients.

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Study of Efficacy of Intradermal Injection of Tranexamic Acid and 50% Glycolic Acid Peeling in Treatment of Melasma

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Abstract

Background: Melasma is one of the most common causes of facial hyperpigmentation which causes cosmetic disfigurement and leads to psychological problems. Although various treatments are available for melasma, it remains a difficult condition to treat.

Aim of the Work: The aim of the study was to evaluate and compare the efficacy of intradermal injection of tranexamic acid and glycolic acid peeling in the treatment of melasma.

Patients and Methods: A total of 112 patients with melasma were divided into two groups: Group A; 56 patients were treated with an intradermal injection of tranexamic acid and Group B 56 patients were treated with glycolic acid peeling 50%. Clinical assessment (according to the modified Melasma area and severity index) was performed for all patients.

Results: There was a statistically significant difference between the studied groups as regards the response to different therapeutic modalities with the best results in Group A than Group B. There was the statistically significant difference between A and B, Group A showed a better response than Group B.

Conclusion: This signifies that tranexamic acid is more effective than commonly used 50% glycolic acid peel. Furthermore, the recurrence of melasma was found to be less in tranexamic acid as compared to glycolic acid 50%.

Key words: Glycolic acid, Injection Tranexamic acid, Melasma, Tranexamic acid

INTRODUCTION

Melasma is a common disorder of hyperpigmentation of face among Asians which is difficult to treat, and the treatments are often ineffective due to its higher rate of recurrence.^[1] Among the newer modalities, tranexamic acid is being compared with 50% glycolic acid peel which is a commonly used method in the treatment of melasma. Tranexamic acid inhibits ultraviolet induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes which ultimately results in decreased free arachidonic acids and a diminished ability to produce prostaglandins, and this decreases

melanocyte tyrosinase activity.^[2] Glycolic acid peel effect is derived from its chemo exfoliating properties which depend on facilitating the removal of melanized keratinocytes leading to melanin pigment loss and acceleration of skin turnover.^[3]

Aims and Objectives

The aim of the study was to compare the efficacy of intradermal injection of tranexamic acid with 50% glycolic acid peel in the treatment of melasma.

Inclusion Criteria

All patients are presenting to the dermatology OPD with features of melasma.

All patients willing for follow-up and giving informed consent.

Exclusion Criteria

The patients with a history of hormonal therapy such as contraceptive pills (during the past 12 months). Bleeding disorders or concomitant use of anticoagulants such as warfarin.

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Topical treatment (1 month before the study) such as triple combination therapy.

Active herpes simplex, facial warts, or active dermatoses.

History of hypersensitivity to any of the components of the formula of the study. Pregnant or lactating females.

PATIENTS AND METHODS

Study Setting

This study was conducted at OPD of the Department of Dermatology, BRDMC, Gorakhpur, UP.

Study Design

The study design was a randomized control trial.

Study Population

The patients with melasma attending a tertiary centre OPD Table 1.

Intervention

- Group A: Intradermal injection of tranexamic acid + 30SPF sunscreen
- Group B: 50% glycolic acid peel + 30SPF sunscreen.

Expected Outcome

At least 10% difference in two regimen treatment efficacy response.

Sample Size

Sample size was calculated using G power Vesion 3.1.9.2 using effect size of 0.57, alpha error of 5%, power – 80%, and the calculated sample size was 100 (50 in each group).

Sampling Technique

Consecutive sampling for 3 months duration from January 2017 to March 2017.

Procedure

A total of 112 patients were included in the study and divided into two groups:

- Group A: Included 56 patients treated with an intradermal injection of 0.05 mL of tranexamic acid solution in normal saline (4 mg/mL) into the melasma lesion at 1 cm interval using sterile insulin syringe, weekly for 12 weeks Figure 1.^[7]
- Group B: Included 56 patients treated with 50% glycolic acid peeling within a period of 2 min starting at the forehead, continued to the cheeks, the chin and then the nose. The peel was terminated by the dilutional effect of washing with cold water. Done every 2 weeks for 12 weeks Figure 2.^[6]

Proper informed consent was taken, a detailed clinical record prepared, and baseline investigations were done.

All the patients were subjected to complete history taking and examination: With regard to onset of melasma, duration, family history, and aggravating factors.

Wood's lamp examination was done for all patients to determine the type of melasma.^[4]

Digital photographs were taken for all patients at baseline and after the end of the follow-up period.

Criteria of Evaluation

Patients were followed up monthly for 3 months after the last session to detect any recurrence or complications from April 2017 to June 2017.

Final results for clinical improvement were made using following parameters:

1. Modified melasma area severity index score^[5]
2. Clinical efficacy of the treatment response
3. Clinical photographs.

RESULTS

The results are depicted in Figure 3 and Table 2

CONCLUSION

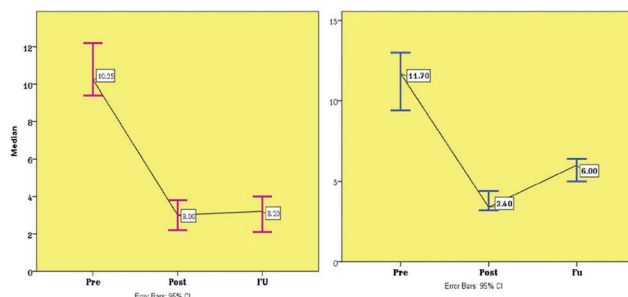
- Improvement in melasma in both the groups with treatment.
- Group A showed significant improvement as compared to Group B.

Table 1: General demographic profile of study subjects (n=112)

Age category		Pattern of melasma	
20–30 year	28 (25%)	Centro facial	50 (44.6%)
31–40 year	58 (51.7%)	Malar	58 (51.7%)
41–50 year	18 (16.0%)	Mandibular	4 (3.5%)
51–60 year	8 (7.1%)	Filtzpatric skin type	
		Type III	12 (10.7%)
		Type IV	52 (46.4%)
		Type V	48 (42.8%)
Sex			
Male	35 (31.2%)		
Female	77 (68.7%)		
Place of residence			
Rural	58 (51.7%)		
Urban	54 (48.2%)		
Type of melasma			
Mixed	104 (92.8%)		
Epidermal (no dermal and indeterminate type found)	8 (7.1%)		

Table 2: Modified MASI Score before and after treatment and after further 3 months of follow up

Modified MASI score	Group A - median (IQR)	Group B - median (IQR)	P value (Man Whitney U-test)
Pre-treatment	10.25 (8.1–14.15)	11.7 (8.8–14.35)	0.40
Post-treatment	3 (1.10–5.60)	3.4 (2.25–5.4)	<0.001
Follow-up	3.2 (1.35–5.05)	6 (4–7.75)	0.46



Efficacy of treatment = (mMASI before – mMASI after)/mMASI before



Figure 1: Group A: Intradermal injection of tranexamic acid (a-c) pre-procedure, (d-f) post-procedure

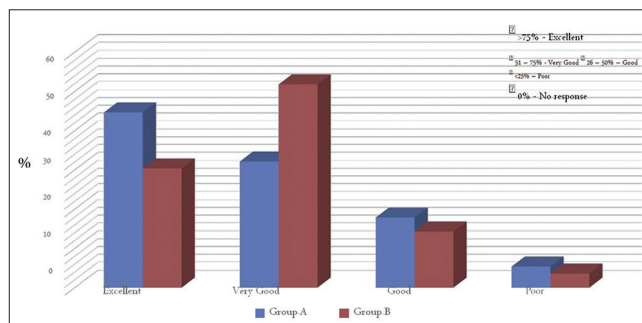


Figure 3: Efficacy of treatment response

- This signifies that tranexamic acid is more effective than commonly used 50% glycolic acid peel. Furthermore, the recurrence of melasma was found to be less in tranexamic acid as compared.

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Fetal Left Ventricle Modified Myocardial Performance Index: Defining Normal Values in the Third Trimester in Rural Central India

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Abstract

Introduction: Myocardial performance index (MPI) is an emerging non-invasive parameter for *in utero* monitoring of fetal well-being.

Purpose: The aim of this study was to determine normal values for fetal left ventricle (LV) modified MPI (Mod-MPI) in Indian population and to assess its relation to advancing gestation and fetal heart rate (FHR).

Materials and Methods: In this study, 60 normal pregnant women were included whose fetuses were having structurally normal hearts. Fetal echocardiography was done to measure the LV Mod-MPI. MPI was calculated after measuring various time intervals including isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT), and ejection time (ET), and the formula used for MPI calculation was $ICT + IRT/ET$. Further, linear regression analysis was done to find a correlation of MPI with the gestation age and FHR.

Results: The normal MPI in the third-trimester fetuses of the Indian population was 0.35 ± 0.03 . The mean ICT was 31.40 ± 2.95 ms, mean IRT was 32.38 ± 3.42 ms, and mean ET was 174.83 ± 6.41 ms. The mean heart rate was 142 ± 6 bpm. The LV Mod-MPI was not significantly associated with either FHR or advancing gestation.

Conclusion: Fetal global cardiac function can be assessed by MPI. FHR, ventricular size, and geometry or image quality do not have any effect on MPI. MPI has a significantly important role in the monitoring of complicated pregnancies.

Key words: Fetal cardiac function, Left ventricle, Myocardial performance index

INTRODUCTION

A significant advancement is noted in fetal cardiology field in the past few decades. Initially, fetal echocardiography was used by Allan *et al.* for the systematic examination of the heart by fetal ultrasound including four-chamber view, outflow tracts, and promoted routine screening for fetal cardiac abnormalities.^[1] Now, cardiac function, cardiac anatomy, and hemodynamic assessment can be done

by echocardiography. Ventricular fractional shortening or ejection fraction can assess the systolic function.^[2] Assessment of diastolic function can be done by pulsed Doppler of ventricular inflows, inferior vena cava, ductus venosus, or umbilical vein. However, these parameters are often a late marker of ventricular dysfunction.

Recently, the modified myocardial performance index (Mod-MPI) is now being used as a noninvasive pulsed wave Doppler-derived measure for the assessment of global myocardial function and important tool in the evaluating fetal cardiology.^[3] Fetal cardiac systolic function in the form of the aortic ejection time (ET) and diastolic function in the form of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT)^[3] can be simultaneously evaluated by Mod-MPI. The Mod-MPI is a potentially useful method of estimating fetal cardiac adaptive changes

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in complicated pregnancies such as intrauterine growth restriction,^[4] maternal diabetes,^[5-7] twin-twin transfusion syndrome (TTTS),^[8] congenital heart malformations,^[9] and preeclampsia.^[10] MPI does not require anatomical imaging; it is independent of heart rate, blood pressure, and ventricular shape as it only requires time intervals.^[11,12] MPI helps in identifying the high-risk population in various pregnancy-related complications and helps the stratifying the patients into high-risk and low-risk group and their subsequent management. Pulsed wave Doppler-derived MPI is widely used first in adults and then in the pediatric population^[13-15] for the quantitative measurement of the global cardiac function.^[16] Cardiac dysfunction in the subclinical phase can be diagnosed by MPI. However, it has limited use in cardiac assessment, and the main reason is lack of normal reference ranges and awareness regarding its role for detection of various fetal conditions. This study was done to determine the normal values for fetal left ventricular (LV) Mod-MPI in the third-trimester fetuses of the Indian population.

MATERIALS AND METHODS

Ethics Statement

All patients enrolled in this study were briefed about the nature, and the course of the study and informed consent in the regional language was taken from them.

Approval from the institutional ethics committee was sought before beginning the study.

Study Design

This was hospital-based, prospective, and diagnostic study.

Study Setting and Period

This study was conducted in ultrasound section of the department of radiodiagnosis from December 2015 to October 2017.

Sample Size

A total of 60 pregnant women with normal pregnancies served as the study group.

Subjects

All pregnant women who were referred to ultrasound section of the department of radiodiagnosis for their routine ultrasound scan at 28–40 weeks of gestation, willing to participate in the study and were having singleton pregnancy were included in the study. The women who were not willing to participate in the study, having multiple gestations, congenital heart disease, preeclampsia, diabetes mellitus, and intrauterine growth restriction were excluded from the study. In case of more than one examination of a fetus, results of the last examination were included from the study.

Equipment Used

Ultrasound examination was performed with a transabdominal 2.5–5 MHz curvilinear transducer and volume transducer on the ultrasonography machines available in the department (VolusonS6 WIPRO GE healthcare ultrasonography machines and Philips Affinity 70 machine).

Study Methodology

After taking the consent, cases were enrolled in the study. All obstetrics ultrasounds were done strictly following the guidelines under the PCPNDT act and after filling of form F (form for maintenance of record in respect of pregnant women by genetic clinic/ultrasound clinic/imaging center) and consent form.

A predesigned, validated, and pre-tested pro forma was used as a study tool to collect information such as name, age, the area of residence, and maternal history for any risk factors for congenital heart disease. Then, after the obstetric ultrasound, fetal echocardiography was done, and MPI was measured.

Technique^[17,18]

The technique used to obtain the LV Mod-MPI was as described by Hernandez-Andrade *et al.* A four-chamber view of the heart with an apical projection of the heart was obtained. The transducer was slightly displaced in the cranial direction where the mitral and aortic valves were visible. Sample gate of about 3–4 mm was placed at a location to include both the lateral wall of ascending aorta and the internal leaflet of the mitral valve as shown in Figure 1. The gain was reduced so that noise and artifacts were reduced on US screen display. High wall motion filter was set to avoid recording slow blood movements. In Doppler settings, fast Doppler sweep velocity (15 cm/s) was used.

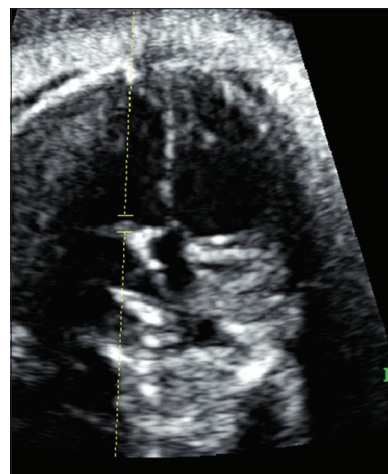


Figure 1: Positioning of the Doppler sample volume for acquisition of the myocardial performance index at the lateral wall of ascending aorta just below the aortic valve leaflet and above the mitral valve leaflet. Both atrioventricular and aortic valves should be visible in the section

The angle of insonation was kept $<30^\circ$. The waveform was obtained, and the clear valve clicks corresponding to the opening and closing of the two valves were apparently imaged to correctly place the time cursors as shown in Figure 2. This estimation should be performed 3 times. Three time periods were estimated as follows: Isovolumetric contraction time (ICT) from the beginning of MV closure to AV opening clicks as shown in Figure 3; Ejection time (ET) from AV opening to AV closure click; Isovolumetric relaxation time (IRT) from AV closure to MV opening click as shown in Figure 3. The Mod-MPI = (ICT + IRT) / ET. For the purpose of the study, if days exceeded weeks by <4 days then the weeks of GA were rounded downward and when days exceeded weeks by ≥ 4 days then the weeks rounded upward.

Postnatal Follow-up

Postnatal follow-up outcomes were recorded. All neonates were evaluated by neonatologist at birth and till discharge from the hospital.

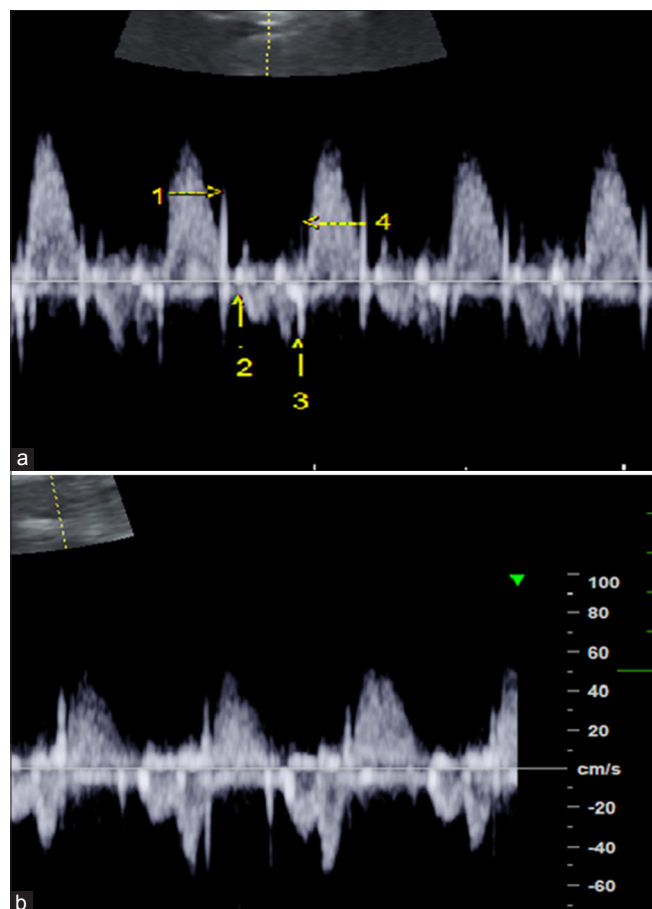


Figure 2: (a and b) The waveform used for the calculation of myocardial performance index and various clicks used for the time measurement. 1 is aortic valve closure click, 2 is mitral valve opening click, 3 is mitral valve closure click, and 4 is aortic valve opening click in figure 8(a)

Statistical Analysis

Data entry was done in the Microsoft Excel spreadsheet. Statistical analysis was done using descriptive and inferential statistics using Chi-square test, Student's unpaired *t*-test, one-way ANOVA, multiple comparison Tukey test, and software used in the analysis were SPSS 22.0 version and GraphPad Prism 6.0 version and $P < 0.05$ is considered as the level of statistical significance. The relationship of the MPI with gestational age and heart rate was measured by linear regression analysis.

RESULTS

A total of 60 pregnant women with single, normal healthy fetuses were enrolled in this study [Table 1].

Fetal ICT, IRT, ET, and fetal heart rate (FHR) were measured in all fetuses [Table 2]. Mean ICT was 31.40 ± 2.95 ms, mean IRT was 32.38 ± 3.42 ms, and mean ET was 174.83 ± 6.41 ms. The mean heart rate was 142 ± 6 bpm. Mean Mod-MPI was 0.35 ± 0.03 .

The correlation coefficient analysis revealed no correlation between MPI and the gestational age ($r = 0.04$) [Table 3] and MPI and the FHR [Table 4].

DISCUSSION

Assessment of fetal cardiac function and to predict potential progression to dysfunction is still under evolution. Fetal cardiac dysfunction can be measured by the LV Mod-MPI and creates a viable and reproducible *in utero* fetal monitoring for the fetal well-being. MPI can detect

Table 1: Distribution of patients according to gestational age in the third trimester (28–40 weeks)

Number of patients	Mean gestational age (weeks)	Mean \pm MPI
60	35.8 \pm 1.54	0.35 \pm 0.03

Table 2: Comparison of fetal parameters and LV modified MPI parameters

Variable	Study group
Maternal mean age (years)	27.53 \pm 2.20
Gestational age (mean weeks)	35.8 \pm 1.54
EWF (g)	2721 \pm 509.26
AFI (cm)	11.06 \pm 3.01
Modified LV MPI	0.35 \pm 0.03
ICT (ms)	31.40 \pm 2.95
IRT (ms)	32.38 \pm 3.42
ET (ms)	174.83 \pm 6.41

EWf: Expected fetal weight, AFI: Amniotic fluid index, MPI: Myocardial performance index, ICT: Isovolumetric contraction time, IRT: Isovolumetric relaxation time, ET: Ejection time

the subclinical diastolic dysfunction,^[19] and it could serve as a guide to clinicians to establish the timing of delivery and ultimately will reduce the perinatal morbidity and mortality. Increased MPI is highly sensitive and specific for the prediction of adverse perinatal outcome including stillbirth or neonatal death.^[20,21,27] Mod-MPI has potential to improve fetal surveillance, and we can stratify the high-risk pregnancies into high-risk or low-risk pregnancies. IRT is the important parameter which becomes abnormal early in myocardial dysfunction mainly because of reduced calcium uptake.^[22] Previously published reference values for MPI values varied from 0.22 to 0.53.

Multiple studies have been done to determine the normal values of MPI in the fetus [Table 5] and with varied results.

Table 3: No correlation between gestational age and Tei index

Gestational Parameters	Mean±SD	n	r value	P value
Gestational age	39.06±1.02	60	0.04	0.25, not significant
Tie index	0.35±0.015	60		

SD: Standard deviation

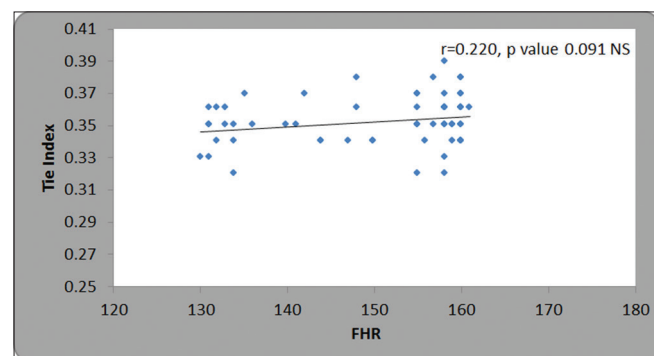


Table 4: No correlation between Tie index and FHR

Gestational Parameters	Mean±SD	n	r value	P value
Tie Index	150.15±11.03	60	0.220	0.091, not significant
FHR	0.35±0.01	60		

FHR: Fetal heart rate, SD: Standard deviation

Table 5: Comparison with the previous similar studies

Study	Year	Number of patients	Modified MPI
Tsutsumi <i>et al.</i> ^[3]	1999	135	0.43±0.03
Eidem <i>et al.</i> ^[23]	2001	125	0.36±0.06
Friedman <i>et al.</i> ^[24]	2003	74	0.53±0.13
Chen <i>et al.</i> ^[29]	2006	225	0.22±0.05
Hernandez-Andrade <i>et al.</i> ^[17]	2007	557	0.37±0.029
Ghawi <i>et al.</i> ^[25]	2013	420	0.464±0.08
Nair and Radhakrishnan ^[26]	2016	200	0.42±0.03
Present study	2017	60	0.35±0.03

Tsutsumi *et al.* were the first to use Tei index for the assessment of fetal global myocardial function. The LV MPI was significantly lower (0.43 ± 0.03) in the third trimester beyond 34 weeks of gestation as compared to the second-trimester fetuses between 18 and 26 weeks of gestation (0.62 ± 0.07).^[3] The LV myocardial maturational changes significantly increased in the late gestation, and global ventricular function got affected by these maturational changes. This leads to the difference in MPI in the above-mentioned study. A similar decrease in MPI with advancing gestation was also noted by Chen *et al.*^[29] In contrast to this, Friedman *et al.*, Parasuraman *et al.*,^[30] and Russel and McAuliffe^[31] reported that the MPI values did not show any significant correlation with gestational age and heart rate.^[24] Our study correlated well with the fact that the MPI has no correlation with either gestational age or heart rate. The technique for MPI measurement has been improved with time. Tsutsumi *et al.*, in 1999, first reported the use of the MPI using two waveforms, and therefore, two cardiac cycles were used for measurements.^[3] Then, further, Friedman *et al.* proposed a new position for the Doppler sample volume in 2003 and from which the LV MPI can be calculated from a single Doppler waveform.^[24] Raboisson *et al.*, in 2003, proposed that the Doppler click of the aortic valve opening be used as a landmark which helped to better estimate the time intervals of MPI calculation.^[16] In 2005, Mod-MPI was introduced by Hernandez-Andrade *et al.* in which they used the beginning of opening and closing Doppler clicks of both the aortic and mitral valves as measurement landmarks for the different time periods.^[22] Using this method, there was a significant reduction in the inter- and intra-observer variability, and thus, reproducibility of the index in fetal medicine was improved.

The clinical applications for MPI in early detection and counseling were investigated. Fetal cardiac dysfunction was assessed by MPI in a variety of pathological conditions including intrauterine growth restriction,^[4] maternal diabetes,^[5-7] TTTS,^[8] congenital heart malformations,^[9] preeclampsia,^[10] and fetal inflammatory response syndrome in fetuses with preterm premature rupture of membranes.^[28] and MPI was significantly increased in the above-mentioned studies. Increased MPI is highly sensitive and specific for the prediction of adverse perinatal outcome including stillbirth or neonatal death.^[20,21,27]

It is already reported that machine settings and technique used for MPI evaluation significantly affect the reproducibility, and it may account for the variation in the wide range of normal values. The accurate role of MPI values in complicated pregnancies is limited due to lack of universal normal reference ranges. To establish a universal reference range of MPI, large multicenter studies

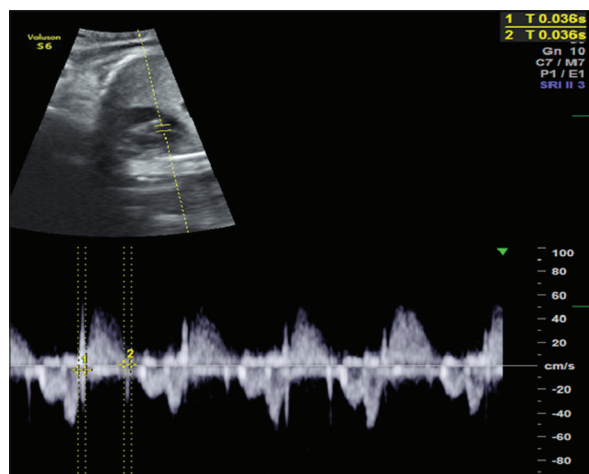


Figure 3: The measurement of isovolumetric contraction time (1) from the mitral valve closure click to the aortic valve opening click. Isovolumetric contraction time was measured 36 ms. Number 2 is showing isovolumetric relaxation time, measured 36 ms

are needed to measure the MPI using standardized machine settings and technique.

Limitation

The possibility of intraobserver errors from the study cannot be excluded as all the observations were made by a single operator.

CONCLUSION

The normal range of the LV Mod-MPI in normal fetuses of the Indian population was defined by our study. The LV MPI values appear to be independent of GA and FHR. MPI can be used as a screening/follow-up tool for global cardiac function in normal and complex fetal hearts. Subclinical fetal cardiac dysfunction can be measured by the LV Mod-MPI and creates a viable and reproducible *in utero* fetal monitoring for the fetal well-being. MPI should be considered as an adjuvant in the initial diagnosis in fetuses with complex heart diseases and their subsequent follow-up scans. Prospective studies are needed to further delineate these relations.

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Chronic Right Iliac Fossa Pain Relieved by Appendicectomy? A Fact or Myth?

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Abstract

Background: Although chronic right iliac fossa (RIF) abdominal pain is a common clinical condition, the diagnosis and treatment are still under debate. In spite of literature evidence, the existence of recurrent or chronic appendicitis continues to be debated especially, whether chronic appendicitis really exists and whether it can explain the persistent or chronic RIF abdominal pain.

Aim: The aim of the study was to study the undiagnosed chronic RIF pain, in which the ultrasonogram and computerized tomography scan showed no definite findings and whether those subset of patients will be relieved after elective laparoscopic appendicectomy.

Methods: A total of 60 patients, 12–60 years of age, with undiagnosed chronic RIF abdominal pain underwent diagnostic laparoscopy and appendicectomy. 10 patients were excluded from the final analysis because of the presence of an obvious associated non-appendicular pathology also. Patients were followed up for 6 months at regular intervals (1, 3, and 6 months) and were assessed for pain relief. The association between clinical outcome and the histopathological outcome was studied.

Results: The histopathological examination of appendices revealed appendicitis in all patients. Intra-operative evidences of chronic appendicitis were seen in 42 (84%) patients. 47 (94%) patients were completely pain-free on follow up, and only 3 (6%) patients had persistence of pain.

Conclusions: Patients with chronic RIF abdominal pain (without an obvious diagnosis on preoperative evaluation) can safely undergo exploratory laparoscopy and appendicectomy. Chronic appendicitis is a diagnosis of exclusion with intraoperative and histopathological evidence. Patients with RIF abdominal pain and RIF tenderness with otherwise normal findings on sonology are having chronic or recurrent inflammation of the vermiform appendix and are fully curable by laparoscopic appendicectomy.

Key words: Appendicectomy, Laparoscopy, Right iliac fossa pain

INTRODUCTION

Recently, chronic right iliac fossa (RIF) abdominal pain has drawn more attention because of its high incidence, significant morbidity and significant costs to health care. Patients often complain of pain in the RIF of the

abdomen or months to year's duration for which various diagnostic and therapeutic interventions were carried out with no relief. The vermiform appendix is one of the most common sites of inflammatory pathology in the abdomen.^[1] Traditionally, the only well documented and clinically significant one among the inflammations of the appendix has been the "acute appendicitis." However, the lack of objectivity in the diagnostic algorithms in case of appendicitis, in general, has led to many clinical confusions and increased patient morbidity. On the one hand, there is a huge number of cases which are underdiagnosed and on the other, a significant series of cases with a high negative appendicectomy rate (NAR). In this context, we believe, that the basic fact about the

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inflammatory disorders of the appendix is that these can present with a spectrum of character and severity,^[2,3] so that, the accurate positive diagnosis of appendicitis cannot be defined just by traditional parameters such as tachycardia, rebound tenderness, leukocytosis, the Alvarado scoring system, ultrasonogram (USG), or even by computerized tomography (CT) of the abdomen. Here, we present a series of pathologically proven chronic or recurrent inflammation of the vermiform appendix, all of which presented with chronic RIF abdominal pain, without the traditionally relied on clinical features and sonological evidence to support, but with an excellent cure rate following laparoscopic appendicectomy.

Aim

The aim of the study was to study the undiagnosed chronic RIF pain, in which the USG and CT scan showed no definite findings and whether those subset of patients will be relieved after elective laparoscopic appendicectomy.

METHODS

It was a prospective interventional study, carried out from June 2016 to June 2017. Patients with RIF abdominal pain ranging from 6 weeks to 5 years in duration, which remained undiagnosed, were chosen for the study. Inclusion criteria: Patients aged 12–60 years, suffering from chronic or recurrent RIF abdominal pain for more than 6 weeks who had been treated conservatively by antibiotics and analgesics without the classical clinical and/or sonological features of acute appendicitis. Exclusion criteria: Patients with chronic RIF abdominal pain but also with a history of chronic back pain (previous spine surgery and diagnosed disc prolapse), previous abdominal surgery (except diagnostic laparoscopy or laparoscopic sterilization), gynecological diseases (pelvic inflammatory disease), and known urological diseases (renal stones and ureteric stones). 10 patients were excluded postoperatively as they had associated uterine and/or adnexal lesions as well. All patients were preoperatively subjected to hemogram, renal function test, random blood sugar, urine routine examination, abdominal USG, and chest radiography. All patients were subjected to CT scan abdomen to rule out other pathology. All 60 patients underwent thorough diagnostic laparoscopy and those with obvious non-appendicular pathology, which could interfere with final analysis, were excluded. All specimens were subjected to histopathological examination. All patients were followed up in the outpatient department for up to 6 months (1, 2, and 6 months). Patients were scored for pain as completely relieved and pain persistent/increased. The clinical outcome was studied in relation to pathological reports.

RESULTS

A total 60 patients were included in the study. 10 patients were excluded after diagnostic laparoscopy due to coexisting PID/ovarian cyst. Of the 50 patients who were finally included, 32 (64%) were male and 18 (46%) were female. All patients had various degrees of RIF tenderness. None had tachycardia or leukocytosis. USG abdomen detected probe tenderness in 36% patients and these three patients had sonologically visible appendix of 6–10 mm diameter. 88.8% patients showed features of chronic appendicitis such as pale, narrow, and fibrosed appendix with periappendicular adhesions to various extents. At the end of 6 months, 47 (94%) patients were completely pain-free. There were 3 (6%) patients with pain remaining even after 6 months. There was no patient whose pain was worse than before. NAR in this series is zero. 37 patients had histopathological proof of chronic inflammation of the appendix. 13 patients showed pathological changes suggestive of acute on chronic appendicitis.

DISCUSSION

Consensus regarding a chronic inflammatory process in the vermiform appendix as a cause of chronic RIF abdominal pain is lacking. Hitherto, the only well-recognized form of inflammation of the appendix is the acute appendicitis.^[4] Even though it is widely accepted that the diagnosis of acute appendicitis is largely clinical, the low confidence level for this particular diagnosis for any given clinician has led to unnecessary dependence on investigative modalities such as USG or CT scan, a state which has led to a huge percentage of under-diagnosis and under-treatment, thereby constituting an unacceptable level of morbidity in patients suffering from RIF pain. The recurrence rate in suboptimally treated (by intervention other than surgical) appendicitis is of great concern too.

There is a divergence of opinion regarding the clinical entity of chronic appendicitis, as a cause of recurrent pain in the RIF. These patients may not present with the traditionally accepted clinical features of an inflamed appendix. Instead, they complain of months to years of RIF abdominal pain. They may have had multiple medical evaluations and conservative treatment in the past for this pain. The patients may describe an initial episode with more classic symptoms of acute appendicitis, for which no treatment was received or treated conservatively. The diagnosis of chronic appendicitis can be difficult, as hematology and radiological studies are typically normal. HPE evaluation confirms the diagnosis of chronic inflammation.^[2,3] As the diagnosis is often uncertain preoperatively, laparoscopy can be a useful tool to allow exploration of the abdomen.^[5]

Recurrent appendicitis refers to a pattern of symptoms with mild, self-limited attacks of RIF pain that typically last for hours before resolving spontaneously with histological evidence of appendicitis.

Chronic appendicitis refers to constant well-localized RIF abdominal pain and tenderness with no other identifiable pelvic or abdominal disease. If appendicectomy completely relieves the pain and pathologic findings include chronic inflammation of the appendix, then the diagnosis of chronic appendicitis is confirmed.^[6,7]

In our study, pain abdomen was the universal complaint in all 60 patients (100%). Anorexia and nausea/vomiting were present in 10% patients. The recurrence rate in suboptimally treated (by interventions other than surgical) acute appendicitis (due to failure to confirm the diagnosis) and the suffering due to undiagnosed chronic RIF abdominal pain are unacceptably high. Overemphasis on clinical parameters such as tachycardia, rebound tenderness, and laboratory parameters such as leukocytosis and sonological evidence has eventually led to a doubtful diagnosis and a harmful increase in resorting to CT scan of the abdomen, at the end of all, the patient remains undiagnosed and untreated for elusive appendicitis. While relying too much on the traditionally overemphasized clinical and investigative parameters to make a diagnosis of an inflammatory process in the appendix, we tend to forget that any inflammation can present with varying degrees of severity and character, so that the clinical and laboratory interpretation must not be restricted by too rigid and dogmatic concepts.

In our series of 60 patients who presented with chronic RIF abdominal pain, the only clinical sign of a probable inflammatory process in the RIF was a varying degree of RIF tenderness. None of them had tachycardia (as defined by a resting heart rate of more than 100 beats/min), rebound tenderness or elevated body temperature. No patients showed leukocytosis (as defined by a total leukocyte count of more than 11000 cells/mm³). All 60 patients underwent exploratory laparoscopy. 10 patients had a demonstrable non-appendicular pathology also in and around the pelvis. All others had an otherwise normal abdomen as far as laparoscopy could demonstrate, except for the fact that 88.8% of patients had features of the chronic inflammatory process in and around the appendix as described by a narrowed, pale, and fibrosed appendix with periappendiceal adhesions of varying degrees. Histopathological analysis of the appendicular specimen proved that all appendices were pathological and so the NAR is zero. 94% of patients had the complete cure of RIF abdominal pain. 6% had persistent pain presumably due to stump appendicitis.

Laparoscopy is changing the approach toward chronic RIF abdominal pain. It is a diagnostic as well as a therapeutic tool. An exploratory and interventional (appendicectomy) study was conducted by Kolts *et al.* in 44 pediatric patients having recurrent RIF abdominal pain.^[8] 15 patients (34%) had abnormalities other than appendix during exploratory laparoscopy. Out of 44 patients, 32 (72.7%) were found to have histologic abnormalities in the appendix on 2 years follow-up, complete resolution of abdominal pain occurred in 25 (56.8%) patients, partial resolution in 6 patients (13.6%), and no response in 13 patients (29.6%). Hence, the conclusion of the study was that laparoscopic appendicectomy performed during exploratory laparoscopy is a useful treatment for chronic or recurrent RIF abdominal pain and can also be a good diagnostic tool for other diseases processes in the abdomen.

Another study was conducted by Roumen *et al.* for chronic RIF abdominal pain.^[9] It was a double-blinded randomized control trial. Of 40 patients, 18 patients underwent laparoscopic appendicectomy and 22 patients only diagnostic laparoscopy. Post-operative pain scores and histopathology of appendix were compared between the two groups. Out of 18 patients in the laparoscopic appendicectomy group, 7 appendices were found to be normal, and 11 showed signs of appendicopathy. At 6 months follow-up they observed that higher proportion of patients in the appendicectomy group had significant improvement in pain than the other. It was concluded that persistent or recurrent RIF pain can be treated successfully by elective laparoscopic appendicectomy in properly selected cases and there was no significant relationship between post-operative pain scores and the histopathology findings of the appendices.

Al-Araji performed appendicectomy in 58 patients with chronic or recurrent RIF pain of 3 months to 3 years duration.^[10] Out of 58 patients, 54 (93.1%) had gross changes of chronic inflammation in the appendix and surrounding tissues. Only 17 specimens were subjected to HPE, and 16 showed chronic inflammatory changes. On follow-up, 56 (96.5%) patients were completely pain-free.

In a study by Charles *et al.*, 10 patients underwent an elective appendicectomy for chronic RIF pain.^[11] No macroscopic abnormalities were seen during surgery. Histopathological analysis showed inflammatory changes in 8 out of 10 patients. The conclusion of the study was that significant reduction of pain can be achieved after an appendicectomy in all patients suffering from chronic RIF abdominal pain.

In a recent study on chronic RIF abdominal pain by Gedam *et al.* they performed laparoscopic appendicectomy in

30 patients.^[12] In this study, 22 (73.4%) out of 30 patients had recurrent appendicitis, and 26 (86.6%) patients had complete pain relief after appendicectomy at 6 months follow-up. The conclusion of the study was that laparoscopy is an invaluable tool in diagnosing conditions other than chronic appendicitis existing concurrently in patients with chronic RIF pain. There is no relation between the relief of pain and histopathology of the appendix. Nevertheless, chronic RIF abdominal pain can be relieved by performing laparoscopic appendicectomy.

Another study conducted by Popovic *et al.*, 41 out of 53 cases of chronic RIF abdominal pain underwent laparoscopic appendicectomy.^[13] The study concluded that long-term results are similar in both laparoscopic appendicectomy and without appendicectomy groups. There was no relationship between clinical improvement and histopathology of appendices. The study also mentioned that appendicectomy should be performed even though there is no macroscopically visible reason because of the intraluminal changes.

In another study by Charlesworth and Mahomed in the pediatric population, 16 children underwent laparoscopic appendicectomy for chronic RIF abdominal pain.^[14] There was an early improvement in 14/16 patients. This figure had improved to a 100% on extended follow-up. Median follow-up was 19 months (range 1–47). The conclusion of the study was that symptomatic improvement can be expected to be 88% immediately and up to 100% in the long term. The study supports laparoscopic appendicectomy in all patients presenting with chronic RIF pain in spite of negative hematological and radiological investigations.

CONCLUSION

The vermiform appendix is a common site of inflammatory disorder and is a major surgical cause of morbidity. Other than acute appendicitis, appendicular inflammation can also present with chronic or recurrent RIF abdominal pain of

milder degrees but without tachycardia, leukocytosis, and sonological evidence. The hematological and radiological studies do not contribute the diagnosis of chronic or recurrent appendicitis. However, intra-operative findings on laparoscopy and histopathology of the removed appendix confirm the diagnosis. The diagnosis of this entity is largely clinical and laparoscopic appendicectomy is curative.

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Seroprevalence of Transfusion Transmitted Infections among Blood Donors – A 5-Year Tertiary Care Hospital Study at Western Ahmedabad

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Abstract

Background: Transfusion transmitted infections (TTIs) are still a major threat to society as screening methods employed are not 100% full proof and long window periods of these infections.

Aim: The aim of this study is to estimate the seroprevalence of major TTIs in Western Ahmedabad and to highlight the important measures to reduce its prevalence rate.

Materials and Methods: This retrospective study was conducted at GMERS Medical College and Civil Hospital, Sola, Ahmedabad, from September 2012 to August 2017 with strict blood donor screening criteria. Serum of the accepted donors was tested for hepatitis B surface antigen (HBsAg), antibodies to human immunodeficiency virus (HIV) Type 1 and 2, hepatitis C virus (HCV) using the third generation enzyme-linked immunosorbent assay kits; syphilis using rapid plasma reagin card test, and malaria by peripheral smear study.

Results: A total of 8844 donors were accepted. Majority (97.98%) were male donors. Voluntary donors were more than replacement donors. Overall, seroprevalence of TTIs was 1.27%. Among TTIs hepatitis B had highest seroprevalence (0.75%), followed by HCV (0.23%), HIV (0.14%), and syphilis (0.13%). No donors were positive for malaria. There was increasing yearly trend of hepatitis B during 5-year study. TTI prevalence was higher in replacement donors (0.89%) as compared to voluntary donors (0.38%).

Conclusion: We should ensure safe blood supply to the recipients and lower the rate of TTIs by focusing on four key measures: Stringent donor screening, encouraging voluntary donor recruitment, introducing highly sensitive screening tests, and proper education of seropositive donors.

Key words: Blood donor, Hepatitis B virus, Hepatitis C virus, Human immunodeficiency virus, Syphilis and malaria, Transfusion transmitted infections

INTRODUCTION

As a part of integrated strategy of any well-organized blood transfusion service to provide safe blood supply to the recipients, blood should be collected from voluntary

non-remunerated donors tested for transfusion transmitted infections (TTIs) and unnecessary blood transfusions must be avoided.^[1] It has claimed that with every unit of blood, there is a 1% chance of transfusion-associated complications including transfusion transmitted diseases.^[2] Unsafe blood transfusions ultimately cost human lives and communities in terms of morbidity, mortality, and socioeconomic consequences. Human immunodeficiency virus (HIV) prevalence in adult population in India is 0.2–0.3%,^[3] hepatitis B surface antigen (HBsAg) prevalence varies from 1% to 3% with an average of 4.7%,^[4] hepatitis C virus (HCV) carriers in India are around 12–13 million.^[5] As per drug and cosmetic act, 1945 (amended from time to

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time) and NACO (National AIDS Control Organization) guidelines, it is mandatory to test every single blood unit for HIV, hepatitis B virus (HBV), HCV, syphilis, and malaria.^[6] In India, NACO has recommended the third and fourth generation enzyme-linked immunosorbent assay (ELISA) testing for antibodies to HIV I and II.^[7] The present study was conducted with the aim to assess the seroprevalence of TTIs among apparently healthy blood donors (BDs) at our blood bank and to emphasize the critical importance of measure to reduce the rate of TTIs.

MATERIALS AND METHODS

This retrospective study was conducted over a period of 5 years from September 2012 to August 2017 at the blood bank of GMERS Medical College, Civil Hospital, Sola, Ahmedabad, Gujarat, after Approval of Ethical Committee of our institute. Data were collected from the records of blood bank. All voluntary donors (in-house donors and outdoor blood donation camps organized by blood bank) and replacement donors (from relatives and friends of the patients admitted at Sola Civil Hospital) were included in the study. Predonation counseling and screening was done as per “donor registration and consent form” and standard operating procedure of our blood bank. Donors aged 18–60 years with weight >45 kg and hemoglobin concentration > 12.5 g% were accepted. Hemoglobin concentration was measured by Hemocue 301 instrument. Serum samples of all BDs were allowed to clot manually at room temperature and then centrifuged at 2500 rpm for 5 min to obtain serum and then tested for HIV, HBV, HCV, syphilis, and malaria. For HIV, HBsAg, and HCV third generation,

ELISA kits (for Anti-HIV Type I and II - Erba Lisa HIV by Transasia Biomedicals Ltd.; for HBsAg – Merilisa by Meril Diagnostics Pvt., Ltd.; and for HCV - Erba Lisa HCV by Transasia Biomedicals Ltd) were used. Syphilis was tested by rapid plasma reagin card test by Reckon Diagnostics Pvt., Ltd. Malaria testing was done by thick

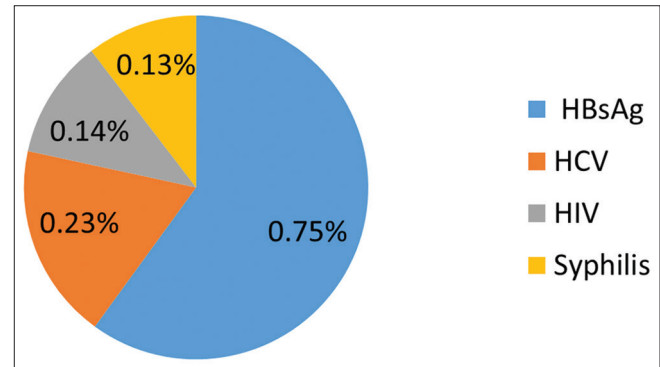


Figure 1: Pattern of seroprevalence in the prFGCsent study

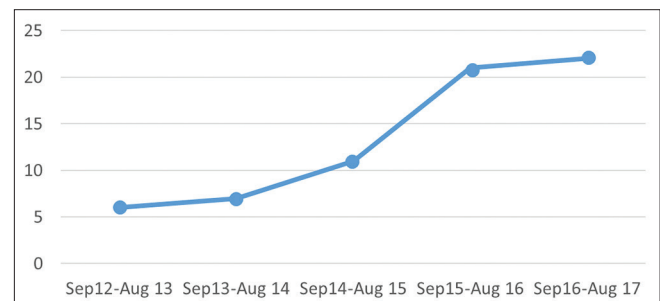


Figure 2: Yearly increasing trend of hepatitis B virus seropositivity

Table 1: Age and sex wise distribution of non-reactive and reactive donors

Age group	Male		Female		Total	
	Number of donors	Reactive	Number of donors	Reactive	Number of donors	Reactive
18–20	1214	07	38	00	1252	07
21–30	3029	40	76	00	3105	40
31–40	2169	29	40	00	2209	29
41–50	1250	26	15	01	1265	27
51–60	1004	10	09	00	1013	10
Total	8666	112	178	01	8844	113

Table 2: Year wise trend of voluntary and replacement donors with their TTI status

Year	Voluntary donors		Replacement donors		Total	
	Number of donors	TTI positive	Number of donors	TTI positive	Number of donors	TTI positive
Sep 12-Aug 13	1187	11	206	04	1393	15
Sep13-Aug 14	1243	03	447	10	1690	13
Sep14-Aug 15	1334	05	334	13	1668	18
Sep15-Aug 16	1234	04	327	29	1561	33
Sep16-Aug 17	1637	01	895	23	2532	24
Total	6635	34	2209	79	8844	113

TTI: Transfusion transmitted infection

and thin peripheral smear examination using Field's stain. Collected data were entered into Microsoft Excel sheet. Statistical analysis was done by Statistical Package for the Social Sciences Version 17. Qualitative data were assessed by frequency and percentage table. The association among various study parameters was determined by Chi-square test and $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 8844 donors were accepted. Most of them were male (8866–97.98%); female donors were only 178 (2.02%) [Table 1]. Voluntary donors were more (6636–75.02%) as compared to replacement donors (2209–24.98%) [Table 2]. Age group wise distribution of the donors show that majority (5314–60%) of BDs were from 21 to 40 years age group with 69 (61% of total positive) seropositive donors among them [Table 1]. Of total BDs, 113 (1.27%) were seropositive. Among them, 13 donors were HIV positive, 67 donors were HBsAg positive, 21 donors were

HCV positive, and 12 donors were positive for syphilis [Table 3]. Hence, overall estimated seroprevalence for TTIs is 1.27% and that of HIV, HBsAg, HCV, and syphilis were 0.14%, 0.75%, 0.23%, and 0.13%, respectively [Figure 1]. Of all seropositive donors, 34 were voluntary donors and 79 were replacement donors having overall seroprevalence of 0.38% and 0.79%, respectively [Table 2]. Increasing yearly trend of HBsAg during 2012–2017 was observed [Figure 2]. All the donor tested were negative for the presence of malarial parasite.

DISCUSSION

Among BDs, dominance of male donors (97.98%) and voluntary BDs (75.02%) was observed. In developing countries like India, because of social taboo and cultural habits, female donors hesitate to donate blood as well as iron deficient and menstruating age group females are deferred during screening because of low hemoglobin percentage. Male donors also showed increasing yearly trend of seropositivity [Figure 3]. Overall, seroprevalence of TTIs was 1.27%. HBV showed highest seroprevalence (0.75%) which is statistically significant ($P < 0.001$). HCV, HIV, and syphilis had seroprevalence of 0.23%, 0.14%, and 0.13%, respectively [Figure 1]. These findings are comparable with other Indian studies like Bhawani *et al.*,^[8] Jasani *et al.*,^[9] Chandekar *et al.*,^[10] Karmakar *et al.*,^[11] and Arya *et al.*^[12] [Table 4]. All these studies show highest prevalence of hepatitis B among TTIs. The present study also showed increasing yearly trend of HBV during 5 years [Figure 2]. HBV positivity suggests either a carrier state or an active infection. HIV transmission is possible during “window period” even if each unit is tested for HIV antibodies. This can be minimized by better selection of low-risk donors by stringent screening. Overall, seroprevalence was lower in voluntary non-remunerated donors (0.38%) than in replacement donors (0.89%). All BDs were found negative for malaria as presenting symptoms of malaria such as fever; weakness renders the patients from donating blood as well excluded by screening and examination.

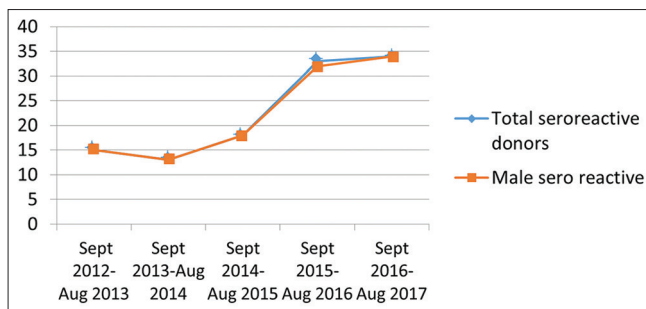


Figure 3: Increasing yearly trend of seroprevalence in male donors

Table 3: Year wise trend of seroprevalence of TTIs

Year	HIV	HBV	HCV	Syphilis	Malaria	Total
Sep12-Aug 13	04	06	03	02	00	15
Sep13-Aug 14	01	07	04	01	00	13
Sep14-Aug 15	00	11	05	02	00	18
Sep15-Aug 16	02	21	04	05	00	32
Sep16-Aug 17	06	22	05	02	00	35
Total	13	67	21	12	00	113
Seroprevalence (%)	0.14	0.75	0.23	0.13	00	1.27

TTI: Transfusion transmitted infection, HIV: Human immunodeficiency virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus

Table 4: Comparison of seroprevalence of TTIs among other studies in India

Author and year	Place	HIV (%)	HBV (%)	HCV (%)	Syphilis (%)
Bhawani <i>et al.</i> 2004–2009	Andhra Pradesh	0.39	1.41	0.84	0.08
Jasani <i>et al.</i> 2004–2011	Piparia-Vadodara	0.25	1.35	0.16	0.90
Chandekar <i>et al.</i> 2007–2012	Mumbai	0.26	1.3	0.25	0.28
Karmakar <i>et al.</i> 2009–2011	Kolkata	0.60	1.41	0.59	0.23
Arya <i>et al.</i> 2010–2015	Bikaner	0.10	1.60	1.18	0.89
Present study 2012–2017	Ahmedabad	0.14	0.75	0.23%	0.13%

TTI: Transfusion transmitted infections, HIV: Human immunodeficiency virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus

CONCLUSION

In the present study, overall, seroprevalence of TTIs was 1.27% with highest rate and increasing yearly trend of HBV was observed. Replacement donors were found harboring more TTI rate. This alarms us about the fact that TTIs are inevitable in health care setups and we must take adequate measures to lower the risk and prevalence of TTIs such as strict donor screening, voluntary donor recruitment, and retention strategies access to highly sensitive assays such as nucleic acid testing and effective education of reactive donors.

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Effects of Anticonvulsant Retigabine on Pain Hypersensitivity Diabetic Rats with Neuropathy

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Abstract

Background: Diabetes is a chronic condition that affects millions of the world population. One of the most serious complications of diabetes is a neuropathic pain (pain due to nerve injury/dysfunction) that affects about 30–55% of diabetic patients. This nerve dysfunction can lead to numbness, weakness, and spontaneous/ongoing (stimulus independent) pain, and stimulus-evoked (allodynia and hyperalgesia) pain. This pain hypersensitivity is believed to be due to neuronal hyperexcitability. However, the mechanism of this neuronal hyperexcitability is unknown.

Aims: Therefore, the aim of this research work was to examine the hypothesis that a subtype of K⁺ channels known as Kv7 channels (that play an important role in controlling hyperexcitability) is involved in the pathophysiology of diabetic neuropathy.

Methods and Results: To examine this hypothesis, we use Darat model of diabetic neuropathic pain (DNP), known as streptozotocin (STZ) model (which involves an injection of 60 mg/kg of STZ; i.p), STZ is a toxin to pancreaticβ-cells that release insulin. We used this model to examine the effects of activating KV7 channels with retigabine (10 mg/kg) on behavioral signs of mechanical allodynia and heat hyperlagisa in the diabetic (STZ treated) rats. Our results show that retigabine (as elective KV7 channel activator that has recently been licensed for treating partial-onset seizures (epilepsy), which, like DNP, is characterized by neuronal hyperexcitability) significantly reduced both allodynia and hyperalgesia.

Conclusions: These findings indicate that retigabine may represent a potential therapeutic alternative for DNP. However, further investigations are needed because of the small number of animals tested.

Key words: Anticonvulsant, Hypersensitivity, Pain

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders resulting in hyperglycemia due to an absolute or relative reduction in insulin production or its action. The chronic state of this disorder will result in multiple serious complications, end organ damage and dysfunction in, i.e., retina, kidneys, cardiovascular system, and nervous system. The International Diabetes Federation in 2011 estimated an overall prevalence

of DM to be 366 million, and it is expected to raise to 552 million by 2030. DM has many complications, one of which is neuropathic pain (nerve pain).^[1] It is estimated that 28–55% of diabetic patients develop neuropathic pain.^[2] Normally, pain is caused directly by noxious stimuli on nerve fiber endings that sense pain or by inflammatory mediators in damaged tissue, but the neuropathic pain is caused by a primary neuronal injury or dysfunction.^[3] The nerve dysfunction can cause numbness, weakness, and spontaneous pain as well as stimulus-evoked pain. The pain is spontaneous and sometimes continues, and it has the character of burning, shooting, or shock.^[4] The stimulus-evoked pain includes allodynia and hyperalgesia. Allodynia is pain triggered by stimuli that are normally non-painful, and it is induced by very light stimulation, such as a wind or skin contact with clothing while hyperalgesia is increased pain caused by stimuli that are normally painful.^[5]

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There are many etiologies of neuropathic pain, such as infection, inflammation, trauma, malignancy, and metabolic disorders such as diabetes, neurotoxins, and neuronal compression.^[6] Pain is normally perceived when peripheral sensory nerves and neurons, i.e., in the skin, transmit impulses to the brain. Pain signals are normally generated only when there is actual or threatened tissue damage, but in the case of chronic pain conditions such as during diabetic neuropathy, there is the spontaneous activity of these nerves or neurons so that pain can be felt without any external stimulus. Nerve impulses, also called action potentials, are generated by protein molecules that represent ion channels that regulate the flow of ions mainly sodium (Na⁺) and potassium (K⁺) across the neuronal membrane. When Na⁺ ions move inward by activation of Na⁺ channels, the neuron becomes more positive inside, and its tendency to transmit nerve impulses is increased. In contrast, when K⁺ ions move outward by activation of K⁺ channels, the neuron becomes more negative inside, and its probability of generating nerve impulses is reduced.

There is evidence that during neuropathic pain states, there is an increase in transcription and axonal trafficking of Na⁺ channels as well as a reduction in expression of K⁺ channels, including Kv7 channels.^[5] The Kv7 channels play an important role in controlling hyperexcitability of neurons (generating more impulse than normal) and normally act as a “brake” on neuronal excitability. However, because of the decrease in the expression of Kv7 channels^[7] and increase in Na⁺ channels during chronic pain states, the neurons become hyperexcitable and generate ectopic activity, i.e., an abnormal activity that is spontaneously generated in an abnormal site.^[5]

Although there are some palliative treatments for neuropathic pain that aim to reduce the pain,^[8] successful therapy for the debilitating condition of diabetic neuropathic pain (DNP) remains a challenge because the currently available drugs are ineffective and have significant side effects. Therefore, the current study is aimed at assessing the effects of retigabine, a selective activator of Kv7 channels on pain hypersensitivity in diabetic rats with neuropathy. Retigabine has high efficacy and good tolerability in treating adults with partial seizures,^[9] a condition, like DNP, characterized by neuronal hyperexcitability. In addition, it has been suggested that retigabine, through specific activation of neuronal KCNQ/Kv7 channels, may have therapeutic potential for neuropathic pain based on findings using a rat model of temporomandibular disorders.^[10] Therefore, retigabine may also have therapeutic potential in treating DNP.

MATERIALS AND METHODS

Twelve male Sprague Dawley rats (250–300 g weight) were used for pain behavioral testing (see below).

Induction of DM in Rats

Rats were used for induction of diabetic neuropathy. To induce this model, the rats were injected intraperitoneally with 60 mg/kg streptozotocin (STZ), STZ is a toxin to pancreatic β -cells that release insulin. The severity of the induced DM was detected daily by measuring body weights, clinical manifestations, and blood sugar concentration. The observation period was up to 4 weeks. Rats were classed as diabetic if their blood glucose level was >250 mg/dL.

Drug Administration

Retigabine, the selective activator of kv7 channels was injected subcutaneously into the rat's hind paw to examine the effects activating KV7 channels on pain hypersensitivity in the STZ diabetic model. Retigabine was dissolved in tween 80 and physiological saline (Sigma, St. Louis, MO, USA). The mixture of the vehicle in the present work contained tween 80 and physiological saline in 1:9 ratio (v/v). The drug solutions were given at a volume of 10 μ l/kg to the rats intraperitoneally.

Behavioral Tests

There are many signs represent neuropathic pain behavior in animals of which two types of evoked pain behavior were studied as signs of neuropathic pain. These were mechanical hypersensitivity/allodynia (decreased withdrawal threshold to mechanical force) and heat hypersensitivity/hyperalgesia (decreased withdrawal latency to a noxious stimulus).

An automated von Frey type system known as a dynamic plantar esthesiometer touch stimulator (Ugo Basile, Comerio, Italy) was used to examine the presence of behavioral signs of mechanical allodynia. Mechanical allodynia was indicated by decreased withdrawal thresholds to pressure. This mechanical force (pressure) was applied to the mid-plantar aspect of the hind paw with a blunt metal filament, through an elevated mesh. The rats were placed in plastic chambers on a wire mesh table, and tests were performed after the animals were acclimatized for about 30 min. The mechanical force applied to the rat's hind paw increased gradually to 50 g until the rat showed a withdrawal response. The force (in grams) that elicited a withdrawal response was automatically displayed and recorded. To prevent any tissue damage a cutoff of 50 g was imposed. An interval of 2–3 min between subsequent investigations on the same hind paw was allowed. Allodynia was considered when there was a decrease in withdrawal threshold to the mechanical force. The average of four latency measurements for each hind paw was taken.

Heat hyperalgesia was indicated as reported previously^[11] by reduced paw withdrawal latency to a noxious heat stimulus applied to the plantar aspect of the hind paw using a planter (Hargreaves) analgesy-meter (Ugo Basile, Comerio, Italy). A laser radiant heat source was placed under 2-mm thick glass floor on which each rat was placed. Once the stimulus began a timer was activated, and the timer stopped automatically once a photocell detected a withdrawal response. During each session, an average of three latency measurements for each hind paw was taken. An interval of 5 min between successive stimuli on the same hind paw was allowed to reduce the possibility of sensitization.

Data Analysis

Statistical analysis was performed using IBM SPSS statistics software (the 19th edition, USA) for windows. Most of the data showed normal distribution; they are hence presented as a mean \pm standard error of the mean. Comparison between pre-drug and post-drug mean values was made using a paired *t*-test. $P < 0.05$ was used as the criterion of statistical significance.

RESULTS

To confirm that rats treated with streptozotocin (STZ) developed pain behaviors of mechanical and heat hypersensitivity (allodynia and hyperalgesia), we compared pain behavior values 4 weeks after induction of diabetes with pretreatment (baseline) values. A significant reduction in the mean paw withdrawal threshold (MWT) from a mechanical stimulus [Figure 1], or in the mean paw withdrawal latency (HWL) from a noxious heat stimulus [Figure 2] was taken as indicators of mechanical allodynia and heat hyperalgesia, respectively. These results indicate that STZ rats developed DNP.

Having established that the STZ rats developed DNP, we then examined the effects of activating Kv7 channels with retigabine, a selective blocker of Kv7 channels, on behavioral signs of mechanical allodynia and heat hyperalgesia in these diabetic rats (diabetic neuropathy model). We compared pain behavior values 2–3 h after retigabine injection with those of vehicle (0.9% physiological saline). 12 rats were used for testing heat hyperalgesia and mechanical allodynia. Six rats were injected with retigabine and the other six injected with vehicle for each test. The results show that retigabine caused a significant increase in both the MWT ($P < 0.01$) and in the mean paw withdrawal latency ($P = 0.045$) [Figure 1], indicating that retigabine reduced mechanical allodynia ($P < 0.01$) and heat hyperalgesia ($P = 0.045$). The average mean of withdrawal threshold (mechanical allodynia) in rats treated with the vehicle was 22.15 g

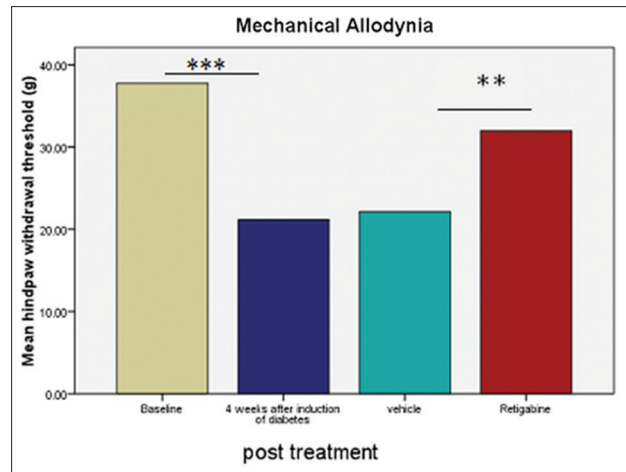


Figure 1: Effects of retigabine on mean hind paw withdrawal threshold in rats 4 weeks after streptozotocin treatment. Baseline: Normal rats without diabetic neuropathy, vehicle: 2–3 h after vehicle injection as compared 2–3 h after retigabine injection, * $P < 0.001$, ** $P \leq 0.01$**

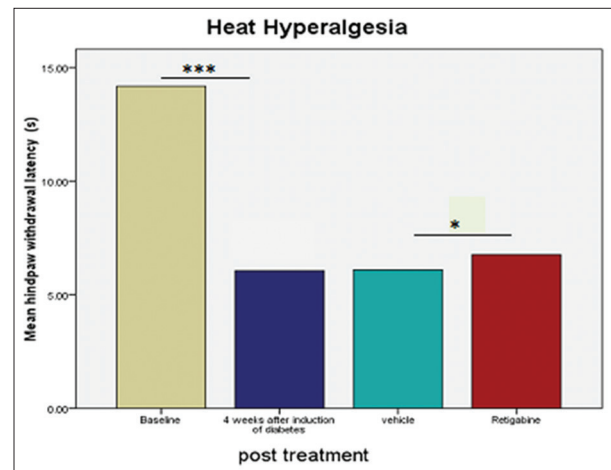


Figure 2: Effects of retigabine on mean hind paw withdrawal latency in rats 4 weeks after streptozotocin treatment. Baseline: Normal rats without diabetic neuropathy, vehicle: 2–3 h after vehicle injection as compared to 2–3 h after retigabine injection, * $P < 0.001$, * $P < 0.05$**

compared to 31.98 g caused by retigabine injection. The mean withdrawal latency in rats treated with retigabine was longer than that of vehicle rats (6.76 vs. 6.09 s) [Figure 1].

DISCUSSION

The main aim of the current work was to examine if activating Kv7 channels with the anticonvulsant retigabine, blocks or reduces pain hypersensitivity in diabetic rats with neuropathic pain (DNP). Interestingly our results show that activation of these channels by subcutaneous injection of retigabine into the rat's hind paw reduced the behavioral signs of both mechanical allodynia and heat hyperalgesia.

As mentioned in the introduction, neuropathic pain is a serious complication of DM that has a negative impact on the nervous system causing hyperalgesia, allodynia, and spontaneous/ongoing pain in human patients. A few animal models of DNP have been developed to investigate its pathophysiology^[12] including the widely used STZ rat model, which involves the injection of STZ (60 mg/kg, i.p.). The interesting thing about this model is that the pain hypersensitivity that is manifested in human patients with DNP is also manifested in this rat model of DNP. Therefore, we used this model to assess the effects, on pain hypersensitivity in this model, of the anticonvulsant retigabine, a selective agonist of the KV7 channels (which play a key role in controlling neuronal hyperexcitability)^[7] and which are believed to be involved in chronic pain states (see introduction).

To the best of our knowledge, there have not been any previous studies evaluating the effects of retigabine on DNP. However, there was a study that evaluated the analgesic effect of retigabine on temporomandibular joint pain.^[10] This study suggested that retigabine may be therapeutically beneficial for temporomandibular joint pain^[10] through suppression of central hyperexcitability by specific activation of neuronal KCNQ/Kv7, thus supporting our findings. Moreover, retigabine may prove to be useful in the treatment of a diverse range of disease states in which neuronal hyperexcitability is a common causative factor according to a stud.^[13] In addition, another research showed that retigabine had high efficacy and good tolerability in treating human adults with refractory partial seizures.^[9] Taken these studies together, retigabine has good potential in alleviating DNP.

CONCLUSIONS AND RECOMMENDATIONS

The findings of the present study together with the previous findings of animal studies using other models of chronic pain suggest that retigabine may alleviate hyperalgesia and allodynia associated with chronic pain conditions including diabetic neuropathy. However, further investigations are needed because of the small number of rats that were used

in the present experiments. It will also be interesting to see whether lower doses of retigabine would also alleviate pain hypersensitivity associated with DNP. These findings are not unexpected given that retigabine has recently been released to market for treatment of epilepsy which, like DNP, is characterized by neuronal hyperexcitability.

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Role of Multidetector Computed Tomography Scan in Evaluation of Neck Mass

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Abstract

Introduction: Neck masses are frequently encountered in general population and hospitals. It is important to differentiate a malignant neck lesion from a benign lesion. Early and precise diagnosis helps in choosing the line of management.

Aims and Objectives: To determine sensitivity and specificity of multidetector computed tomography (MDCT) scan in the differentiation of benign and malignant neck mass in comparison with histopathological diagnosis.

Materials and Methods: Hospital based observational prospective cross-sectional study was conducted in the Department of Radio diagnosis, Pt. JNM Medical College Raipur, and associated Dr. BR Ambedkar Hospital Raipur (C.G.) from January 2016 to September 2017 on 60 patients of all age who presented with neck mass. Contrast-enhanced scans using non-ionic contrast media (60–80 ml at the rate of 3 ml/s) were performed spirally.

Result: In our study, 60 patients of neck masses were included. MDCT was diagnosed 31 (51.7%) patient of neck mass as benign neck mass and 29 (48.3%) patient of neck mass as malignant, however, on histopathology 29 (48.3%) patient of neck mass were diagnosed as a benign and 31 (51.7%) patient of neck mass were diagnosed as a malignant. Sensitivity, specificity, positive predictive value, and negative predictive value of MDCT scan to differentiation between benign and malignant neck mass in comparison with histopathology was 90.32%, 96.55%, 96.55%, and 90.32%, respectively. Significant association was note between two diagnoses ($P < 0.0001$).

Conclusion: MDCT had high sensitivity and specificity in differentiation of benign versus malignant neck mass lesion which helps in the further planning of management of these lesions but requires histopathology for better management.

Key words: Benign neck masses, Malignant neck masses, Multidetector computed tomography

INTRODUCTION

Neck masses are frequently encountered in general population and hospitals. Neck masses are broadly divided into two groups - nodal masses and non-nodal masses. Nodal masses may be neoplastic or reactive in nature. Non-nodal masses include congenital, inflammatory, neural, neoplastic, vascular, and mesenchymal origin.

It is important to differentiate a malignant neck lesion from a benign lesion. Early and precise diagnosis helps in choosing the line of management (surgical/conservative) depending on the type of lesion and location which help in reducing the morbidity and mortality. Hence, the imaging modality that we use should have high sensitivity and specificity.

Clinical examination alone is limited in its ability to accurately assess the extent and size of head and neck tumors, especially or submucosal extension of disease and extent of nodal metastasis.^[1]

Plain radiography and ultrasonography are initial imaging modalities, but they have their own limitations.

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Recent studies have reported that advances in cross-sectional imaging now allow detailed evaluation of anatomy and pathology of the neck.^[2] Nowadays computed tomography (CT) is very important diagnostic imaging modality performed in patients in whom the presence of a head and neck mass is either evident or suspected.^[3]

CT has found an increasing application in the evaluation of neck masses both congenital and acquired, and is currently one of the most powerful and versatile imaging procedures for the evaluation of neck masses.^[4] Multislice spiral CT provides volumetric helical data, thereby permitting optimal multiplanar and three-dimensional reconstructions and isotropic imaging rapid scan acquisition reduces motion artifacts, as well as permits phonation studies. Imaging during phonation and/or Valsalva maneuver to assess vocal cord mobility in pathologies involves hypopharynx and larynx.

CT provides critical anatomical information about lesions involving the neck. It is also important to define the site of origin, extent and characterization of the lesion on contrast administration it helps in differentiation between benign and malignant neck mass. In malignant lesions, CT can determine the extent of the disease allowing accurate planning for surgery and radiation ports.

This study is an effort to assess the role of multidetector CT (MDCT) to the differentiation between benign and malignant neck mass and thus helps in deciding further course of management.

MATERIALS AND METHODS

Hospital based observational prospective study with cross-sectional data collection was conducted in the Department of Radio diagnosis, Pt. JNM Medical College Raipur and associated Dr. BR Ambedkar Hospital, Raipur (C.G.), after taking clearance from ethical committee from January 2016 to September 2017 on 60 patients of all age who presented with neck mass. In our study patient having complains of neck mass and incidentally diagnose neck mass on MDCT scan was included. Patient unwilling to take part in the study, pregnant women, patient with deranged renal function test, patient with neck masses on radiotherapy and post-operative patient of neck masses was excluded. Informed written consent was taken. The patient was kept on empty stomach for 4–6 h before performing the scan and check for renal function test. Supine with the neck mildly hyperextended so that the palate was roughly perpendicular to the tabletop. When possible patients were scanned with quiet breathing and swallowing suspended using SIEMENS SOMATOM 128-slice single source definition AS + MDCT and non-ionic contrast media (60–80 ml at the rate of 3 ml/s) contrast-enhanced scans

were performed spirally. Scanning covered the region from the base of the skull to the 4th thoracic vertebra using 2-mm section thickness and 1 mm increment. Tube voltage was approximately 120 kV, and tube current was approximately 150 mAs/slice.

Statistical Methods

Fischer's exact test or Chi-square test was used to analyze the significance of the difference between frequency distribution of the data. Student's *t*-test was used to compare between two categorical variables. $P < 0.05$ was considered as a statistically significant.

RESULT

The number of patients included in this study was 60. Histopathological analysis of these lesions revealed 29 (48.3%) benign lesions and 31 (51.7%) malignant lesions.

Our study included 60 patients of all age. The peak age incidence of breast mass lesion was 50–60 years and overall male to female ratio were 1.6:1.

In our study, neck swelling (90%) was most common clinical complaint. In our study, out of 60 patient there was 16 (36.36%) patient had nodal masses and 44 (73.33%) had non-nodal masses. Out of 16 nodal masses, there were 10 (62.5%) metastatic nodal masses, 5 (31.25%) lymphomas, 1 (6%) tubercular lymphadenopathy, and 1 (6%) were other. In our study mean maximum short axis diameter for metastatic nodal masses 5.11 cm, for nodal masses of lymphomas 3.11 cm and tubercular nodal masses 1 cm.

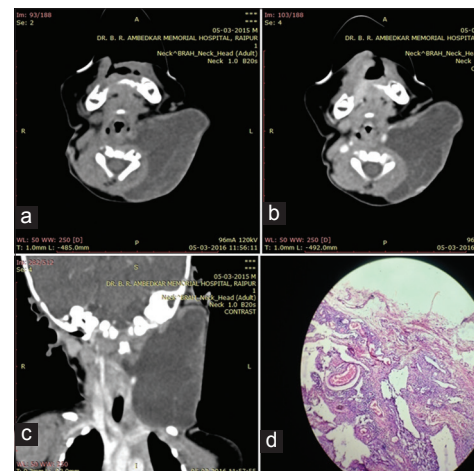


Figure 1: Case 1 - Cystic Hygroma: 6-month-old baby came with complaint of left side neck swelling. (3a) Axial non contrast image shows well defined cystic lesion. (3b and c) Axial and coronal post-contrast image shows nonenhancing well defined cystic lesion with maintain fat plane with surrounding structure. Computed tomography final diagnosis was benign cystic lesion likely cystic hygroma. (3d) H and E (x10) stain section shows large irregular vascular space lined by flattened epithelial cell

In all nodal masses, 75% was multiple and 25% was single. In present study, 11 (78.57%) malignant and 1 (50%) benign nodal masses shows necrosis, 11 (78.57%) malignant and all benign nodal masses shows heterogeneous enhancement and 3 (21.42%) malignant nodal masses shows homogeneous enhancement, 11 (78.57%) malignant and 1 (50%) benign nodal masses shows extra capsular spread, and 10 (71.42%) malignant and 1 (50%) benign nodal masses shows loss of fat plane with adjacent structure.

In our study out of 60 patients, 44 patients have non-nodal mass.

In the present study, all benign and 2 malignant non-nodal masses had well define border, 15 (88.23%) malignant non-nodal masses had ill-defined border and ill-defined border not found in benign non-nodal masses. All cystic non-nodal masses were benign.

In our study one benign lesion was hyperdense on plain CT, 9 (33.33%) benign and 12 (70.58%) malignant non-nodal masses were heterogeneous on plain CT, one benign lesion shows homogenous enhancement, 10 (37.03%) benign and 16 (94.11%) malignant non-nodal masses had heterogeneous enhancement, all nonenhancing non-nodal lesions were benign, 6 (22.22%) benign, and 1 (5.88%) malignant non-nodal masses shows peripheral enhancement.

In present study 7 (25.92%) benign and 14 (82.35%) malignant non-nodal masses had necrosis 14 (82.35%)

malignant non-nodal masses had infiltration of the adjacent structure [Figures 1 and 2].

In our study, 60 patients of neck masses were included. MDCT was diagnosed 31 (51.7%) patient of neck mass as benign neck mass and 29 (48.3%) patient of neck mass as malignant, however, on histopathology 29 (48.3%) patient of neck mass were diagnosed as a benign and 31 (51.7%) patient of neck mass as a malignant.

Sensitivity, specificity, positive predictive value, and negative predictive value of MDCT scan to differentiation between benign and malignant neck mass in comparison with histopathology were 90.32%, 96.55%, 96.55%, and 90.32%, respectively. Association of histopathological diagnosis with diagnosis on CT scan was analyzed using Chi-square test. Significant association was note between two diagnoses ($P < 0.0001$).

DISCUSSION

Imaging plays a major role in diagnosis and planning treatment of patients with neck masses. The radiologist must have a thorough knowledge of the modalities and techniques available to select the most efficient imaging protocol to solve the diagnostic problem. According to James Haynes *et al.*, contrast enhanced CT (CECT) is the initial diagnostic test of choice in adult neck masses.

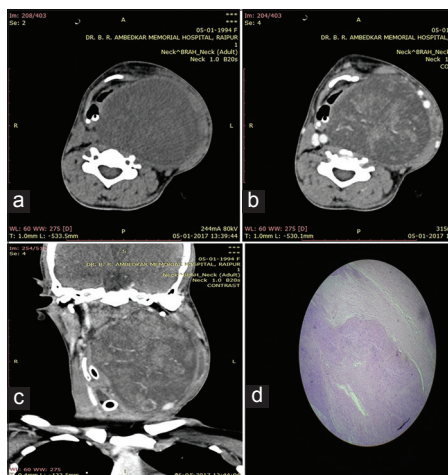


Figure 2: Schwannoma: Case - 2 23-year-old female came with complaint of left side neck swelling and difficulty in breathing. (4a) Axial non contrast image shows well defined heterogeneous noted in the left side of neck. (4b and c) Axial and coronal post-contrast image shows well defined heterogeneously enhancing lesion with maintain fat plain with surrounding structure. Computed tomography final diagnosis is benign lesion likely peripheral nerve sheath tumor. (4d) H and E stain (x4) shows alternative band of Antoni A and Antoni B area composed of spindle cell

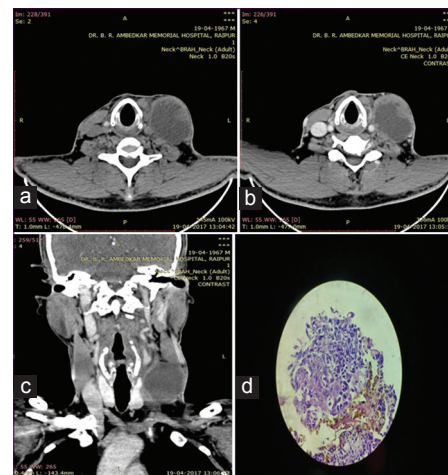


Figure 3: Case - 3 metastatic squamous cell carcinoma: 50-year-old male came with complaint of the left side neck swelling. (5a) Axial plain image shows rounded heterogeneously hypodense lesion noted at Left III and IV level. (5b and c) Axial and coronal post-contrast image shows rounded heterogeneously enhancing lesion with central area of necrosis with infiltration of sternocleidomastoid muscle noted in Left III and IV level. Computed tomography final diagnosis was malignant nodal mass. (5d) H and E (x10) stain section shows solid sheet of malignant cell which is pleomorphic, having high N: C ratio and coarse chromatin

In our study, 60 patients with clinically palpable neck masses were evaluated using CECT and the masses divided in two broad category-nodal neck masses and non-nodal neck masses.

Nodal masses were evaluated in term of size, shapes, numbers, necrosis, enhancement pattern, extracapsular spread, and fat plane with an adjacent structure.

Non-nodal masses were evaluated in term of margins (well-defined and ill-defined), plain CT appearances of masses (cystic, hypodense, hyperdense, isodense, and heterogeneous), enhancement pattern (homogeneous, heterogeneous, nonenhancing, and peripheral enhancement), necrosis, infiltration, and calcification.

In our study, 60 patients were included of all age. Maximum numbers of patients were age group 50–60 years that is 13 patients out of the 60.

Out of the 60 patients were included in the study, 37 (61.6%) were males and 23 (38.33%) were females. The overall male to female ratio was 1.6:1.

In our study, neck swelling was most common clinical complaint. Out of 60 patients, 54 (90%) having neck swelling and other clinical complains includes pain (23.33%), dysphagia (6%), fever (6%), and dyspnea (3.33%). Many patients had more than one complaint.

Most common neck masses in our study were non-nodal neck masses. In our study out of 60 patient, there was 16 (36.36%) patient had nodal masses and 44 (73.33%) had non-nodal masses.

Out of 16 nodal masses, there were 10 (62.5%) metastatic nodal masses, 5 (31.25%) lymphomas, 1 (6%) tubercular lymphadenopathy, and 1 (6%) were other.

In our study, all nodal masses have maximum short axis diameter more than >8–9 mm for Level II and >7–8 mm for rest of neck. With mean maximum short axis diameter for metastatic nodal masses 5.11 cm, for nodal masses of lymphomas 3.11 cm and for tubercular nodal masses 1 cm. Van den Brekel *et al.* suggested a minimal axial diameter of 8–9 mm in Level II and 7–8 mm for the rest of neck.^[5]

All malignant nodal masses (metastatic and lymphomas) were spherical in shape, however, in benign one was oval/bean shape and one was a spherical shape.

In all nodal masses, 75% was multiple and 25% was single [Table 1].

10 (100%) out of 10 metastatic nodal masses, 1 (25%) out of 4 nodal masses of lymphoma, and 1 (50%) out of 2 benign nodal masses were shows necrosis [Table 1].

In our study, all metastatic nodal masses, all benign nodal masses and 25% of nodal masses of lymphoma shows heterogeneous enhancement, however, 75% nodal masses of lymphoma were shown homogeneous enhancement [Table 1].

In our study 9 out of 10 metastatic nodal masses, 2 out of 4 nodal masses of lymphoma and 1 out of benign nodal masses were shows extracapsular spread. 8 out of 10 metastatic nodal mass, 2 out of 4 nodal mass of lymphoma

Table 1: MDCT characteristics of various nodal masses

Characteristics	Number of cases (%)				
	Metastatic (n=10)	Lymphoma (n=4)	Tubercular (n=1)	Other (n=1)	Total (n=16)
Size					
>8–9 mm for Level II and >7–8 mm for rest of neck	10 (100)	4 (100)	1 (100)	1 (100)	16 (100)
<8–9 mm for Level II and <7–8 mm for rest of neck	-	-	-	-	-
Shape					
Spherical	10 (100)	4 (100)		1 (100)	15 (93.75)
Oval/bean shape			1 (100)		
Number					
Single	4 (40)	-			4 (25)
Multiple	6 (60)	4 (100)	1 (100)	1 (100)	12 (75)
Necrosis	10 (100)	1 (25)	-	1 (100)	12 (75)
Enhancement					
Homogeneous	-	3 (75)	-		3 (18.75)
Heterogeneous	10 (100)	1 (25)	1 (100)	1 (100)	13 (81.25)
Peripheral	-	-			
Extracapsular extension	9 (90)	2 (50)	-	1 (100)	12 (75)
Loss of fat plane with adjacent structure	8 (80)	2 (50)	-	1 (100)	11 (68.75)

MDCT: Multidetector computed tomography

and 1 out of benign nodal masses were shows loss of fat plane with adjacent structure [Table 1 and Figure 3].

In our study out of 60 patients, 44 patients have non-nodal mass. Out of 44 patients, non-nodal mass of 29 patients had well-defined border in which non-nodal mass of 27 patients appears as benign and non-nodal masses of 2 patients appears as malignant on histopathology. Hence, well-defined border more common in benign lesion but can occurs in malignant lesion [Table 2].

15 patients of non-nodal masses (out of 44) have ill-defined border. All 15 patients diagnosed as malignant on histopathology. In our study ill-defined border was only occurs in malignant lesion [Table 2].

13 out of 44 patients of non-nodal masses were purely cystic which appears benign on histopathology. In our study, purely cystic lesion was benign [Table 2].

On plain scan, one hyperdense lesion was found in our study which diagnosed as benign on post-operative follow-up. Hence, hyperdense lesion on plain scans more likely benign [Table 2].

21 non-nodal masses (out of 44) were appears heterogeneous in density on plain CT. On histopathology, 9 were appears benign and 12 were appears malignant. Hence, heterogeneous lesion on plain CT can be benign or malignant [Table 2].

There was one homogeneously enhancing non-nodal mass lesion noted in CECT (out of 44) which was diagnosed as a fusiform aneurysm on digital subtraction angiography [Table 2].

Out of 44 non-nodal neck masses 26 were appears heterogeneous on CECT neck. On histology 10 non-nodal neck masses diagnose as a benign and 16 non-nodal neck masses diagnose as a malignant [Table 2].

10 non-nodal neck masses (out of 44) were nonenhancing on CECT neck. On histopathology, all nonenhancing lesions were diagnosed as a benign. Hence, nonenhancing lesions were more likely benign [Table 2].

There were peripheral enhancements seen in 7 non-nodal neck masses in which 6 diagnosed as benign and 1 diagnosed as a malignant on histopathology [Table 2].

Out of 44 non-nodal neck masses, 21 were shows necrosis on CECT neck in which 7 was diagnose as a benign and 14 was diagnose as a malignant on histopathology. Necrosis was more common in malignant lesion but can also occur in benign [Table 2].

14 non-nodal masses neck (out of 44) was shows infiltration of adjacent structure in which all non-nodal masses of neck were diagnosed as a malignant on histopathology [Table 2].

In our study, 60 patients of neck masses were included. MDCT was diagnosed 31 (51.7%) patient of neck mass as benign neck mass and 29 (48.3%) patient of neck mass as malignant, however, on histopathology 29 (48.3%) patient of neck mass were diagnosed as a benign and 31 (51.7%) patient of neck mass as a malignant [Table 3].

In correlation with histopathology, MDCT was wrongly diagnosed 3 patients as a benign which was diagnosed as a malignant on histopathology and 1 patient as malignant which was diagnosed as a benign on histopathology.

Table 2: MDCT characteristic of non-nodal mass

Characteristics	Benign*	Malignant*	Total
	Number of case n-27 (%)	Number of case n-17 (%)	Number of case n-44 (%)
Margin			
Well defined	27 (100)	2 (11.7)	29 (65.90)
Ill defined	0 (0)	15 (88.23)	15 (34.09)
Density on plain CT			
Cystic	13 (48.14)	0 (0)	13 (29.54)
Hyperdense	1 (3.7)	0 (0)	1 (2.27)
Hypodense	4 (14.81)	6 (35.29)	10 (22.7)
Isodense	0 (0)	0 (0)	0 (0)
Heterogeneous	9 (33.33)	12 (70.58)	21 (47.72)
Enhancement			
Homogeneous	1 (3.70)	0 (0)	1 (2.27)
Heterogeneous	10 (37.03)	16 (94.11)	26 (59.09)
Non-enhancement	10 (59.09)	0 (0)	10 (22.27)
Peripheral	6 (22.22)	1 (11.76)	7 (15.9)
Necrosis	7 (25.92)	14 (82.35)	21 (47.72)
Infiltration	0 (0)	14 (82.35)	14 (31.81)
Calcification	4 (14.81)	3 (17.6)	7 (15.90)

*Benign and malignant diagnosed on histopathology. MDCT: Multidetector computed tomography, CT: Computed tomography

Table 3: Diagnostic significance of MDCT scan for benign and malignant neck mass

CT diagnosis	Histopathology diagnosis		Total
	Benign	Malignant	
Benign	28 90.3%	3 9.7%	31 100.0%
Malignant	1 3.4%	28 96.6%	29 100.0%
Total	29 48.3%	31 51.7%	60 100.0%

MDCT: Multidetector computed tomography, CT: Computed tomography

Sensitivity, specificity, positive predictive value, and negative predictive value of MDCT scan to differentiation between benign and malignant neck mass in comparison with histopathology were 90.32%, 96.55%, 96.55%, and 90.32%, respectively. Association of histopathological diagnosis with diagnosis on CT scan was analyzed using Chi-square test. Significant association was noted between two diagnoses ($P < 0.0001$).

Sensitivity, specificity, positive predictive value, and negative predictive value of our study were high, however, less than to the previous study. This may be due to low sample size and variability in duration of lesion when CT was done as compared to the previous study.

Previous study results show:

Gupta *et al.*, 45 patients with neck masses were prospectively evaluated using multislice spiral CT. The accuracy of multislice CT for predicting the benign or malignant nature of the mass, and its extent was found to be very high, i.e., 97%, and 100%, respectively, and the accuracy for predicting the final diagnosis was 62%.^[4]

Shrestha *et al.*, this was a hospital-based, prospective study conducted in the Department of Radio diagnosis, Kasturba Medical College, Mangalore, from 2005 to 2008. A hundred consecutive patients referred for CT scan examination presenting with complaints related to the involvement of neck spaces or presence of palpable neck masses was enrolled in this study considering histopathology as the gold standard, the sensitivity of CT in detecting malignant/benign lesions

was 96.5% with a specificity of 100%. The positive predictive value was 100% and the negative predictive value 95.2%.^[6]

Charan *et al.*, an observational prospective study was conducted in 100 patients with clinically suspected neck lesions or patients who were referred for CT scan for further characterization. The sensitivity and specificity of the study are 95.7% and 77.5%, respectively, with positive predictive value and negative predictive value of 90.4% and 88.9%, respectively. Accuracy was found to be 90% ($P < 0.001$).^[7]

Ravi 100 patients with neck masses were evaluated using MDCT. Non-contrast and contrast enhanced CT examination of all the patients was carried out. Thus, the accuracy of the newer multislice CT for predicting the benign or malignant nature of the mass and local extent of the mass lesion was found to be very high, i.e., 98% and 100%, respectively. However, CT was 76% accurate in predicting the final pathological diagnosis.^[8]

CONCLUSION

MDCT had high sensitivity and specificity in the differentiation of benign versus malignant neck mass lesion which helps in the further planning of management of these lesions but requires histopathology for better management.

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A Clinical Study on Quality of Life Instrument Used in Assessing Adolescents with Chronic Bronchial Asthma

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Abstract

Aim of the Study: The aim of the study was to study the quality of life (QOL) using an instrument “Pediatrics QOL questionnaire” in adolescents with bronchial asthma.

Materials and Methods: A total of 76 adolescents undergoing treatment for bronchial asthma were assessed of their QOL. A similar number of normal adolescents were used as control group. All the data were collected using “Pediatrics QOL questionnaire” from the children and their parents/guardians who had taken care of the child for at least 6 months using standard prescribed treatment by physicians.

Results and Discussion: A total of 152 children including 76 asthmatics and 76 normal children were included in the study. All the children were assessed using QOL instrument on four domains of QOL: Physical, emotional, social, and educational. The children with asthma had a more compromised QOL in the physical domain.

Conclusions: Children with chronic diseases have a relatively compromised QOL and focusing simply on control of primary illness may not address the full range of child's emotional and behavioral difficulties. Multidisciplinary team management is essential in achieving an improved QOL and patient satisfaction.

Key words: Adolescents, Bronchial asthma, Instruments for quality of life, Quality of life

INTRODUCTION

The term “quality of life” (QOL) is used to refer the individuals' subjective satisfaction with important aspects of life, physical and mental well-being, social relationships, social and individual activities, individual satisfaction, and health maintenance.^[1] One of the QOL-related components is the health-related QOL (HRQOL). It is based on the definition provided by the World Health Organization (WHO). The constitution of the WHO (1946) states that: “Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.”^[2] Recent studies showed the relationship between

the specific effects of the pediatric chronic disease in children and QOL. Children and adolescents with chronic disease will often have a lower QOL as seen in Duchenne Muscular Dystrophy,^[3] asthma,^[4] and heart disease.^[5-7] Bronchial asthma is the most common respiratory crisis encountered in pediatric clinical practice. Children and adolescents with asthma are troubled not only by symptoms such as shortness of breath, cough and wheeze but also by the physical, social, educational, and emotional impairments that they experience as a result of having asthma.^[8] The WHO has estimated that 16 million disability-adjusted life years are lost annually due to asthma, representing 1% of the total global disease burden. It is a public health problem not just for high-income countries; it occurs in all countries regardless of the level of development.^[9] Pediatric asthma accounts for a large proportion of childhood hospitalizations, health-care visits, absenteeism from daycare/school and missed work days by parents.^[10] Chronic Illnesses cause stigma, a loss of self-esteem and family strain. Various studies have shown that asthma caused adolescents and children to feel self-pity,

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poor self-opinion, poor peer relations, and social isolation. It also leads to anxiety and strain in caregivers of asthma patients.^[11] Thus, direct assessment of QOL is necessary to understand the impact of the disease on patient's well-being as well the effect of treatment undertaken. It cannot be assumed that similar relationships to QOL seen in adults with asthma will hold true for adolescents.^[12] In asthma, there are several reasons to examine adolescents as a unique group distinct from young children and adults.^[13] There are very few studies which have focused on adolescents. The present study is an attempt to understand the impact of bronchial asthma on the QOL of adolescents based on a clinical study in a tertiary teaching hospital of Kerala.

Type of the Study

This was a prospective, cross-sectional comparative clinical study.

Institute of Study

This study was conducted at KMCT Medical College Teaching Hospital.

Period of Study

This study was from February 2014 to January 2017.

MATERIALS AND METHODS

The study was conducted in a tertiary teaching hospital of Kerala among the adolescent children attending the pediatric outpatient department (OPD) with complaints of chronic bronchial asthma. An Ethical Committee Clearance was obtained before the commencement of the study. An Ethical Committee approved consent letter was used during the study. 76 adolescent children were clinically assessed using the answers to the QOL questionnaires filled up by the parents and/or guardians.

Inclusion Criteria

1. Adolescent children suffering from chronic bronchial asthma for more than 6 months duration were included.
2. Adolescents who are under treatment for chronic bronchial asthma were included.
3. Parents and or guardians who are taking care of the adolescents were included in giving the answers to the QOL questionnaire.

Exclusion Criteria

1. Coexisting other chronic or severe acute diseases.
2. Parents who are unable to understand and answer the pediatric QOL questionnaires.
3. Adolescents with developmental retardation.
4. Adolescents hospitalized for acute attacks of bronchial asthma in the last 1 month affecting adversely QOL index.

76 adolescent children who were attending the pediatric OPD for minor illnesses were included as a control group. The socioeconomic status was graded using the Modified Kuppaswamy scale, modified for the current cost inflation index. The population was composed of two groups: Group A – Adolescents aged 9–18 years of age, known bronchial asthmatics on treatment. Group B – Normal adolescents aged 8–18 years having no chronic disease served as controls.

Instrument Used

Pediatric QOL inventory, version 4.0 was used for the study.^[6] It is based on a modular approach to measure HRQOL in children and teenagers over a wide age range. The instrument was translated into vernacular by a linguistic expert. The instrument had two parts: (1) Parent form and (2) child form: Each consisting of 23 questions. It was a generic instrument that included a broad spectrum of child and family-focused health areas divided into four domains. These were physical, emotional, social, and educational domains, each having further subdivisions. The standard recall period was past 1 month. The responses were measured on a 5-point rating score from never to almost always. The items of the four scales were grouped together on the actual questionnaire for ease of creating scale scores. To create scale scores, the mean was computed as the sum of the items over the number of the items answered. If more than 50% of the items in the scale were missing, the scale score was not computed. The total score was computed as the sum of all the items over the number of items answered on all the scales. All the data were analyzed using standard statistical methods.

OBSERVATIONS AND RESULTS

Among the 76 adolescent children in Group A, there were 49 (64.47%) males and 27 (35.52%) were females with a male to female ratio of 1.81:1. In Group B the males were 50 (68.42%) and females were 26 (31.57%) with a male to female ratio of 1.92. In Group A children aged 8–12 were 43 (56.57%) and aged 13 to 18 were 33 (43.42%). In Group B children aged 8 to 12 were 45 (9.21%) and aged 13 to 18 were 31 (40.78%). In Group A the mean age was 9.18 ± 2.6 and in Group B the mean age was 9.34 ± 2.3 . In Group A the children belonging to urban residential areas 53 (69.73%) and rural areas were 23 (30.26%). In Group B the children belonging to urban residential areas 51 (66.10%) and rural areas were 25 (32.89%). In Group A children belonging to upper socioeconomic class were 21 (27.63%), middle group were 27 (35.2%), and lower group were 28 (36.84%). In Group B children belonging to upper socioeconomic class were 25 (32.89%), middle group were 26 (34.21%), and lower group were 25 (32.89%). The demographic data of bronchial asthma

and control group were matching and significant statistically with $P < 0.05$ (P taken as significant at <0.05) in variables related to gender incidence in females, rural incidence and socioeconomic groups [Table 1].

The mean parent and child scores for bronchial asthma and normal children were calculated and tabulated in Table 2. Asthmatic children experienced a poor QOL in all four domains with maximum affect on physical and emotional domains. Parents of asthmatic children had also reported significantly lower scores in all domains especially physical, emotional, and educational domain as well as parent total score. The scores were relatively lower in children aged 13–18 years when compared to 8–12 years age group. QOL of children as reported by parents was significantly impaired with higher daytime or nighttime frequency especially in the physical domain. Each domain had a significant contribution to total parent and child score [Table 3]. In bronchial asthma, physical domain had greatest contribution to total score in the parent as well as child scores. There was no significant correlation between age at onset, duration of illness or family history with QOL in any domain except for the negative impact of family history on parent score in social and educational domains in bronchial asthma children. Although the mode of treatment, i.e., inhaled bronchodilator or steroids or oral medication had no significant difference in asthma children and the control group.

Each domain had a significant contribution to total parent and child score [Table 3]. In asthma, physical domain had greatest contribution to total score in parent as well as child scores when compared to the control group.

DISCUSSION

HRQOL was introduced to modern medicine to assess and evaluate the QOL in patients following treatment to various diseases. Spirits of life and therapy are not separate from physical health. A QOL perspective can identify sensitive child and adolescent issues that may be affected by illness or disability of treatment.^[14,15] Various studies have confirmed that chronic morbidities are high-risk factors for poor psychosocial outcomes; low self-esteem, behavioral problems, and academic difficulties.^[16,17] Among the many indices developed for measurements of QOL are all in adults; those for children are still in developing stage. As the present study is a small, no new instrument of measurement of QOL was introduced in this paper but an instrument bused by Marino *et al.*^[6] was used. In the present study, the QOL in children with bronchial asthma was studied and compared with a normal control group of adolescents. The two groups were compared on

four dimensions of QOL: Physical, emotional, social, and educational. It was observed that in this study asthmatic children had significantly lower scores in all the domains as well as total child score. Parents of asthmatics also reported a poor QOL in all the domains, especially physical, emotional, and educational domains. Varni *et al.*^[18] in their study showed low scores in the physical, emotional, and educational domains, while having relatively better scores in social domain in adolescents with asthma. When compared to normal children also they found the significantly lower score in all domains. Fuhlbrigge *et al.*^[19] observed that bronchial asthma has potential interference with society in terms of QOL. Okelo *et al.*^[12] showed in their study more of emotional problems faced by adolescent asthmatics than other variables. Asthmatic children had a poor QOL in comparison to normal children in all the domains, with physical, emotional, and

Table 1: The demographic data (Group A and B; n=76)

Variables	Age groups	B. asthma (%)	Controls (%)	P
Age (years)	8–12	43	45	0.321
	13–18	33	31	0.368
	Mean±SD	9.18±2.6	9.34±2.3	
Gender	Male	49 (64.47)	50 (68.42)	0.641
	Female	29 (35.52)	26 (31.57)	0.029
Residence	Urban	53 (69.73)	51 (66.10)	0.186
	Rural	23 (39.73)	25 (32.89)	0.047
Socioeconomic groups	Upper class	21 (27.63)	25 (32.89)	0.024
	Middle class	27 (35.2)	26 (34.21)	0.041
	Lower class	28 (36.84)	25 (32.89)	0.031

SD: Standard deviation, B. asthma: Bronchial asthma

Table 2: The mean parent and child score for bronchial asthma and normal children

Variable	Asthma group		Normal group	
	Parent domain	Child domain	Parent domain	Child domain
Physical	64.2–15.2	68.0–11.3	83.2–11.4	89.1–9.4
Emotional	63.1–15.7	70.2–13.1	81.6–12.5	87.3–10.9
Social	79.2–19.2	84.3–13.6	88.2–12.4	90.8–10.4
Education	66.5–17.1	72.0–12.8	79.4–13.5	81.4–11.8
Total score	68.6–13.7	71.4–10.5	85.1–9.2	86.5–9.4

Table 3: The contribution of parent and child domain scores to total score

Quality of life domain	Control group		Asthma group	
	Parent domain	Child domain	Parent domain	Child domain
Physical	0.453	0.416	0.448	0.466
Emotional	0.282	0.319	0.276	0.290
Social	0.253	0.233	0.280	0.293
Education	0.341	0.337	0.250	0.285

educational domain affected more than social. Rydstrom *et al.*^[20] identified that asthmatic children have significant impairment in physical and emotional domains. Austin *et al.*^[21] observed that adolescents with asthma had a more compromised QOL in the physical domain. When compared to gender predilection to affection of QOL in diseases, it was reported that females were more disturbed than males in adults. But studies to compare the gender predilection in children are not readily available.^[22] The present study was found to be in concurrence with the study by Felder-Puig *et al.*^[22] In a similar study by Zandieh *et al.*^[23] they found HRQOL in boys were more disturbed than girls and also in caregivers of male asthmatic patients than caregivers of female asthmatic patients. Socioeconomic class had significantly affected parent physical score in asthma children. It could be due to lack of resources for regular treatment, financial stress or lack of awareness to utilize health-care services. The increased frequency of symptoms (daytime or nighttime) had significantly lowered QOL especially in parent physical domain, child physical, emotional, and education domain score as well as child total score. The daytime frequency had an inverse correlation with child physical domain and parent emotional domain score. However, duration of current episode had no significant correlation with child outcome of QOL. Mode of treatment (inhaled steroid, bronchodilator, or oral medication) had no significant impact on parent and child score in asthmatic group in any domain. This can be due to double impact of severity of disease requiring multidrug therapy and the side effects of the drugs. It remains a challenge to the pediatrician treating children with chronic disorders to improve the QOL and not his disorder. It remains difficult to assess the QOL of the using the pediatric instruments available. Even extensive interviews and physical examination and additional clinical tests may not be sufficient to assess the impact a chronic disorder results in affecting the child's well-being. A multi-disciplinary approach only can assist in the holistic care and assessment of the child and its family. A change of attitude from pediatricians is always required, toward measurement of functional status and subjective perception of illness, as well as to evaluate the HRQOL.

CONCLUSIONS

To optimize the health care in the management of childhood chronic disorders, instruments of quality of health should be used by the pediatricians to evaluate the impact of chronic disorder on all aspects of a child's functioning in daily life. The assessment should also assess the limitations which are relevant to the child as these interfere in his daily life. Regular counseling sessions and encouragement should be undertaken during their follow-up visits. Recognizing the high risks of chronic diseases

and an approach of multidisciplinary team management of children will result in significant improvement in the quality of life and ultimately patient satisfaction.

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A Clinical Study of Dilated Cardiomyopathy With Correlation to Electrocardiography and Echocardiography: A Cross Sectional Study

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Abstract

Introduction: Cardiomyopathy is a primary disorder of the heart muscle with abnormal myocardial performance. It is an important cause of heart failure and accounts for up to 25% of all cases of heart failure. In view of the high prevalence of chronic heart failure due to underlying dilated cardiomyopathy (DCM) and the lack of data on DCM, this study was undertaken.

Materials and Methods: 1-year cross-sectional study was conducted on 30 cases of DCM from medical ward of Rajendra Institute of Medical Sciences, Ranchi. Cases were selected as per laid down inclusion and exclusion criteria and were evaluated clinically, hematologically, biochemically and by chest X-ray, electrocardiograph, and echocardiography.

Result: Majority of the patients was above the age of 60 years of with male to female ratio 1.3:1. Most common presentations were dyspnea, easy fatigability, and pedal edema. Other common presentations were a history of paroxysmal nocturnal dyspnea, cough, palpitation (56.6%) orthopnea (53.3%), chest pain (40%), abdominal pain (33.3%), and syncope (16.6%). Ectopic beats were seen in 53.3%, tachycardia in 46.6%, and atrial fibrillation in 13.3% of patients. Left bundle branch block was seen in 40% of subjects. Cardiomegaly was seen in all the patients on chest radiograph. The most common type of DCM was ischemic DCM comprising 33.3% of all cardiomyopathies followed by diabetic cardiomyopathy (23.3%) and peripartum cardiomyopathy (16.6%).

Conclusion: DCM is an important cause of heart failure affecting all age group and both sexes. It is commonly associated with ischemia DCM and commonly present as a biventricular failure.

Key words: Cardiomyopathy, Diabetic cardiomyopathy, Dilated cardiomyopathy, Ischemic cardiomyopathy

INTRODUCTION

Cardiomyopathy is a primary disorder of the heart muscle that causes abnormal myocardial performance and is not the result of disease dysfunction of other cardiac structures. It is distinctive because it is not the result of pericardial, valvular, hypertensive or congenital diseases.^[1]

Dilated cardiomyopathy (DCM) represents the final common pathway produced by a variety of ischemic, toxic, metabolic, and immunological mechanisms damaging the heart muscle. DCM is an important cause of heart failure and accounts for up to 25% of all cases of heart failure. The incidence of DCM is reported to be 5–8 cases per 100,000 population per year. It occurs 3 times more frequently in males as compared to females. It is also more common in blacks.^[2] The most common clinical presentation is heart failure, usually left ventricular (LV) failure. The patient can also present with symptoms secondary to arrhythmias, stroke, or sudden death.^[3]

In view of the high prevalence of chronic heart failure due to underlying DCM and the lack of data on DCM, this study was undertaken.

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Aims and Objectives

1. To study the clinical profile of patients with DCM.
2. To study the electrocardiographic and echocardiographic profile of these patients.

MATERIALS AND METHODS

A total of 30 cases of DCM were selected as per inclusion and exclusion criteria from medical ward of Rajendra Institute of Medical Sciences, Ranchi.

Study Design

This was a 1-year cross-sectional study.

Inclusion Criteria

Clinical criteria

Patients with symptoms and signs of heart failure were included in this study.

Echocardiography criteria

- LV ejection fraction <45%
- LV end-diastolic dimension >3 cm/body surface area
- Global hypokinesia
- Dilatation of all the chamber of heart were included in this study.

Exclusion Criteria

- Valvular heart disease
- Congenital heart disease.

A total of 30 patients were selected as per inclusion and exclusion criteria. Selected patients were evaluated clinically. Investigations done were complete blood count, random blood sugar, liver function test, kidney function test, thyroid function test, echocardiogram (ECG), Chest X-ray, echocardiography, and other relevant investigations pertinent to certain cases such as ischemic cardiomyopathy, diabetic cardiomyopathy, and alcoholic cardiomyopathy included coronary angiography and hemoglobin A1C.

OBSERVATIONS AND RESULTS

Demographic Profile [Table 1]

Majority of the patients were above the age of 60 years of which males comprised 56.60% and females comprising 43.25%. Among males the majority of cases were above the age of 60 years whereas in females there was clustering of cases among young adults and middle-aged population. Some female cases were below the age of 19 years.

Symptom Profile [Table 2]

All the patients presented with exertional dyspnea. Easy fatigability was seen in 83.3% of subjects constituting the second most common symptom followed by pedal edema

in 70% of patients. History of paroxysmal nocturnal dyspnea (PND) and cough was seen in 60% of subjects followed by palpitation (56.6%) orthopnea (53.3%), chest pain (40%), abdominal pain (33.3%), and syncope (16.6%).

Physical Signs [Table 3]

Basal crepitations were seen in 93.33% of the subjects. Pedal edema was present in 76.6%. Apical pansystolic murmur was present in 46.6% with LV systolic³ seen 46.6%. Pansystolic murmur in tricuspid area was seen in 10% while right ventricular (RV) S3 was seen 20% of our patients. Systolic blood pressure <100 mmHg was seen in 26.6% and one patient had stroke.

Abnormalities of Peripheral Pulse [Table 4]

Abnormalities of peripheral pulse included tachycardia, bradycardia, ectopic beats, atrial fibrillation, and pulsus alternans, ectopic beats were seen in 53.3%, tachycardia in 46.6%, and atrial fibrillation in 13.3% of patients. Bradycardia and pulsus alternans were seen in 3.3% of subjects.

Electrocardiographic Profile [Table 5]

The most common abnormality was ventricular ectopics seen in 46.6% of patients. Sinus tachycardia and left bundle branch blocks were seen in 40% of subjects. Right bundle branch block was observed in 13.3%. Non-specific ST-T changes were seen in 26.6% whereas atrial fibrillation was present in 13.3%. LV hypertrophy was seen in 20% and left atrial enlargement in 13.3% of subjects. Complete heart block was seen in only 1 patient (3.3%). The axis was normal in majority. Left axis deviation was seen in 13.3% and right axis deviation in 6.6%.

Chest Radiographic Profile [Table 6]

Cardiomegaly was seen in all the patients on chest radiograph. The cardiothoracic ratio was more than 0.7 in 13.3%, between 0.6 and 0.7 (moderate) in 40% and mild cardiomegaly, i.e. between 0.5 and 0.6 in 46.6% of subjects. Pulmonary plethora was seen in 53.3% while pleural effusion was seen in 20% of patients.

Echocardiographic Profile [Table 7]

The mean LV ejection fraction was 30.87%. The LV ejection fraction was <20% in 6% of patients. It was between 20 and 29% in 40%, between 30 and 39% in 36.6% of patients, and between 40 and 45% in 16.6% of patients. The mean LV end-diastolic diameter was 5.86 cm with majority, i.e., 53% of subjects having LV end-diastolic diameter more than 6 cm. The mean LV end-systolic diameter was 4.75 cm with majority of patients (66%) having end systolic diameter more than 5 cm. Global hypokinesia and dilatation of all four chambers were seen in all the patients. In our study 73.3% had mitral regurgitation, 10% had tricuspid regurgitation, and pericardial effusion was seen in 6% of patients.

Table 1: Demographic profile

Age group (years)	n (%)		
	Male	Female	Total
1–19	0 (0)	2 (6.65)	2 (6.65)
20–30	3 (10)	3 (10)	6 (20)
40–59	4 (13.3)	4 (13.3)	8 (26.6)
>60	10 (33.3)	4 (13.3)	14 (46.66)
Total	17 (56.33)	13 (43.25)	30 (100)

Table 2: Symptom profile

Symptoms	n (%)
Dyspnea	30 (100)
Palpitation	17 (56.6)
PND	18 (60)
Orthopnea	16 (53.3)
Chest pain	12 (40)
Pedal edema	21 (70)
Cough	18 (60)
Abdominal pain	10 (33.3)
Easy fatigability	25 (83.3)
Syncope	5 (16.6)
Asymptomatic	None (0)
Miscellaneous	7 (23.3)

PND: Paroxysmal nocturnal dyspnea

Table 3: Physical signs

Signs	n (%)
Basal crepitations	28 (93.33)
Raised JVP	22 (73.3)
Hepatomegaly	14 (46.6)
Pedal edema	23 (76.6)
LV S3	14 (46.6)
RV S3	6 (20)
Pan systolic murmur at apex (MR)	14 (46.6)
Pan systolic murmur in tricuspid area (TR)	3 (10)
SBP<100 mgHg	8 (26.6)
Focal neurological deficit	1 (3.3)

JVP: Jugular venous pressure, SBP: Systolic blood pressure, LV: Left ventricular, RV: Right ventricular

Table 4: Abnormalities of peripheral pulse

Pulse	n (%)
Tachycardia	14 (46.6)
Bradycardia	1 (3.3)
Atrial fibrillation	4 (13.3)
Ectopic beats	16 (53.3)
Pulsus alternans	1 (3.3)

NYHA Class [Table 8]

Majority of the patients were in NYHA Class III (33%) and Class IV (46%) group.

Heart Failure [Table 9]

Biventricular failure was seen in 80% of patients isolated LV failure was seen in 16.6% and RV failure in 3.3%.

Table 5: Electrocardiographic profile

Parameters	n (%)
QRS axis	
Normal	24 (80)
Left axis deviation	4 (13.8)
Right axis deviation	2 (6.6)
Arrhythmias	
Sinus tachycardia	12 (40)
Atrial ectopics	3 (10)
Atrial fibrillation	4 (13.3)
SVT	2 (6.6)
Ventricular ectopics	14 (46.6)
Ventricular tachycardia	1 (3.3)
Complete heart block	1 (3.3)
Left bundle branch block	12 (40)
Right bundle branch block	4 (13.3)
ST-T changes	8 (26.6)
Atrial enlargement	
LAE	4 (13.3)
RAE	2 (6.6)
Ventricular hypertrophy	
LVH	6 (20)
RVH	2 (6.6)
Both	1 (3.3)

SVT: Supraventricular tachycardia, LAE: Left atrial enlargement, RAE: Right atrial enlargement, LVH: Left ventricular hypertrophy, RVH: Right ventricular hypertrophy

Table 6: Chest radiographic profile

Cardiothoracic ratio (%)	n (%)
50–60	14 (46.6)
60–70	12 (40)
>70	4 (13.3)
Pleural effusion	6 (20)
Pulmonary plethora	16 (53.3)

Table 7: Echocardiographic profile

Parameter	Range (%)	n (%)
Ejection fraction	40–45	5 (16.6)
	30–39	11 (36.6)
	20–29	12 (40)
	< 20	2 (6.6)
LVEDD	4.5–49 cm	4 (13.3)
	5.0–5.9 cm	10 (33.3)
	> 6 cm	16 (53.3)
LVSD	3.5–4.0 cm	6 (20)
	4.0–4.9 cm	10 (33.33)
	> 5 cm	14 (46.6)
MR		21 (73.3)
TR		3 (10)
Pericardial effusion		2 (6.6)

MR: Mitral regurgitation, TR: Tricuspid regurgitation, LVEDD: Left ventricular end - diastolic diameter, LVESD: Left ventricular end - systolic diameter

Etiological distribution [Table 10]

The most common type of DCM was ischemic DCM comprising 33.3% of all cardiomyopathies followed by diabetic cardiomyopathy (23.3%) and peripartum cardiomyopathy (16.6%). Idiopathic DCM was seen in 13.3% of subjects while alcoholic cardiomyopathy was

Table 8: NYHA class

NYHA class	n (%)
Class I	1 (3.3)
Class II	5 (16.6)
Class III	10 (33.3)
Class IV	14 (46.6)

NYHA: New York Heart Association

Table 9: Heart failure

Compartment involved	n (%)
LVF	5 (16.6)
RVF	1 (3.3)
Biventricular	24 (80)

LVF: Left ventricular failure, RVF: Right ventricular failure

Table 10: Etiological distribution

Cardiomyopathy	n (%)
Ischemic	10 (33.3)
Idiopathic	4 (13.3)
Diabetic	7 (23.3)
Peripartum	5 (16.6)
Alcoholic	2 (6.6)
Miscellaneous	2 (6.6)

seen in 6.6%. Miscellaneous group included 1 case each of β -thalassemia intermedia and polymyositis.

DISCUSSION

The present study 30 patients were evaluated, and their clinical profile, electrocardiographic, echocardiographic profile and the incidence of DCM in relation to other types of cardiomyopathies in patients admitted in RIMS Ranchi recorded.

In our study, DCM was predominantly seen in the elderly population. Of the total 30 subjects, males comprised 56.6% and females 43.25% in males, DCM was most commonly seen in the elderly (mean age 56.88 ± 15.99 years). In females DCM was predominantly seen middle age (41.15 ± 20.19 years). In our study, the mean age was 52.9 ± 15.1 years in males and $51.3.9 \pm 17.7$ years in females.^[4] In another study, the mean age was 64.4 years in males and 55.5 years in females.^[5]

In our study, the most common type of DCM was ischemic DCM being present in 33.3% of our patients, followed by diabetic cardiomyopathy seen in 23.3%. Peripartum cardiomyopathy was the third most common type seen in 16.6% of patients while idiopathic and alcohol cardiomyopathy was seen in 13.3% and 6.6%, respectively. The miscellaneous group included 2 patients; one with β -thalassemia intermedia on long-term blood transfusion patient has polymyositis

associated with DCM. DCM is known to occur in up to 50% of patients with polymyositis. Hazebroek *et al.*^[6] worked on DCM and stated that in up to 50% cases, exact cause remains initially unknown; this condition is called idiopathic DCM. Improved diagnostic methods most notably the advancement in molecular and immunohistological biopsy techniques and genetic research have endorsed a new era in the diagnosis and classification of a patient with idiopathic DCM. These insights have led to novel etiology based treatment strategies and improved outcomes.

The most common presentation in our study was biventricular failure which was seen in 80% of cases. Isolated LV failure was seen in 16.6% of patients, most of these were ischemic DCM. Predominant RV failure was seen in one patient with alcohol cardiomyopathy. Majority of the patients were in NYHA Class IV (46.6%) and Class III (33.3%) while 16.6% were in NYHA Class II. Breathlessness was the most common symptom noticed in all patients. PND was seen in 18 patients (60%) while orthopnea was present in 16 patients (53.3%).

The QRS axis was normal in 80% of our subjects with left axis deviation in 13.6% and right axis deviation in 6.6% which were in concordance with all the other studies. Sinus tachycardia was the most consistent finding in the Ahmad *et al.* study being found in up to 69% of patients.^[4] Our study showed sinus tachycardia in 40% of patients. Other ECG parameters such as ventricular ectopic, LBBB, Atrial fibrillation, and atrial ectopic were comparable to those in all the other studies (Rihal *et al.*, 2005).^[7]

CONCLUSION

Dilate cardiomyopathy is an important cause of heart failure affecting all age group and both sexes but predominantly in an elderly male. It is commonly associated with ischemia DCM and diabetes mellitus. It commonly presents as a biventricular failure with III or IV NYHA class, sinus tachycardia and low ejection fraction echocardiographically.

List of abbreviation

ECG: Electrocardiography
DCM: Dilated cardiomyopathy
PND: Paroxymal nocturnal dyspnea
LV: Left Ventricle
RBS: Random blood sugar
RV: Right ventricle

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Correlation of Surface Landmarks Based Insertion Length of Right Subclavian Central Venous Catheter with Post Insertion Location of Catheter Tip

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Abstract

Background: Subclavian central venous catheterisation (CVC) is done in critically ill patients requiring long-term central venous access. There is no gold standard for evaluating depth of insertion for catheter. In this study we correlated desired length of central venous catheter based on surface landmarks.

Objectives: We conducted this study with two objectives, first is to estimate the appropriate insertion length of right subclavian central venous catheter using topographical measurements and other is to observe and quantitate the side effects which occur (if any) during central venous cannulation.

Materials and Methods: After obtaining informed written consent from the patient's relatives, fifty patient were enrolled for central venous catheterizations via the right subclavian vein (SCV). The infraclavicular approach was used. Topographical measurement based on surface landmarks (insertion point of the needle, through the ipsilateral clavicular notch to just below the insertion point of the second right costal cartilage to the manubriosternal joint) was performed by placing the catheter with its own curvature over the draped skin. The central venous catheter (CVCs) was inserted and secured to a depth determined topographically. The location of CVCs tip around the carina was observed on the post procedure chest X-ray.

Results: The average insertion length in male was 13.2 cm and in female was 11.9 cm. In 95.1% of female patients and 89.6% of male patients, the tip was at or above the level of carina (≤ 1 cm). It was considered correct if the tip was just above or at the level of the carina in the right-sided catheters.

Conclusion: It is concluded from the study that CVC insertion depth can be estimated using the topographical measurement with the CVCs itself. Moreover, this method requires no additional cost and/or time-consuming procedures.

Key words: Central venous catheter tip, Topographic method, Right subclavian central venous catheterisation

INTRODUCTION

Central venous catheterization (CVC) is common practice among surgeons, anesthesiologists, and emergency room physicians during the preparations for major surgical procedures such as open-heart surgery as well as for

intensive care monitoring and rapid restoration of blood volume. They provide long-term venous access.^[1]

Central venous lines are inserted through major veins such as the subclavian, internal jugular, or femoral veins. The safe and successful performance of a CVC requires a specific knowledge of anatomy in addition to a working knowledge.

The subclavian vein (SCV) has a caliber of 1–2 cm in adults and is thought to be held open by its surrounding tissues, even in severe circulatory collapse.^[2] This route may be preferred in trauma patients with a suspected cervical spine injury. This route is best avoided in patients requiring long-term renal replacement as there is a significant risk

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of venous stenosis, which causes problems for existing or future arteriovenous fistulae. It is also best to avoid in patients with abnormal clotting or bleeding diathesis. Serious, immediate complications are uncommon but occur more frequently than other routes. Pneumothorax is one of the most common major complications with an overall incidence of 1–2% this figure increases to 10% if multiple attempts are made. Extravasation injury may result from CVCs lying so proximal that one or more of the catheter openings lie outside the vessel lumen, but such incidence is non-lethal.

Various techniques have been developed to ensure correct placement of CVCs. Although X-ray or fluoroscopy is often used, while insertion with electrocardiographic guidance and echocardiography guided techniques are that may assure correct CVC tip position, but such confirmatory techniques are not used routinely.^[3]

Optimal positioning of the tip of a CVC is a complex and controversial subject. Misplacement of CVC tip can rarely cause erosion of the catheter through the right atrium (RA) or right ventricle, leading to haemothorax, hydrothorax, or cardiac tamponade and can be fatal. It is, hence, recommended to locate the tip in the superior vena cava, outside the pericardium to avoid cardiac tamponade.^[4] There is ongoing controversy as to whether CVC tips should always lie above the pericardial reflection.^[5] Cadaver studies^[6] and computerized tomography in adults have shown the carina to be above the level of pericardium. The pericardium cannot be seen on a chest X-ray that is routinely done to check the position of the catheter tip. However, carina can be easily identified on a chest X-ray and can be used as a reference point for optimal position of CVC tip. For CVC tips lying below the pericardial reflection, there is a small but potentially fatal risk of pericardial tamponade if the CVC tip erodes through the vessel wall. Other problems of catheter placement in the RA include arrhythmias, placement in the coronary sinus, and tricuspid valve damage. Vessel wall erosion also seen when the CVC tip lies above the pericardial reflection usually causing hydrothorax or hydromediastinum from the extravasated fluid, but this is less likely to have a fatal outcome.

The carina is a reliable landmark to guide appropriate and safe positioning of the CVC tip above the pericardial reflection and to minimize the risk of cardiac tamponade.^[7] The angle of Louis, the forward prominence formed by the manubriosternal joint is a surface anatomical landmark that shares the same horizontal plane with the tracheal carina.^[8]

The present study evaluates the ideal CVC tip position merely by the help of landmarks rather than by post-procedure of chest X-ray. It is cheap, easy, and avoids

unnecessary exposure to radiation. Post-procedural X-ray is done only to verify whether the landmark-guided catheter insertion leads to correct catheter tip positioning in superior vena cava or not. If it is below the carina level repositioning is done.

METHODS

This study is carried out in patients admitted to the Department of Surgery from January 2015 to December 2016 at N.S.C.B. Medical College, Jabalpur, In whom subclavian CVC was deemed necessary were recruited into the study after approval from Ethics Committee. Informed consent was obtained from the patient's relative. Patient is requiring emergency CVC insertion (shock), requiring emergency surgeries (perforation peritonitis and blunt trauma abdomen) were included in this study. Patient refusal, pediatric patient, child <18 years, pregnancy, systemic sepsis, deranged coagulation, local skin infection, connective tissue disorder, gross anatomical deformities of neck and chest (barrel chest and pigeon chest) were excluded from the study. The right SCV was cannulated using a Triple Lumen CVC set (Meditech™, Innovative Health Solution, New Delhi, India) as per the institutional protocol for CVC insertions.

After antiseptic skin preparation and sterile draping, CVC was performed with the Seldinger technique. Infraclavicular approach was used for SCV catheterization. After insertion of Guidewire, the patient's head and neck were placed in the neutral position.^[9] Earlier to determine the adequate depth for catheter insertion, we performed topographical measurement by placing the catheter naturally with its own curvature over the draped skin (without direct contact with the skin), starting from the insertion point of the needle through the ipsilateral clavicular notch to the insertion point of the second right costal cartilage to the manubriosternal joint [Figure 1]. The CVC was then inserted and secured to the depth determined topographically.^[10]

After the insertion of CVC, the position of CVC tip, in relation to the carina, was confirmed and measured by post-operative full inspiration chest radiograph (CXR). Results are divided into three groups - first CVC tips positioned above the carina level, second at the level of carina, and third group were those below the carina [Figure 2]. CVC tip beyond 0.5 cm below the carina was repositioned.

All the records are rechecked for their completeness and consistencies before collection. Nonnumeric entries are coded into nominal/ordinal distribution before analysis. Categorical variables are summarized in frequency and percent distribution and Chi-square or Fisher's exact

test is performed as appropriate. ANOVA is used for assessment of relative size of variance among group means. Continuous variable is analyzed using mean \pm standard deviation (SD) or median with interquartile range as appropriate. Matched test of analysis is performed to estimate the level of concordance. Statistical analysis is done with SPSS for window.

RESULTS

Table 1 shows number and percentage of males and females selected for the study among total participants. There were no catheterization failures during the study period.

Table 2 shows catheter tip position with respect to carina for all the participants. It shows number of times tip was below, at the level or above the carina.

Table 3 shows catheter tip position with respect to corresponding vertebral level for all the participants. It shows number of times tip was at 4th, 5th, or 6th vertebrae. In 80% cases, tip was at level of the 5th thoracic vertebra.

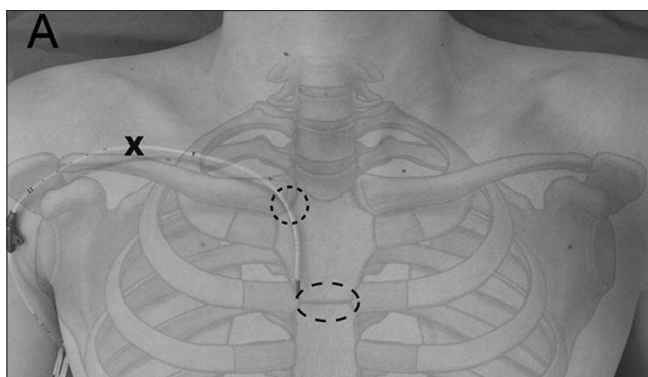


Figure 1: Topographical landmarks of subclavian vein

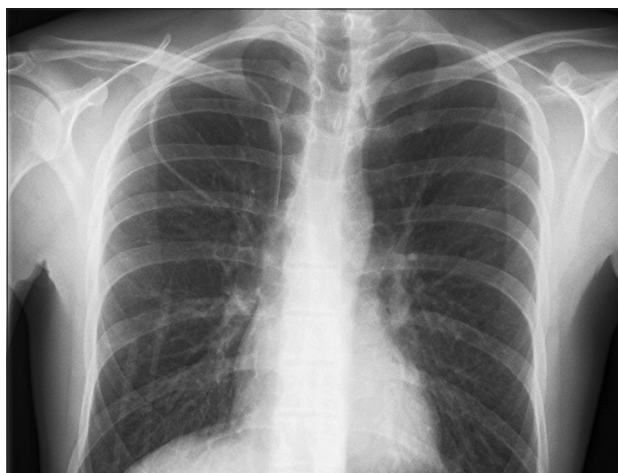


Figure 2: X-ray chest showing catheter and catheter tip

Table 4 shows catheter tip position with respect to corresponding intercostal space for all the participants. It shows number of times tip was at 4th, 5th, or 6th intercostal space. In 84% cases, tip was at the level of 5th intercostal space.

Table 5 shows mean topographical length and age of participants with standard deviation. Where mean value of age is 37.84 ± 11.456 years (SD) and mean value of topographical length is 12.672 ± 0.7817 cm (SD).

Table 6 shows sex-wise distribution of age and topographical length. Where mean age for females is 36.05 ± 10.082 years

Table 1: Sex-wise distribution

Sex	Frequency (%)
Female	21 (42.0)
Male	29 (58.0)
Total	50 (100.0)

Table 2: Catheter tip position with respect to carina

Tip position	Frequency (%)
Below the carina	4 (8.0)
At the level of carina	35 (70.0)
Above the carina	11 (22.0)
Total	50 (100.0)

Table 3: Catheter tip position with respect to corresponding vertebral level

Corresponding vertebral level	Frequency (%)
4 th	3 (6.0)
5 th	40 (80.0)
6 th	7 (14.0)
Total	50 (100.0)

Table 4: Catheter tip position with respect to corresponding intercostal space

Corresponding intercostal space	Frequency (%)
4 th	4 (8.0)
5 th	42 (84.0)
6 th	4 (8.0)
Total	50 (100.0)

Table 5: Topographical length with respect to age of participants

Statistical parameters	Age	Topographical length (cm)
Mean	37.84	12.672
SD	11.456	0.7817
Minimum	20	11.0
Maximum	63	14.0

SD: Standard deviation

standard deviation (SD) and mean age for males is 39.14 ± 12.366 years (SD). The mean topographical length for females is 11.943 ± 0.4915 cm (SD) and mean topographical length for males is 13.200 ± 0.4575 cm (SD).

Table 7 shows sex-wise frequency and percentage of catheter tip position with respect to carina. In females, 95.2% (85.7 + 9.5) case belongs to at the level or just above to the carina while in males this value is 89.6% (58.6 + 31).

Table 8 shows mean value of catheter length (cm) corresponding to carina levels. This mean value at the level of carina is 12.6 cm.

Table 9 Shows statistical analysis of topographical length between the groups (i.e. at level of carina, above the carina and below the carina) and within the group. This is a

Table 6: Sex wise distribution of age and topographical length

Sex	Age	Topographical length (cm)
Female		
<i>n</i>	21	21
Mean	36.05	11.943
SD	10.082	0.4915
Minimum	22	11.0
Maximum	55	13.0
Male		
<i>n</i>	29	29
Mean	39.14	13.200
SD	12.366	0.4575
Minimum	20	12.5
Maximum	63	14.0

SD: Standard deviation

Table 7: Sex wise frequency and percentage of catheter tip position with respect to carina

Characteristics	Frequency (%)
Female	
Below the carina	1 (4.8)
At the level of carina	18 (85.7)
Above the carina	2 (9.5)
Total	21 (100.0)
Male	
Below the carina	3 (10.3)
At the level of carina	17 (58.6)
Above the carina	9 (31.0)
Total	29 (100.0)

Table 8: Mean value of catheter length corresponding to carina levels

Tip level	<i>n</i>	Mean±SD
Below the carina	4	13.750±0.5000
At the level of carina	35	12.626±0.7543
Above the carina	11	12.427±0.6680

SD: Standard deviation

result of one-way ANOVA for topographical length. It is statistically significant between the groups.

Table 10 shows statistical significance of one level topographical length with respect to other two levels. This statistical significant difference was due to the difference in length between below the carina and at the level of carina and below and above the carina.

Table 11 shows mean value of ages corresponding to carina levels. This relation is nonsignificant.

Table 12 Shows Result of one-way ANOVA for age. The observed age (years) is statistically insignificant, which means age is not a factor for topographical length.

Table 13 shows statistical significance of mean age of participants with different carina levels. This difference was statistically nonsignificant.

Table 9: Statistical significance of topographical length

Source of variation	Sum of squares	df	Mean square	F	P value
Between groups	5.382	2	2.691	5.150	0.009
Within groups	24.559	47	0.523		
Total	29.941	49			

Table 10: Statistical comparison between different groups

Tip position	Tip position	P value
Below the carina	At the level of carina	0.015
	Above the carina	0.009
At the level of carina	Below the carina	0.015
	Above the carina	1.000
Above the carina	Below the carina	0.009
	At the level of carina	1.000

Table 11: Mean value of ages corresponding to carina levels

Tip level	<i>n</i>	Mean±SD
Below the carina	4	47.50±12.014
At the level of carina	35	38.29±11.105
Above the carina	11	32.91±10.756
Total	50	37.84±11.456

SD: Standard deviation

Table 12: Result of ANOVA for age

Source of variation	Sum of squares	Df	Mean square	F	P value
Between groups	647.668	2	323.834	2.632	0.083
Within groups	5783.052	47	123.044		
Total	6430.720	49			

Table 14 shows that there was no association between level of carina and sex.

Table 15 shows descriptive statistics about catheter tip position and topographical length at different levels of carina, separately for males and female.

DISCUSSION

Desired localization of CVC tip has been always a controversial topic. The traditionally preferred position of the catheter tip is in the distal third of the SVC to minimize complications such as catheter migration, extravasation of irritant agents, vascular perforation, local vein thrombosis, catheter malfunction, and cranial retrograde injection.^[8]

Only transesophageal echocardiography can accurately detect a CVC tip in relation to superior vena cava (SVC) and RA,^[11,12] but its availability as a bedside tool is limited to major hospitals.

A recent study conducted by Vinay and Tejesh in 2016, suggests the superiority of the topographical method

over the formula method given by Peres in 1990.^[13] We incorporated a post-procedure chest X-ray (CXR) that confirms the position of the catheter tip^[14] can also detect malpositions, pneumothorax, and kinking. The carina is radiologically identifiable in about 96% of all chest x-rays (CXRs) at the interspace between the fourth and fifth thoracic vertebrae.^[15] Carina is an ideal radiological landmark for tip of CVC catheter.

In our study, the average insertion length in male was 13.2 cm (12.5 cm to 14 cm) while the average length of catheter insertion in female was 11.9 (11–13 cm) which corresponds to positioning 80% in 5th posterior intercostal space and 84% in 5th thoracic vertebrae. In 95.1% of female patients and 89.6% of male patients, the tip was at or above the level of carina (≤ 1 cm). It was considered correct if the tip was ≤ 1 cm above and ≤ 0.5 cm below from carina level. Based on the CXRs the catheters were repositioned which were beyond the range. Our range encompasses 92% cases of our study which strongly signifies our method.

A study by Kim *et al.*,^[10] who estimated the desired length of right and left-sided CVC using surface landmarks. They showed that mean tip position of right-sided CVC inserted in SCV was 0.9 cm above the carina. Another study shown almost similar but the placement of tip was 0.2 cm below the carina.^[9] These both studies are giving the similar results as our. One more study states the similar conclusion, but observed length was more than our topographical length this may be due to ethnic variation.^[16]

Some other derived formula^[13] while other used technique (tailored technique)^[17] to improve tip position. Some found electrocardiographic method is better than fluoroscopy method while others were in favor of echocardiographic method.^[18] Our study result is not absolute perfect, but they are very close to perfection without using expensive, rarely available devices. No complication is seen in our study.

CONCLUSION

It can be concluded from the study that appropriate length of CVC of right SCV is correlated with surface

Table 13: Relation of mean age of participants with different carina levels

Tip position	Tip position	P value
Below the carina	At the level of carina	0.367
	Above the carina	0.087
At the level of carina	Below the carina	0.367
	Above the carina	0.502
Above the carina	Below the carina	0.087
	At the level of carina	0.502

Table 14: Statistical association between level of carina and sex

Tip position	Sex		Total	Pearson Chi-square	Df	P value
	F	M				
Below the carina	1	3	4	4.314	2	0.116
At the level of carina	18	17	35			
Above the carina	2	9	11			
Total	21	29	50			

Table 15: Descriptive statistics about catheter tip position and topographical length at different levels of carina

Sex	Tip position (topographical length) (cm)	n	Minimum	Maximum	Mean \pm SD
Male	Below the carina	1	13.0	13.0	13.0 \pm 0.0000
	At the level of carina	18	11.5	12.8	11.978 \pm 0.3639
	Above the carina	2	11.0	11.2	11.100 \pm 0.1414
Female	Below the carina	3	14.0	14.0	14.000 \pm 0.0000
	At the level of carina	17	12.9	13.9	13.312 \pm 0.3100
	Above the carina	9	12.5	12.9	12.722 \pm 0.1302

SD: Standard deviation

landmarks, and the approximate CVC insertion depth can be estimated using the topographical measurement with the CVC itself, along with the pathway of the central veins. Moreover, this method requires no additional cost and/or time-consuming procedures and radiation exposure was minimal.

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Prescription Drug Abuse in the United States of America and a Proposed Multilevel Intervention Based on Social Ecological Model

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Abstract

With a five-fold increase in the prevalence of prescription drug abuse, it is a raising epidemic in the United States of America. Opioids, benzodiazepines, amphetamines, and dextroamphetamine are commonly abused drugs. Public taxpayers in the states pay about \$72 billion because of economic burden caused by prescription drug abuse. There have been interventions in the past but with limited success. This paper sheds lights on the prevalence, current prevention programs, and a proposed multilevel intervention based social ecological model. To tackle the problem of prescription drug abuse further studies based on multilevel interventions warranted.

Key words: Amphetamines, Drug abuse, Intervention, Opioids, Prescription drugs, Social ecological model

INTRODUCTION

According to Mayo Clinic, “prescription drug abuse is defined as the use of prescription medications in a way not intended by the doctors. Prescription drug abuse can be explained through various scenarios such as from taking a friend's prescription painkiller for a backache to snorting or injecting ground-up pills to get high” (Mayo Clinic, 2015).

There is a substantial rise in the prevalence of prescription drug abuse, with a five-fold increase in the U.S from the late 90's (Warner, 2011). The most frequently abused drugs are opioids, Central nervous system depressants like benzodiazepines, and stimulants such as amphetamines and dextroamphetamine (NIDA, 2016). The upward surge in abuse of prescription drugs has reached a total of around 14 million people in the U.S.

Men are twice prone to abuse prescription drugs compared in women (Rao and Schappert, 2003). There have been studies estimating the economic burden of the prescription drug abuse which is about \$72 billion, and this cost is covered by the public taxpayers (Prescription for Peril, 2007). There is a significant variation with race and ethnicity; American Indians/whites have the highest percentage of prescription drug abuse (Paulozzi *et al.*, 2008). Geographic variation has been extensively studied; northwest and southeast have been noted to have the highest percentage of overdose rates due to prescription drug abuse (McDonald *et al.*, 2012).

According the Mayo Clinic, prescription drugs' risk factors are identified as the following: (1) Alcohol and tobacco addiction, (2) age - high-risk group includes early 20's, (3) certain pre-existing psychiatric conditions, (4) lack of knowledge about the long-term harmful effects, (5) peer pressure and social environment, and (6) easier access to medicine.

The side effects of prescription drug abuse are many. These side effects include immunologic effects, hormonal changes, hyperalgesia, sleep changes, bladder disturbances, and cardiac effects. Immunologic effects: Prescription drug abuse results in increased frequency of diseases.

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The pathophysiology is due to the immunomodulation at the central and peripheral receptors. Immunomodulation results in decreased natural killer cells, inhibits T-cell proliferation, decreased phagocytosis and nitric oxide release (Radulović and Janković, 2002). Hormonal changes: Decreased levels of testosterone results in decreased energy, decreased libido, and erectile dysfunction (Daniell, 2002). Decreased levels of estrogen results in reduced bone mass, osteoporosis, and sexual dysfunction (Daniell, 2008). Decreased levels of luteinizing hormone result in amenorrhea and hypomenorrhea (Oltmanns *et al.*, 2005). Decreased levels of gonadotropin-releasing hormone result in a decreased level of androgen hormone levels (Petraglia *et al.*, 1986). Hyperalgesia: It is also known as increased pain sensitivity. Opioid abuse causes increased secretion of the excitatory neurotransmitters, as well as changes in the spinal neurons due to apoptosis of the GABA neurons (Mao *et al.*, 2002). Sleep changes: They are common in opioid abuse, which includes an increased number of shifts in sleep-waking states (Koren *et al.*, 2000), decreased sleep time, sleep efficiency (Kurz and Sessler, 2003), delta sleep, and REM sleep (Pickworth *et al.*, 1981). Constipation and bladder disturbances: Most people suffer from constipation and bladder disturbances as a side effect. Chronic constipation can result in hemorrhoids, obstruction of the bowel resulting in possible bowel rupture; which in turn result in high rates of mortality and morbidity (Benjamin *et al.*, 2008). Cardiac effects: Vasodilation and hypotension as a result of histamine release are attributed to morphine abuse (Brunton *et al.*, 2006). Methadone abuse has been linked to Torsade des Pointes and QT prolongation syndrome (Shah, 2002).

Purpose

This paper provides information on the prevalence of the prescription drug abuse, the associated risk factors and effects of prescription drug abuse. This paper also sheds light on the prevention programs which are enforced in the society. This paper highlights the gaps in the safe use of the prescription drugs and prescription drug abuse. Based on theories from Social and Behavioral Health, we propose a multilevel intervention program based on the Social Ecological Model.

Current Public Health Interventions

At the moment, there are some policies in place to combat prescription drug abuse, but more needs to be done. Prescription drug monitoring programs (PDMPs) have recently been put in place to track and trace physician prescribed controlled substances. Thus, far 49 states have an active PDMP (CDC, 2016). This is a good step in the right direction, but all states should be on board. Missouri is the only state without a PDMP, and this must be addressed. An issue with the program is that not every state requires

a provider to check the PDMP before prescribing certain controlled substances. PDMPs have illustrated changes in prescribing behaviors, use of multiple providers by patients, and decreased substance abuse treatment admissions (CDC, 2016). Legislation should be introduced requiring all physicians to check the PDMP system before prescribing.

The safe drug disposal act of 2010 signed by President Obama is another intervention which amended the Controlled Substances Act to provide individuals and patients who have lawfully acquired controlled substances an easy and safe way of disposing unused and expired controlled substances (Phillips, 2012). Unused controlled substances can be delivered by individuals to Drug Enforcement Administration (DEA) approved entities for safe and proper disposal. In addition, long-term care facilities and individuals entitled to a decedent's property can dispose of a resident's controlled substances to a DEA-designated disposal program (Phillips, 2012). Moreover, the National Prescription Drug Take Back Day occurs every 6 months. It is a critical tool in combating prescription drug abuse because an overwhelming number of prescription drug abusers report obtaining drugs from medicine cabinets, families, and friends (Phillips, 2012). The safe drug disposal act is the only piece of legislation to have been successfully signed into law since 2010. All other recently proposed prescription drug policy interventions have died in Congress.

Social Ecological Model: A Model for Proposed Intervention

The social ecological model is a model that incorporates five levels of influence specific to health behavior: Individual, interpersonal, institutional, community, and public policy. We believe the model should be utilized more often as a

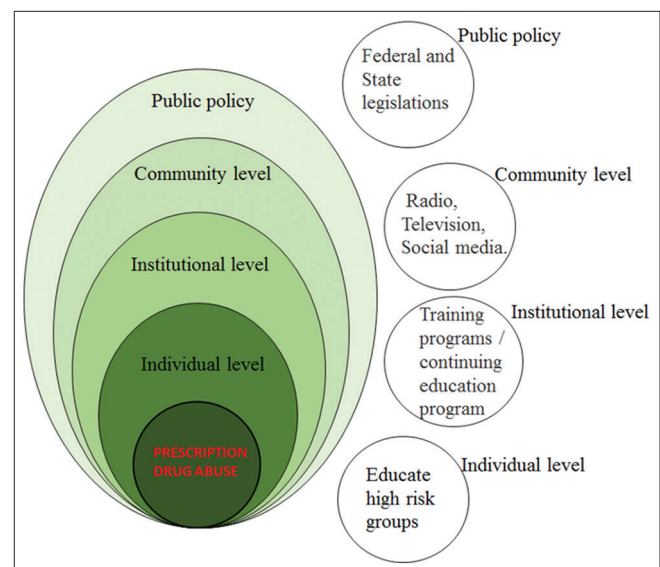


Figure 1: Levels of intervention for prescription drug abuse based on social ecological model

basis for intervention because it takes into consideration social, physical, and cultural aspects of an environment that can impact health. These aspects are crucial to include in any intervention, specifically in regard to prescription drug abuse [Figure 1].

The Ecological Model of Health Behavior emphasizes the environmental and policy contexts of behavior while incorporating social and psychological influences (Glanz, 2008). According to the Social Ecological Model, there are five sources of influence on health behavior including: Interpersonal, intrapersonal, institutional, community, and public policy. Therefore, this model has been chosen because of its ability to provide a comprehensive framework for understanding multiple and interacting determinants of health. The ultimate purpose of the Ecological Model of Health Behavior is,

“To inform the development of comprehensive intervention approaches that can systematically target mechanisms of change at several levels of influence. Behavior change is expected to be maximized when environments and policies support healthful choices, when social norms and social support for healthful choices are strong, and when individuals are motivated and educated to make those choices (Glanz, 2008).”

The Social Ecological Model of Health Behavior recognizes individuals as embedded within larger social systems and describes the interactive characteristics of individuals and environments that underlie health outcomes (Golden and Earp, 2012). This demonstrates the key strength of this particular model, its focus on multiple levels of influence. This allows for expanded options for interventions and impacts multiple aspects of environmental influence. Unlike interventions that only reach individuals who choose to participate, this model incorporates community, institutional, and policy influences that affect entire populations (Glanz, 2008). Interventions which involve policy and environmental aspects, “establish settings and incentives that can persist in sustaining behavior changes (Glanz, 2008).” Individually directed interventions can often times become poorly maintained, whereas this model can avoid that problem.

Recommendations

A multilevel intervention should involve education and legislative strategies. The education strategy should focus on high school students, providers, and the general public. Education of high school students will focus on the addictive qualities of prescription pain medication, and the particular side effects associated with abuse of these drugs. Education should also focus on better training of providers regarding safe storage and disposal, identification

of treatment and treatment of pain, alternative modalities including acupuncture, improved coordination with pain management clinics, and integration of mental illness assessments. Finally, public education campaigns through mediums such as television and social media should be engaged. The legislative aspect will focus on state and legislative support for physical and mental examinations before the prescription of painkillers, mandatory creation of state databases to track prescription drugs and require doctors to check before prescribing, and prioritization of resources for treatment programs. As can be seen, this is a multilevel approach involving the individual, institutional, community, and policy level of the Social Ecological Model of public health intervention. This intervention can be broken down into four levels:

Individual level

Educate high school students. Many young people believe prescription drugs to be safer than illegal drugs. In 2014, youths 12–17 years of age and young adults 18–25 years of age were more likely to have misused prescription drugs in the past year than adults 26 years or older (Substance Abuse, 2015).

Institutional level

Educate providers on mental health, non-pharmacological pain treatment alternatives such as acupuncture and non-narcotic therapy, and substance abuse and overdose prevention through training programs or continuing education programs. These modules should urge providers to coordinate pain management with complementary and integrative care providers.

Community level

Public education campaigns on non-sharing of prescription medications as well as safe storage, use, and disposal of medications. Messaging through radio, television, billboards, and social media.

Policy level

Support federal legislation to require individuals to have physical and mental examinations before they are prescribed pain medications. Support federal legislation requiring all states to create a PDMP that tracks each time an individual patient is prescribed a controlled substance by a provider. Legislation must also be supported requiring physicians to check the PDMP before the prescribing. Re-introduction of the prescription drug abuse prevention and treatment act of 2013 mandating provider education and supporting public education. Finally, policy should encourage federal and state legislatures to prioritize resources for support of evidence-based substance abuse treatment programs that include medication-assisted treatment and supportive counseling (American Public Health Association, 2015).

CONCLUSION

The issue of prescription drug abuse has been apparent for many years. As mentioned in this study, there has been a substantial rise in the prevalence of prescription drug abuse in the U.S since the late 90's. So far, previous interventions have been successful yet limited. To deal with this public health epidemic that is claiming millions of lives in the U.S., an approach and intervention using the social ecological model are needed to reduce the rate of abuse of prescription drugs. Therefore, to tackle this, we concluded that it must be done through a multilevel approach which involves targeting the individuals, the institutions, the communities, and the policymakers.

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A Clinical and Epidemiological Analysis of First-time Febrile Seizures in Children

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Abstract

Background: Febrile seizures (FSs) are the most common neurological disorder observed in the pediatric age group. In pediatric practice, seizures account for 1% of all emergency visits. They are usually defined as seizures occurring after 1 month of age associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures.

Aim of the Study: The aim of this study is to analyze the clinical and epidemiological spectrum in children with a first attack of acute seizure disorder and its prevalence rates of various etiologies.

Materials and Methods: A total of 127 children presenting with FSs to the emergency department were evaluated at a tertiary teaching hospital of Kerala between October 2015 and September 2017. Demographic details, clinical findings, laboratory investigations, computed tomography (CT)/magnetic resonance imaging (MRI) scan brain studies, diagnoses, and hospital course were compared between FSs and patients with AFSs. These variables were also compared between patients with simple and complex FSs and among different age groups.

Observations and Results: Among 127 patients, 80 children presented with FSs (62.99%) and the remaining children with AFSs 47 (37%). 68/80 children (85%) presenting with FSs were aged below 6 years. The type of seizures was generalized tonic/clonic seizures in 49/80 of the febrile group (61.25%). The etiologies observed were electrolyte imbalance and hypoglycemia. CT scan was done in 45/127 (35.43%) children and found to be abnormal in 15/45 children (33.33%). Similarly, MRI scan was done in 18/127 (14.17%) children and found to be abnormal in 9/18 children (50%).

Conclusion: Primary care pediatricians should evaluate children presenting to the ED with a first seizure for age, coexistence of fever, seizure type, associated symptoms, and history of head injury. Routine investigations of electrolytes, blood sugar, and emergency brain imaging studies should be arranged based on detailed history taking and thorough physical examinations but should not be performed routinely.

Key words: Children, Convulsions, Febrile, Fever, Seizures

INTRODUCTION

Febrile seizures (FSs) were described in 1980 by a consensus conference held by the National Institutes of Health as “an event in infancy or childhood usually occurring between 3 months and 5 years of age, associated with fever, but without evidence of intracranial infection or defined cause.”^[1] However, the definition does not

exclude children with prior neurological impairment and neither provides specific temperature criteria nor defines a “seizure.” A definition from the International League Against Epilepsy was introduced as “a seizure occurring in childhood after 1 month of age associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures.”^[2] FSs in children below 5 years account for the most common type in the out-of-hospital and ED settings.^[3,4] The incidence of non-FSs in children ranges from 89 to 134 per 100,000 person years.^[5] FSs are classified as simple or complex types.^[6] Simple seizures are generalized last <15 min and do not recur within 24 h, and complex FSs are prolonged, recur more than once in 24 h, or are focal.^[7] Complex FSs may indicate a more

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serious disease process, such as meningitis, abscess, or encephalitis. Whereas, status epilepticus is a severe type of complex FS defined as single seizure or series of seizures without interim recovery lasting at least 30 min. Among the various etiological factors causing FSs, viral infections, either exanthematous or non-exanthematous infections are the commonest and predominant causes. Human herpes simplex virus 6 was found to be the etiologic agent in roseola in about 20% of a group of patients presenting with their first FSs.^[7] *Shigella* gastroenteritis was also found to be associated with FSs.^[7] One study suggests a relationship between recurrent FSs and influenza A.^[7,8] FSs are known to run in families. In a child with FS, the risk of FS is 10% for the sibling and almost 50% for the sibling if a parent has FSs as well; the mode of inheritance is unclear.^[9] Although the exact molecular mechanisms of FSs are yet to be understood, underlying mutations have been found in genes encoding the sodium channel and the gamma-aminobutyric acid a receptor.^[10,11] Emergency care physicians in the casualty or emergency department (ED) usually have to face the challenge in primarily examining, ordering necessary investigations, and treating the first attack seizures children. After initial stabilization, the child in the ED physician has to decide whether to admit or discharge. Misdiagnosis or misjudgment carries the potential risk of legal problems. It can cause family anxiety, lead to excessive hospital stay, and possibly result in life-threatening events. In the present context, a study was conducted prospectively to analyze the prevalence of various etiologies and the clinical spectrum of seizure disorders in children who presented to the ED with the first attack of acute seizure disorder.

Type of Study

This was a prospective, cross-sectional, and analytical study.

Period of Study

The study duration was from October 2015 to September 2017.

Institute of Study

This study was conducted at KMCT Medical College Hospital, Kozhikode.

MATERIALS AND METHODS

A total of 127 children with first-time seizures attending the ED of a tertiary teaching Hospital in Kerala were included in this study. The children were classified as Group A: Children with fever and Group B: Children without fever. An Ethical Committee Clearance was obtained before commencing the study. An ethical committee cleared consent letter from parents was used for the study. The history was elicited from either one of them parents.

Inclusion Criteria

1. Children aged from 1 month to 12 years were included.
2. Children with first-time history of seizures alone were included.
3. Children with both generalized and focal epileptic features were included.
4. Children with or without a history of fever were included.
5. Children with a family history of FSs in the siblings or parents were included in the study.

Exclusion Criteria

1. Children aged above 12 years and below 1 month were excluded.
2. Children with a previous history of seizures were excluded.
3. Children with a history of tuberculosis were excluded.
4. Children with a recent history of exanthemata were excluded.
5. Children with a history of kernicterus were excluded.

All the children were initially attended by the emergency medicine physician and followed by the consultant pediatrician on call. All the children were subjected to thorough clinical examination. The following demographic data were collected: Sex, family history of seizures, type of seizures, associated symptoms (fever, cough, rhinorrhea, vomiting, diarrhea, and headache), and developmental history. Laboratory tests undertaken were as follows: White blood count, C-reactive protein, stool rotavirus antigen test, serum electrolytes, blood sugar and cerebrospinal fluid (CSF) analysis, computed tomography (CT) scan/magnetic resonance imaging (MRI) scan, electroencephalography (EEG) findings, duration of hospital stay, final diagnosis, anticonvulsants given in the ED, admission to intensive care unit (ICU), general ward, and pediatric observation unit. Children with temperature more than 38°C were grouped under febrile type: Group A. Children with temperature <38°C were grouped under afebrile type: Group B. The type of seizures was classified as generalized tonic-clonic (GTC) and generalized tonic. Status epilepticus was defined as “a single epileptic seizure of more than 30 min or a series of epileptic seizures during which function is not regained between convulsion events in a period more than 30 min long.” In addition, FSs were classified as simple FSs or complex FSs. A simple FS lasts <15 min, is initially generalized in nature, and occurs once during a 24 h period. In contrast, a complex FS lasts more than 15 min, has focal features at any time, or recurs within a 24-h period. Children were divided into three age groups: Infant group (<1 year), preschool age group (1–6 years), and school age group (7–12 years). All the data were analyzed using standard statistical methods.

OBSERVATIONS AND RESULTS

Among 127 patients, 80 children presented with FSs (62.99%) and the remaining children with AFSs 47 (37%). 68/80 children (85%) with FSs were aged below 6 years. 38/47 children with AFSs were below 6 years of age (80.85%). The incidence of seizures of both groups was statistically significant with $P = 0.012$ (P significant at <0.05). The type of seizures was GTC seizures in 49/80 (61.25%) children of FSs and 28/47 of the children with AFSs (59.57%). The incidence of GTC in both the groups was statistically significant with P value at 0.018 (P significant at <0.05). Among the FS children, simple pattern of seizures was observed in 39/49 children (61.22%) and complex pattern in 10/49 (20.40%) children. The incidence of family history was also statistically significant in both groups with p value at 0.031 (P significant at <0.05) [Table 1]. 9/80 children showed delayed mile stones in the febrile group and 3/47 in the afebrile group. The most common types of delayed milestones included developmental delay and language development delay.

It was observed that cough and rhinorrhea were more common in children of febrile group than with afebrile group. Laboratory test results were analyzed in the entire study group with seizures and observed that stool rotavirus antigen tests were performed in 42 (33.07%) children with watery diarrhea and it was positive in 08/42 children. Electrolyte imbalance was observed in 15 (08.15%) children. Hypoglycemia was observed in 19/68 (27.94%) children. CSF analysis was abnormal in 08/34 (23.52%) children. White blood cell count showed abnormal values in 56/127 children (44.09%). CT scan was done in

45/127 (35.43%) children and found to be abnormal in 15/45 children (35.55%). Similarly, MRI scan was done in 18/127 (14.17%) children and found to be abnormal in 9/18 children (50%), [Table 2]. C-reactive protein was showing abnormal levels in 41.23% of the children. In 8 children, both CT scan and MRI were done concurrently. The different radiological diagnoses observed among the 19 children were as follows: Subarachnoid hemorrhage ($n = 1$), subdural hemorrhage ($n = 3$), post-traumatic head injury without intracranial hemorrhage ($n = 3$), hydrocephalus ($n = 3$), shaking baby ($n = 2$), aseptic meningitis ($n = 2$), meningoencephalitis ($n = 2$), and encephalitis ($n = 3$). All these children presented clinically with acute symptomatic seizures and did not respond for the initial anticonvulsive therapy. Abnormal results of physical and neurological examinations were found in 12 of these 19 children; consciousness disturbance was the most common abnormal finding. EEG was performed in a total of 21/127 (16.53%) children; among these children, abnormal EEG results were observed in 5/7 in AFSs [Table 2].

After the initial emergency management in the ED, 102/127 of the children (80.31%) were admitted to the pediatric ward, 12/127 (9.44%) to the pediatric ICU, and the remaining 13/127 (10.23%) were discharged after observation in the ED itself. The details of emergency treatment given are shown in Table 3.

DISCUSSION

In the present study, 127 children presenting with seizures with or without fever were included in the study. Children with fever presenting with FSs were 80/127 and without fever were 47/127. 68/80 children (85%) with FSs were aged below 6 years. 38/47 children with AFSs were below 6 years of age (80.85%). FSs have been reported to be one of the most common causes of seizure attack in children.^[11] FSs are the main cause of first attack seizures in children in any given community. Review of literature shows that^[12] 25–40% of children with FSs have a family history of FSs. In the present study, the incidence of family history was observed as 7/80 in febrile group and 1/47 of the afebrile group [Table 1]. It shows the undependability of family history in the history taking among the children presenting with first attack seizures. The underlying causes observed among the children with FSs were as follows: Upper respiratory tract infections in 32/80 (40%), systemic viral infections in 14/80 (17.5%), lower respiratory tract infections in 12 (15%), acute gastroenteritis in 9 (11.25%), enterovirus infections in 8 (12%), and urinary tract infections in 5 (6.25%). A retrospective cohort study showed that diarrhea was the most common associated etiological factor in patients with seizures.^[13-16] In the present

Table 1: Demographic data (n=127)

Observation	With fever - 80 (%)	Without fever - 47 (%)	P value
Gender- 127			
Male - 78	46 (57.50)	29 (61.70)	Not significant
Female - 49	34 (42.50)	18 (38.29)	
Age (year)			
<1	25 (31.25)	13 (27.65)	0.012
1–6	43 (53.75)	25 (53.19)	
7–12	12 (15.00)	09 (19.14)	
Type of seizures			0.018
GTC	49 (61.25)	28 (59.57)	
Generalized tonic	05 (06.25)	04 (08.51)	
Partial	03 (03.75)	02 (04.25)	
Status epilepticus	06 (07.50)	05 (10.63)	
Others	17 (21.25)	08 (17.02)	0.031
Family history of seizure	31 (38.75)	20 (42.55)	
Family history of epilepsy	07 (08.75)	01 (2.12)	
Delayed mile stones	09 (11.25)	03 (6.38)	NS

GTC: Generalized tonic-clonic seizure, NS: Not significant

Table 2: The number of children undergoing laboratory investigations and incidence of abnormal reports (n-127)

Observation	Number of laboratory tests done n (%)	Abnormal (%)	Normal values
Stool Rotavirus	42 (33.07)	08 (19.04)	
WBC count	127 (100)	56 (44.09)	<1 year- 5.0–19.5 1–3 years - 6.0–17.5 4–7 years - 0.5–15.5 8–12 years - 4.5–11.5
Sodium	90 (70.86)	08 (08.88)	135–145 mmol/L
Calcium	94 (74.01)	07 (07.77)	2.2–2.5 mmol/L
C-reactive protein	85 (66.92)	41 (48.23)	<4.8 nmol/L
Blood sugar	68 (53.545)	19 (27.94)	3.3–5.6 mmol/L
CSF analysis	34 (26.77)	08 (23.52)	
CT scan	45 (35.43)	15 (35.55)	
MRI	18 (14.17)	09 (50)	
EEG	21 (16.53)	07 (33.33)	

CT: Computed tomography, CSF: Cerebrospinal fluid, MRI: Magnetic resonance imaging, EEG: Electroencephalography

Table 3: The treatment given to the children with seizures (n-127)

Treatment given	Number of children received treatment	Number of treatment given episodes
Diazepam PR	18	3
Diazepam IV	64	69
Midazolam	07	04
Lorazepam	04	02
Phenytoin IV	06	01
Phenobarbital IM	08	04
Glucose IV	11	02
Endotracheal intubation	09	-

PR: Per rectum, IV: Intravenous

study, rotavirus was confirmed by stool antigen analysis in 8/127 (19.04%) of patients who presented with seizures and diarrhea. We therefore suggest that a stool rotavirus antigen test may be considered if a patient presents with a first attack of seizure and diarrhea in the ED. Among the children with AFSs, one child showed abnormal CT scan findings (1/19 abnormal CT scans), (5.26%). Abnormal EEG recordings were noted in 2/7 abnormal recordings in febrile group. GTC seizures were noted in 49/80 (61.25%) children of FSs. Patients with complex FS pattern were admitted to the ICU more often than patients with simple FS pattern. The GTC type of seizures was observed in more common in preschool age children than in children in other age groups ($P=0.012$) [Table 1]. Except 4/80 children in the febrile group (5%), remaining all children responded to diazepam administration either rectally or intravenous route. Seizures are the most common clinical presentation in cases of meningitis and other intracranial neurological complications, especially in young children. They often result in poor prognosis if diagnosed late or prompt treatment was not initiated; lumbar puncture is required in all children presenting with seizures and meningeal signs.^[17,18] The American Academy of Pediatrics recommends that a lumbar puncture should be considered

in patients aged younger than 18 months who present with FSs.^[11] But whether lumbar puncture should be done or not during the FSs in children still remains a controversy. In the present study, lumbar puncture was performed in 34/127 children (26.77%), and 8/34 (23.52%) children showed abnormal CSF analysis results among febrile group; however, no definite organism was cultured. 1/34 children was diagnosed as encephalitis, and in 1/34 children, it was meningoencephalitis. Neuroimaging examinations of the brain can help emergency physicians to identify some causes of seizures, but it is not necessary to arrange these imaging studies on a routine basis.^[19] In the present study, CT scan was done in 45/127 (35.43%) children and found to be abnormal in 15/45 children (35.55%). Similarly, MRI scan was done in 18/127 (14.17%) children and found to be abnormal in 9/18 children (50%). As in 28 children, both CT scan and MRI are done only 19 imaging studies showed abnormal radiological features; hence, the present study suggests that brain imaging studies should not be routinely in children who present to the ED with a first attack of seizures. Studies showed that routine examinations of glucose, electrolytes, calcium, blood urea nitrogen, and creatinine were not necessary in children whose consciousness levels had returned to baseline, those who had no risk factors for epilepsy, and those with normal physical examination findings.^[20,21] In our study, seizures caused by severe electrolyte imbalance in 08.15% of the children and hypoglycemia were noted in 19 (27.94%) of the children. The present study suggests that electrolyte and blood sugar studies should be arranged based on detailed history-taking and thorough physical examinations and not to be performed routinely. Phenobarbital may have priority over other anticonvulsants for controlling neonatal seizures.^[21] In the present study, diazepam was used in 82/127 (64.56%) of the children in the ED for first attack seizures irrespective of febrile or afebrile nature. Phenobarbital IM was used in 8/127 (6.29%), [Table 3].

Repeat doses were required more frequently among the children aged below 6 years when compared to above 6 years to control seizures in the present study.

CONCLUSIONS

Among the first attack seizures encountered in children, the FSs are more common than AFs. Age, fever coexistence, seizure type, associated symptoms, physical and neurological examinations, and history of head injury may provide important information for primary emergency physicians when evaluating children with a first attack of seizures. Routine examination of brain imaging studies, electrolyte, and blood sugar is unnecessary unless the patients present with an abnormal history or abnormal results of physical or neurological examinations.

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Comparative Evaluation of 30% Ethanolic Extract of Propolis, VivaSens Desensitizer, and Distilled Water for Treating Dentinal Hypersensitivity - A Randomized Controlled Trial

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Abstract

Objective: The aim of the present study was to evaluate and compare the efficacy of 30% ethanolic extract of propolis, VivaSens, and distilled water as placebo in treating dentinal hypersensitivity.

Materials and Methods: A total of 75 teeth with dentinal hypersensitivity were randomly allotted into three groups with 25 teeth in each group. Response to tactile and air stimuli was measured using verbal rating scale initially on the 1st, 14th, 28th, and 60th day, and final assessment was done on the 90th day. A statistical analysis was done using Kruskal–Wallis test and Mann–Whitney U-test for intergroup comparison and for intragroup comparison Friedman test and Wilcoxon signed-ranks test.

Results: The teeth treated with the test groups showed decrease in the mean hypersensitivity values compared to control group, over a period of three months.

Conclusion: It was concluded that propolis and VivaSens were effective in relieving dentinal hypersensitivity and had immediate and sustained effect.

Key words: Dentinal hypersensitivity, Distilled water, Propolis, Verbal rating scale

INTRODUCTION

Dentinal hypersensitivity may be defined as exaggerated response of vital dentin on exposure to chemical, tactile, osmotic, or thermal stimuli, and which cannot be explained by any other form of dental disease. It generally involves the cervical third of facial surface of canines, premolars, and molars as these areas are more prone for exposure due to enamel loss by abrasion, erosion, abfraction, gingival recession, or combination of above-mentioned factors.^[1]

While various theories have been proposed to explain the physiology of dentinal hypersensitivity, the most accepted theory is hydrodynamic theory given by Brannstrom. According to this theory, rapid shift in fluid flow in dentinal tubules in response to external stimuli appears to be responsible for causing odontoblastic pain.^[2]

In general, 10–30% of the individuals in a given population are afflicted by dentinal hypersensitivity. Greatest incidence of dentinal hypersensitivity is seen in the age group of 20–40 years with females showing greater predilection as compared to males, although this difference is not clinically significant.^[3] In spite of being so widespread, it is one of the least successfully treated diseases of the teeth. A plethora of treatment options are currently available in the market for reducing dentinal hypersensitivity. Most of them bring about their therapeutic effect by either partial or complete

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obliteration of dentinal tubules, anti-inflammatory activity, protein precipitation, or sealing the tubules. Although most of the approaches are quite successful in reducing sensitivity, there is still no consensus on as to which product constitutes as the gold standard for the treatment of dentinal hypersensitivity as the duration of relief provided by them varies greatly.^[4]

Propolis is a sticky, non-toxic, brown, and resinous substance collected by honey bees from the exudates of trees and plants. It is then modified by the bees by mixing them with their salivary secretions and wax. Several studies have reported it to have antimicrobial, antiviral, anti-inflammatory, and antioxidant properties. Due to these beneficial biological properties, it has found a wide array of uses in dentistry which includes the prevention of dental caries, as direct pulp capping agent, intracanal medicament, and analgesic.^[5,6] Recent *in vitro* studies have shown that propolis had significant effect in reducing dentinal permeability, but to date, only few *in vivo* studies have been done to test its efficacy as desensitizing agent.^[7,8] VivaSens is another resin-based desensitizing varnish that causes the precipitation of calcium ions and proteins in the dentinal fluid, which leads to mechanical obliteration of the tubules. It is mainly indicated for teeth that have hypersensitivity due to exposed dentin in the cervical third.^[9]

Therefore, the aim of the present *in vivo* study is to evaluate the clinical effect of 30% ethanolic extract of propolis, VivaSens topical desensitizer, and distilled water (as placebo) on the reduction of cervical dentin hypersensitivity.

Null hypothesis was proposed that there will be no difference in the change in the level of dentinal hypersensitivity between 30% ethanolic extract of propolis, VivaSens topical desensitizer, and distilled water.

MATERIALS AND METHODS

The clinical protocol and written informed consent were reviewed and approved by an Ethical Committee before the start of the study.

Inclusion Criteria

1. Patients having a minimum of 24 natural permanent teeth that are free of large restorations or dental prosthetic crowns.
2. Patients having a minimum of three premolars with a pre-operative verbal rating scale (VRS) score of ≥ 1 .
3. Patients with adequate oral hygiene and willing to participate in the study.

Exclusion Criteria

1. Patients with a history of any systemic illness and/or psychological disorder.
2. Teeth having dental caries/fractures in the cervical areas of teeth.
3. Patients on analgesics and/or anti-inflammatory drugs.
4. Teeth with extensive unsatisfactory restorations, prosthesis, or orthodontic appliances involving cervical areas.
5. Patients who had taken any treatment for hypersensitivity within the last 6 months.
6. Patients with clinical or radiographic evidence of pulp pathology.
7. Patients allergic to ingredients used in the study.

Study Procedure

A total of 75 teeth were randomly allotted into three groups with 25 teeth in each group:

Group 1 - 30% ethanolic extract of Indian propolis.

Group 2 - VivaSens desensitizer.

Group 3 - Sterile distilled water as a negative control.

The tooth was assigned randomly into any one of the groups. The randomization procedure was carried out using sequentially numbered opaque-sealed envelopes prepared with simple randomization.

Each tooth receives two stimuli for measuring dentin hypersensitivity:

- Tactile stimuli (clinical probing).
- Air stimuli (blast from dental unit air syringe).

The probe stimulus was applied under slight manual pressure in the mesiodistal direction on the cervical area of the tooth. The air blast was applied with an air syringe for 1–2 s at a distance of 1 cm from the tooth surface to avoid desiccation after isolating the tooth with cotton rolls and examiner's finger.

Criteria for Hypersensitivity Assessment

The degree of hypersensitivity reported by the participant with each stimulus was determined according to the VRS from 0 to 3, in which:

- 0 = No discomfort
- 1 = Minimum discomfort
- 2 = Mild discomfort
- 3 = Intense discomfort.

Application Procedure

- Removal of debris and calculus, if any, around the affected teeth using hand scalers.
- Isolation of the teeth with cotton rolls.
- Drying of tooth surfaces with a cotton pellet.

For Group 1, propolis extract was directly applied onto the site using truncated needle and left to dry for 60 s.

For Group 2, VivaSens desensitizer was manipulated according to manufacturer's instructions and applied with a disposable brush at the cervical region.

For Group 3, sterile water was directly applied on to the site using truncated needle and left to dry for 60 s.

- Care was taken to ensure that none of the products touch other zones of the oral mucosa or adjacent teeth.

The values were collected before the intervention (baseline values) and after each application, on days 1st, 14th, 28th, 60th, and final assessment was done on the 90th day. The patients were instructed not to rinse, eat or drink for 1 h after the treatment and avoid using any other professionally or self-applied desensitizing agent in the course of the investigation.

RESULTS

At baseline: There was no significant difference between Group 1 and Group 2 and Group 1 and Group 3. VRS score in Group 2 was significantly higher than Group 3.

At day 1: There was no significant difference between Group 1 and Group 2. VRS score in Group 1 and Group 2 was significantly higher than Group 3.

At day 14 (before): There was no significant difference between Group 1 and Group 2. VRS score in Group 1 and Group 2 was significantly higher than Group 3.

At day 14 (after): There was no significant difference between Group 1, Group 2, and Group 3.

At day 28 (before): There was no significant difference between Group 1, Group 2, and Group 3.

At day 28 (after): There was no significant difference between Group 1 and Group 2. VRS score in Group 3 was significantly higher than Group 1 and Group 2.

At day 60 (before): There was no significant difference between Group 2 and Group 3. VRS score in Group 2 and Group 3 was significantly higher than Group 1.

At day 60 (after): There was no significant difference between Group 1 and Group 2. VRS score in Group 3 was significantly higher than Group 1 and Group 2.

At day 90: There was no significant difference between Group 1 and Group 2. VRS score in Group 3 was significantly higher than Group 1 and Group 2 [Table 1].

At baseline: There was no significant difference between Group 1 and Group 2. VRS score in Group 1 and Group 2 was significantly higher than Group 3.

At day 1: There was no significant difference between Group 1 and Group 2. VRS score in Group 1 and Group 2 was significantly higher than Group 3.

At day 14 (before): There was no significant difference between Group 1 and Group 2. VRS score in Group 1 and Group 2 was significantly higher than Group 3.

At day 14 (after): There was no significant difference between Group 1, Group 2, and Group 3.

At day 28 (before): There was no significant difference between Group 1, Group 2, and Group 3.

At day 28 (after): There was no significant difference between Group 1 and Group 3. VRS score in Group 1 and Group 3 was significantly higher than Group 2.

At day 60 (before): There was no significant difference between Group 1 and Group 2. VRS score in Group 3 was significantly higher than Group 1 and Group 2.

At day 60 (after): There was no significant difference between Group 1 and Group 2. VRS score in Group 3 was significantly higher than Group 1 and Group 2.

At day 90: There was no significant difference between Group 1 and Group 2. VRS score in Group 3 was significantly higher than Group 1 and Group 2 [Table 2].

Friedman test showed significant difference for tactile sensation between different time intervals in VivaSens group. After this, Wilcoxon signed-ranks test was applied for pairwise comparison which showed following observations:

1. At baseline, VRS for tactile sensation was significantly higher than VRS at day 1, day 14 (before), day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90.
2. There was no significant difference between day 1 and day 14 (before).
3. At day 1 and day 14 (before), VRS for tactile sensation was significantly higher than day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90.
4. There was no significant difference between day 14 (after) and day 28 (before).

5. At day 14 (after) and day 28 (before), VRS for tactile sensation was significantly higher than day 28 (after), day 60 (before), day 60 (after), and day 90.
6. There was no significant difference between day 28 (after), day 60 (before), day 60 (after), and day 90.

Friedman test showed significant difference for tactile sensation between different time intervals in propolis group. After this, Wilcoxon signed-ranks test was applied for pairwise comparison which showed following observations:

1. At baseline, VRS for tactile sensation was significantly higher than VRS at day 1, day 14 (before), day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90.
2. There was no significant difference between day 1 and day 14 (before).
3. At day 1 and day 14 (before), VRS for tactile sensation was significantly higher than day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90.
4. There was no significant difference of D14 with D28 (bef.), D28 (aft.), day 60 (bef.), and day 60 (aft.).
5. VRS at D14 (after) was significantly higher than D90.
6. There was no significant difference between D28 (bef.) and D60 (before).
7. VRS at D28 (bef.) and D60 (before) was significantly higher than VRS at D28 (aft.), D60 (aft.), and D90.
8. VRS at D28 was significantly higher than D90.
9. There was no significant difference between D60 (aft.) and D90.

Friedman test showed significant difference for tactile sensation between different time intervals in water group. After this, Wilcoxon signed-ranks test was applied for pairwise comparison which showed following observations:

1. At baseline, VRS for tactile sensation was significantly higher than VRS at day 1, day 14 (before), day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90.
2. At D1, D14 (bef.), and D14 (aft.), VRS for tactile sensation was significantly higher than day 60 (aft.) and day 90.
3. There was no significant difference between D1, D14 (bef.), D14 (aft.), D28 (bef.), D28 (aft.), and day 60 (bef.).
4. There was no significant difference between D28 (bef.), D28 (aft.), D60 (bef.), D60 (aft.), and D90 [Table 3].

Friedman test showed significant difference for air stimuli between different time intervals in VivaSens group. After this, Wilcoxon signed-ranks test was applied for pairwise comparison which showed following observations:

1. At baseline, VRS for air stimuli sensation was significantly higher than VRS at day 1, day 14 (before),

day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90.

2. There was no significant difference between day 1 and day 14 (before).
3. At day 1 and day 14 (before), VRS for air stimuli sensation was significantly higher than VRS at day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90.
4. There was no significant difference between day 14 (after) and day 28 (before).
5. At day 14 (after) and day 28 (before), VRS for air stimuli sensation was significantly higher than VRS at day 28 (after), day 60 (before), day 60 (after), and day 90.
6. There was no significant difference between day 28 (after) and day 60 (before).
7. At day 28 (after) and day 60 (before), VRS for air stimuli sensation was significantly higher than VRS at day 60 (after) and day 90.
8. There was no significant difference between day 60 (after) and day 90.

Friedman test showed significant difference for air stimuli between different time intervals in propolis group. After this, Wilcoxon signed-ranks test was applied for pairwise comparison which showed following observations:

1. At baseline, VRS for air stimuli sensation was significantly higher than VRS at day 1, day 14 (before), day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90.
2. There was no significant difference between day 1 and day 14 (before).
3. At day 1 and day 14 (before), VRS for air stimuli sensation was significantly higher than VRS at day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90.
4. There was no significant difference between day 14 (aft.) and D28 (bef.).
5. At day 14 (aft.) and D28 (bef.), VRS for air stimuli sensation was significantly higher than VRS at day 28 (after), day 60 (before), day 60 (after), and day 90.
6. At day 60 (bef.), VRS for air stimuli sensation was significantly higher than VRS at day 28 (after), day 60 (after), and day 90.
7. There was no significant difference between VRS at day 28 (after), day 60 (after), and day 90.

Friedman test showed significant difference for air stimuli between different time intervals in water group. After this, Wilcoxon signed-ranks test was applied for pairwise comparison which showed following observations:

1. At baseline, VRS for air stimuli sensation was significantly higher than VRS at day 1, day 14 (before), day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90.

- There was no significant difference between day 1, day 14 (before), day 14 (after), day 28 (before), day 28 (after), day 60 (before), day 60 (after), and day 90 [Table 4].

DISCUSSION

Perception of pain is a subjective phenomenon and depending on the factors involved, psychological makeup, level of anxiety, threshold for pain, and past experience with pain; it varies from one individual to another. Due to these individual variations, dentinal hypersensitivity studies are one of the most difficult studies to be conducted in clinical scenario.^[4]

Dentinal hypersensitivity is a sharp, acute pain of short duration of exposed dentin in response to external stimuli such as thermal, evaporative, tactile, and osmotic/chemical which cannot be attributed to any other form of dental defect or pathology.^[1] There is a high degree of

heterogeneity in terms of methods employed to collect data together with high diversity in studied agents making the interpretation of data a cumbersome process.^[4]

A simple clinical method of diagnosing dentine hypersensitivity (DH) includes a jet of air or using an exploratory probe on the exposed dentin, in a mesiodistal direction, examining all the teeth in the area in which the patient complains of pain. The severity or degree of pain can be quantified either according to categorical scale (i.e., slight, moderate, or severe pain) or using a visual analog scale. In the present study, VRS was used for the quantification of pain with 4° of intensity. It is widely used in clinical research to assess intensity of acute pain.^[4]

Various in-offices, at home products, are currently available in market. In office, approach is generally adopted for localized form, whereas the use of home care products by patients is more for generalized involvement. Effective dentin occlusion offers the greatest prospect for instant and lasting relief of dentin hypersensitivity. Therefore,

Table 1: Comparison of VRS for tactile sensation in different groups at different time intervals

Time intervals	Mean±SD of VRS in different groups			Kruskal–Wallis test	Mann–Whitney U-test
	VivaSens (Group 1)	Propolis (Group 2)	Water (Group 3)		
Baseline	1.80±0.65	2.04±0.61	1.48±0.65	$\chi^2=9.552$, df=2, $P=0.008$ (<0.01), HS	Group 1=Group 2; Group 1=Group 3; Group 2>Group 3
Day 1	1.52±0.51	1.64±0.57	1.16±0.62	$\chi^2=7.600$, df=2, $P=0.022$ (<0.05), S	Group 1=Group 2>Group 3
Day 14 (before)	1.44±0.51	1.52±0.59	1.12±0.33	$\chi^2=8.608$, df=2, $P=0.014$ (<0.05), S	Group 1=Group 2>Group 3
Day 14 (after)	1.20±0.50	0.84±0.69	1.12±0.44	$\chi^2=5.283$, df=2, $P=0.071$ (>0.05), NS	Not applicable
Day 28 (before)	1.12±0.53	0.92±0.64	1.04±0.61	$\chi^2=1.180$, df=2, $P=0.554$ (>0.05), NS	Not applicable
Day 28 (after)	0.60±0.58	0.60±0.58	1.04±0.54	$\chi^2=9.093$, df=2, $P=0.011$ (<0.05), S	Group 3>Group 1=Group 2
Day 60 (before)	0.48±0.51	1.00±0.41	0.92±0.40	$\chi^2=16.499$, df=2, $P=0.000$ (<0.001), VHS	Group 2=Group 3>Group 1
Day 60 (after)	0.32±0.48	0.52±0.51	0.88±0.33	$\chi^2=16.241$, df=2, $P=0.000$ (<0.001), VHS	Group 3>Group 1=Group 2
Day 90	0.32±0.48	0.28±0.46	0.88±0.33	$\chi^2=22.211$, df=2, $P=0.000$ (<0.001), VHS	Group 3>Group 1=Group 2

*NS: Not significant, S: Significant, HS: Highly significant, VHS: Very high significant. VRS: Verbal rating scale, SD: Standard deviation

Table 2: Comparison of VRS for air stimuli in different groups at different time intervals

Time intervals	Mean±SD of VRS in different groups			Kruskal–Wallis test	Mann–Whitney U-test
	VivaSens (Group 1)	Propolis (Group 2)	Water (Group 3)		
Baseline	2.00±0.58	1.88±0.60	1.52±0.65	$\chi^2=8.433$, df=2, $P=0.015$ (<0.05), S	Group 1=Group 2>Group 3
Day 1	1.60±0.65	1.56±0.58	1.12±0.60	$\chi^2=7.748$, df=2, $P=0.021$ (<0.05), S	Group 1=Group 2>Group 3
Day 14 (before)	1.56±0.65	1.56±0.51	1.00±0.50	$\chi^2=13.885$, df=2, $P=0.001$ (<0.01), HS	Group 1=Group 2>Group 3
Day 14 (after)	1.04±0.61	1.08±0.49	1.04±0.46	$\chi^2=0.094$, df=2, $P=0.954$ (>0.05), NS	Not applicable
Day 28 (before)	1.20±0.41	1.04±0.35	1.00±0.58	$\chi^2=2.534$, df=2, $P=0.282$ (>0.05), NS	Not applicable
Day 28 (after)	0.80±0.50	0.48±0.51	0.96±0.35	$\chi^2=12.394$, df=2, $P=0.002$ (<0.01), HS	Group 1=Group 3>Group 2
Day 60 (before)	0.80±0.41	0.76±0.44	1.04±0.35	$\chi^2=6.454$, df=2, $P=0.040$ (<0.05), S	Group 3>Group 1=Group 2
Day 60 (after)	0.52±0.51	0.52±0.51	0.96±0.35	$\chi^2=12.548$, df=2, $P=0.002$ (<0.01), HS	Group 3>Group 1=Group 2
Day 90	0.36±0.49	0.36±0.49	0.96±0.35	$\chi^2=21.555$, df=2, $P=0.000$ (<0.001), VHS	Group 3>Group 1=Group 2

*NS: Not significant, S: Significant, HS: Highly significant, VHS: Very high significant. VRS: Verbal rating scale, SD: Standard deviation

Table 3: Comparison of VRS for tactile sensation between different time intervals in different groups

Time intervals	Mean±SD of VRS in different groups		
	VivaSens (Group 1)	Propolis (Group 2)	Water (Group 3)
Baseline	1.80±0.65	2.04±0.61	1.48±0.65
Day 1	1.52±0.51	1.64±0.57	1.16±0.62
Day 14 (before)	1.44±0.51	1.52±0.59	1.12±0.33
Day 14 (after)	1.20±0.50	0.84±0.69	1.12±0.44
Day 28 (before)	1.12±0.53	0.92±0.64	1.04±0.61
Day 28 (after)	0.60±0.58	0.60±0.58	1.04±0.54
Day 60 (before)	0.48±0.51	1.00±0.41	0.92±0.40
Day 60 (after)	0.32±0.48	0.52±0.51	0.88±0.33
Day 90	0.32±0.48	0.28±0.46	0.88±0.33
Friedman test	$\chi^2=127.232$, df=8, $P=0.000$ (<0.001), VHS	$\chi^2=122.882$, df=8, $P=0.000$ (<0.001), VHS	$\chi^2=35.930$, df=8, $P=0.000$ (<0.001), VHS
Wilcoxon signed-ranks test	Baseline>D1=D14 (before)>D14 (after)=D28 (before)>D28 (after)=D60 (before)=D60 (after)=D90	Baseline>D1=D14 (before)>D14 (after), D28 (before), D28 (after), D60 (before), D60 (after), D90; D14 (after)=D28 (before), D28 (after), D60 (before), D60 (after); D14 (after) >D90; D28 (before)=D60 (before)>D28 (after), D60 (after), D90; D28 (after)>D90 D60 (after)=D90	Baseline>D1, D14 (before), D14 (after), D28 (before), D28 (after), D60 (before), D60 (after), D90; D1, D14 (before), D14 (after)>D60 (after), D90 D1=D14 (before)=D14 (after)=D28 (before)=D28 (after)=D60 (before); D28 (before)=D28 (after)=D60 (after)=D90

VRS: Verbal rating scale, SD: Standard deviation, VHS: Very high significant

Table 4: Comparison of VRS for air stimuli between different time intervals in different groups

Time intervals	Mean±SD of VRS in different groups		
	VivaSens (Group 1)	Propolis (Group 2)	Water (Group 3)
Baseline	2.00±0.58	1.88±0.60	1.52±0.65
Day 1	1.60±0.65	1.56±0.58	1.12±0.60
Day 14 (before)	1.56±0.65	1.56±0.51	1.00±0.50
Day 14 (after)	1.04±0.61	1.08±0.49	1.04±0.46
Day 28 (before)	1.20±0.41	1.04±0.35	1.00±0.58
Day 28 (after)	0.80±0.50	0.48±0.51	0.96±0.35
Day 60 (before)	0.80±0.41	0.76±0.44	1.04±0.35
Day 60 (after)	0.52±0.51	0.52±0.51	0.96±0.35
Day 90	0.36±0.49	0.36±0.49	0.96±0.35
Friedman test	$\chi^2=120.818$, df=8, $P=0.000$ (<0.001), VHS	$\chi^2=124.792$, df=8, $P=0.000$ (<0.001), VHS	$\chi^2=34.546$, df=8, $P=0.000$ (<0.001), VHS
Wilcoxon signed-ranks test	Baseline>D1=D14 (before)>Day14 (after)=D28 (before)>D28 (after)=D60 (before)>D60 (after)=D90	Baseline>D1=D14 (before)>day 14 (after)=D28 (before)>D60 (before)>D28 (after)=D60 (after)=D90	Baseline>D1=D14 (before)=day 14 (after)=D28 (before) =D28 (after)=D60 (before)=D60 (after)=D90

VRS: Verbal rating scale, SD: Standard deviation, VHS: Very high significant

there is a need to develop new product which relieves the symptoms in long run.

This study aimed to evaluate and compare the clinical efficiency of 30% ethanolic extract of propolis, VivaSens desensitizer, and distilled water as placebo in treating dentinal hypersensitivity. Propolis is a natural resinous substance collected from sprouts, exudates of tree, and other parts of plant and modified in beehive by addition

of salivated secretions and wax. Its composition varies according to its origin. Several biological properties have been reported in the literature for propolis such as antimicrobial, anti-inflammatory, antioxidant, and free radical scavenging action.^[10] In 1999, Mahmoud *et al.* conducted a pioneer study on the effect of propolis on dentinal hypersensitivity *in vivo*. In this study, propolis was applied twice daily on teeth with hypersensitivity. It was concluded that propolis had a positive effect in

the control of hypersensitivity. The bioflavonoids in propolis may interact with the dentine, thus forming crystals that reduce fluid movement within dentinal tubules and, consequently, reduce dentine sensitivity. This theory was based on the study by Sabir *et al.*, in which direct pulp capping was performed with propolis-derived flavonoids and mild and moderate inflammation was seen in the pulp chamber at weeks 2 and 4, partial dentin bridge formation was detected beneath the pulp capping material at 4th week.^[8,11]

The result of the present study demonstrated a significant decrease in mean hypersensitivity in both the test group as compared to control group after 90-day period. Intergroup comparison revealed reduction in mean dentinal hypersensitivity in propolis group which was comparable to VivaSens group. This is in agreement with the study of Madhavan *et al.* who found a significant reduction in dentinal hypersensitivity after 3 months application of propolis extract casein phosphopeptide-amorphous calcium phosphate F and sodium fluoride.^[6] Application of propolis resulted in significant reduction in intensity of pain followed by increase in the efficacy of agent over a period of time with maximum relief from the pain by the end of study period, i.e., 3 months.

Another study by Purra *et al.* evaluated the efficacy of saturated solution of propolis for the treatment of dentinal hypersensitivity as compared to distilled water and 5% potassium fluoride. There was no significant difference in the immediate host treatment period but showed a significant decrease at the end of 1st and 2nd week. At 4 weeks and 3 months period, a comparison was made and no significant difference was seen. The immediate effect was attributed to tubular sealing which prevented the flow of dentinal fluid in the tubules and sustained effect was attributed to the stable nature of deposit so formed.^[12]

VivaSens is a protein precipitate type desensitizer that seals exposed dentin by the precipitation of calcium ions and proteins. It contains polyethylene glycol dimethacrylate which triggers the precipitation of plasma proteins in the dentinal tubules. It also contains glutaraldehyde, which is a cross-linking reagent capable of bonding to amine groups of proteins. Potassium fluoride provides additional protection. In the present study, VivaSens desensitizer was effective in reducing dentinal hypersensitivity when compared to propolis at the end of 3 months. This was in accordance with a study done by Asrani *et al.* who evaluated the ability of desensitizing agents VivaSens and laser (diode) on dentinal tubule occlusion and its effectiveness over time using scanning electron microscopy. Both VivaSens and diode laser were equally effective in the

obliteration of dentinal tubules just after application as well as after 15 days of treatment.^[13]

Although when intragroup comparison was made placebo group did not show significant decrease in hypersensitivity when compared to tested group, a strong placebo effect has been reported in the literature concerning dentinal hypersensitivity management which could be attributed to spontaneous healing due to deposition of reparative dentine formation and also other treatment approaches could be present which confound the result.^[4]

The main aim in the treatment of dentinal hypersensitivity is to provide a long-lasting relief, but none of currently available treatment modalities fulfill these criteria. In addition to this, there are no standard clinical procedures in the reported literature to test the given study materials making the comparison of data from these studies difficult. Further, research is needed to clarify the mechanism and etiology of this uncomfortable clinical situation.

CONCLUSION

Within the limitations of this study, it can be concluded that both desensitizing agent, i.e., propolis extract and VivaSens desensitizer were effective in relieving dentinal hypersensitivity. Their effectiveness was not different from each other but was different from the placebo. Furthermore, expanding the use of propolis for DH treatment in dental clinics will help corroborate its effectiveness and safety may result in this product becoming the treatment of choice for moderate and mild dentinal hypersensitivity.

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C-reactive Protein as a Morbidity Predictor in Ischemic Stroke

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Abstract

Introduction: Cerebrovascular accident (CVA) is an important health problem worldwide. Various studies proved that C-reactive protein (CRP) at admission was found to be a predictor of functional disability in ischemic CVA. Inflammation also regulates the production of the acute phase proteins such as CRP, fibrinogen, and serum amyloid A. CRP is one of the substances, present in the atherosclerotic lesion, more specifically in the vascular intima.

Aim: The aim of the study was to evaluate the role of CRP as a morbidity predictor in acute ischemic stroke, to study the CRP level pattern in ischemic stroke and to study the correlation between severity level of stroke and CRP level.

Materials and Methods: The study of CRP in ischemic stroke was carried out in the medical wards of Department of Medicine, Tirunelveli Medical College. We examined the association between the level of CRP at different stages after stroke and outcome.

Results: Among patient with positive CRP, 13 were male and eight were female CRP level status positive in 21 patients. There is no association between age of patient and CRP and age factor does not influence the group pattern. Severe disability is more in CRP positive compared to CRP negative group.

Conclusion: CRP is increased in a significant fraction of ischemic stroke. Patients with increased CRP had invariably more deficit during admission and patients with low CRP had good prognostic outcome 4 weeks after onset of stroke.

Key words: Atherosclerosis, C-reactive protein, Cerebrovascular accident, Ischemic stroke

INTRODUCTION

Cerebrovascular accident (CVA) is an important health problem worldwide. Various studies proved that C-reactive protein (CRP) at admission was found to be a predictor of functional disability in ischemic CVA. Inflammation also regulates the production of the acute phase proteins such as CRP, fibrinogen, and serum amyloid A. CRP is one of the substances, present in the atherosclerotic lesion, more specifically in the vascular intima, where it colocalizes with monocytes, monocyte-derived macro plaques, and lipoproteins.^[1] CRP is a phylogenetically, highly conserved

plasma protein with homologs in vertebrates and many invertebrates, that is part of the systemic response to inflammation. It is an acute phase protein and a member of the family of pentraxins, CRP was originally observed in 1930 in the plasma of patients with acute infections, where it reacts with the C. Polysaccharide of pneumococcus.^[2] The major part of the CRP present in the plasma comes from the liver, where the synthesis of CRP is mainly regulated by interleukin (IL-6), which in turn is unregulated by other inflammatory cytokines such as IL-1 and TNF α . Small amounts of CRP can also be produced locally. CRP had been detected on the surface of about 4% of normal blood lymphocytes, and CRP can be produced locally in the atherosclerotic lesions by smooth muscle cells and monocytic cells. Locally in the atherosclerotic lesions by smooth muscle cells and monocytic cells.^[3] The structure of CRP is important for its stability and the execution of its function. CRP is composed of five identical 21,500 Da subunits. On dissociation of its pentameric structure, CRP subunits undergo a spontaneous and irreversible

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conformational change. The loss of the pentameric structure of CRP results in modified or monomeric CRP (MCRP) which is a naturally occurring form of CRP and is tissue-based rather than the serum-based molecule. MCRP is less soluble than CRP and tends to aggregate, and it has been described to induce mRNA of chemokines and expression of adhesion molecules in human cultured coronary artery endothelial cells.^[4] Thus, next to circulating native pentameric CRP, MCRP can also promote a pro-inflammatory phenotype and exert atherogenic effects in human endothelial cells, although it may be in a less potent manner than native CRP. Most recent studies report that CRP is an independent predictor of risk of atherosclerosis, cardiovascular events, atherothrombosis, hypertension, and myocardial infarction. Of several inflammatory markers studies, CRP emerged the most powerful inflammatory predictor of future cardiovascular and cerebrovascular risk. Furthermore, the patient with elevated CRP levels within 72 h of stroke has an increased risk of mortality.^[5] CRP in ischemic stroke predicts outcome and identifies patients who are at risk for future vascular events and early mortality. CRP has also been found to be elevated in patients with ischemic stroke, correlating with the size of the infarct as evidenced by CT scan. Levels of CRP are consistently associated with cardiovascular disease and predict myocardial infarctions and stroke. Thus, CRP is useful and a reliable predictor of cerebrovascular events.^[6]

Aim

The aim of the study was to evaluate the role of CRP as a morbidity predictor in acute ischemic stroke and the correlation between severity level of stroke and CRP level.

MATERIALS AND METHODS

The study of CRP in ischemic stroke was carried out in the medical wards of Department of Medicine, Tirunelveli Medical College Single center observation prospective hospital based study. Inclusion criteria: Stroke as defined by the WHO is a rapidly developing clinical signs of focal (at times global) disturbances of cerebral function lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin, all patients with computed tomography (CT) proven case of ischemic stroke, first episodes of ischemic stroke, do not satisfy and of exclusion criteria exclusion criteria: Age >75 or <15 years, patients with Tia, patient with previous H/o stroke, TIA, patients with hemorrhagic stroke, tumor, sub arachnoid hemorrhage, patients with head injury within 3 months, CT negative stroke, patient who reserved aspirin treatment outside, patient with H/o hypertension, diabetes, heart disease collagen disorders, hyperlipidemia, and T.B arteritis were excluded. Clinical history was recorded from

either the patient or his/her relatives. Special emphasis was given to presenting complaint, mode of onset, presence or absence of seizures, loss of consciousness, headache, and vomiting. Apart from routine observations, makers of atherosclerosis such as carotid arteries status of peripheral vessels, carotid thrill, and B.P were noted. Each patient was assessed according to a fixed protocol. The first evaluation was conducted 24–48 h after admission. A detailed clinical profile was obtained. Neurological deficits such as aphasia, cranial N Palsies, limb weakness, sensory impairment, cerebellar dysfunction, conjugate gaze deviation, and hemianopia were elicited by a standard comprehensive bedside neurological examination. Functional score was assessed using Barthel index. CRP was measured by the Nephelometric method. Patients were reassessed on the 5th day and condition reviewed. Third evaluation was at 4th week of follow-up. According to the Barthel index, patients were divided into three groups. Barthel index <41 Severely disabled, Barthel index 41–60 moderately disabled, and Barthel index >60 mildly disabled. Detailed analysis of data was performed. Univariate analysis was done by Chi-square test and multivariate analysis by logistic regression.

RESULTS

The following observations were made out of the 49 patients, 21 patients had an abnormal increased CRP and 28 patient had normal level. Among patient with positive CRP, 13 were male and eight were female CRP level status positive in 21 patients (i.e.,) 42.85% CRP level positive in

Table 1: Sex-wise distribution of CRP level

Sex	CRP negative	CRP positive	Total
Male	18	13	31
Female	10	8	18
Total	28	21	49

CRP: C-reactive protein

Table 2: Age-wise distribution of CRP level

Age	CRP negative	CRP positive	Total
>60	12	10	22
<60	16	11	27
Total	28	21	49

CRP: C-reactive protein

Table 3: Outcome score and CRP

Outcome	Barthel index	CRP positive	CRP negative	Total
Severely disabled	<41	15	7	22
Moderately disabled	41–60	6	17	23
Mildly disabled	>60	0	4	4

males 26.5%, percentage positive female is 16.32% Table 1. There is no statistical significance, hence sex does not influence the CRP of the patient since Chi-square test $\chi^2 = 0.0292$ $P > 0.05$. There is no association between age of patient and CRP Chi-square, test $\chi^2 = 0.109$ $P > 0.05$. Hence, age factor does not influence the group pattern (CRP positive) Table 2. Severe disability is more in CRP positive compared to CRP negative group. Barthel index was <41 in severely disabled group. All patients who had aphasia at the time of admission were CRP positive and belonged to the severely disabled group. All patients who had conjugate gaze deviation were CRP positive and belonged to the severely disabled group. All patients with power less than medical research council grade 4 were CRP positive Table 3.

DISCUSSION

Sikka *et al.* (1960, Kanpur) in their study of ischemic cerebrovascular disease (cerebral thrombosis) found, maximum number of cases fell in 5–6th decades with mean age 61.8 years, this study also confirms the same.^[7] A study done in Western European region, male stroke incidence was 33% higher, and stroke prevalence was 41% higher than the female, with large variations between age bands and between population Worldwide, stroke is more common among men, but women are more severely ill.^[8]

In an experimental acute stroke, the release of inflammatory mediators (e.g., IL-1, IL-6, and tumor necrosis factor- α) in direct response to brain injury occurs within 2 h of onset of focal ischemia,^[9] and anti-inflammatory therapies are neuroprotective.^[10,11] Beamer *et al.*^[12] found significantly elevated IL-6 in patients after stroke in whom intercurrent infection had been excluded. Elevated IL-6 and CRP concentrations were present in patients with large established infarcts on CT but not in those with lacunar stroke. In our study, patients with elevated CRP had higher NIHSS scores and were more likely to have CT evidence of cortical infarction on scans performed predominantly within 12 h of admission. These findings support the observations of Beamer *et al.* and are consistent with elevated CRP reflecting the extent of brain infarction. However, since a detailed search for concurrent infection

was not undertaken in our study, it is impossible to exclude the possibility that an acute infection at the time of sampling was responsible for both the poor clinical state and the elevated CRP.

CONCLUSION

The present study identified elevation of CRP in ischemic stroke and a high CRP is clearly associated with more severe stroke and high mortality. Patients with increased CRP had invariably more deficit during admission. Patients with low CRP had good prognostic outcome 4 weeks after onset of stroke. The further periodic advance and follow-up studies should be needed to sort out the possibility that stroke patients may be at greater risk of subsequent cardiovascular complications or death and severe neurological deficit.

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A Study on Noise-induced Hearing Loss of Police Constables

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Abstract

Introduction: Noise is defined as aperiodic complex sound. Noise is a common cause of hearing loss in adults. Hearing loss due to injurious noise at the workplace is referred to as occupational noise-induced hearing loss (ONHL). Research has shown that sounds >85 dB can cause damage to our hearing. Policemen are the people who are exposed to traffic noises than any other people and are the least to care an audiological evaluation.

Aim: The aim of the study was to study the incidence of NIHL in police constables and to study the effect of age, personal habits such as smoking/drinking and medical conditions such as diabetes and hypertension on hearing loss.

Materials and Methods: The subjects were 50 police personnel (43 - males and 7 - females). A detailed history was taken regarding the number of years of service, past ear disease, and past medical conditions affecting hearing. All the subjects underwent routine ear nose and throat examination and pure tone audiometry to identify detectable hearing loss. All the subjects had normal hearing on recruitment.

Results: NIHL was present in 94% of subjects. The severity of NIHL was mild in 26% of subjects.

Conclusion: NIHL is preventable. The NIHL is common in traffic policemen. Early detection and prevention of hearing loss will play a major role in improving the quality of life in traffic police.

Key words: Hearings loss, Noise, Prevalence, Sensorineural hearing loss

INTRODUCTION

Hearing loss associated with exposure to noise has been well known in boilermakers, iron and copper smith, artillery, and salt refineries. Urbanization and excessive household noise also play a significant proportion of noise trauma nowadays.^[1] Occupational hazard in case of a traffic policeman is not just to ignore which play a major role in their lifestyle and behavior. Exposure to intense sound can result in temporary or permanent hearing loss which depends on several factors including the acoustic characteristics of the sound such as intensity, duration, and

frequency content, length of exposure, and susceptibility of the individual.^[2] Noise-induced hearing loss (NIHL) is caused by sustained, repeated exposure to excessive sound levels. NIHL is a major preventable occupational health hazard. The main site of impairment is the outer hair cells of the cochlea, where the damage is irreversible. Initial exposure to excessive sound level causes temporary dullness of hearing (temporary threshold shift) which usually recovers within 24 h of exposure.^[3-5] If there is repeated sustained exposure, the threshold shift becomes permanent (permanent threshold shift) due to nerve fiber degeneration. Health effects of noise include both the auditory as well as non-auditory effects. The harmful effects of noise on hearing have been known since the middle of the 19th century and condition like "Boilermaker's deafness" are documented. In the early times, the noise was limited to working places such as industry and construction sites. Today the profile of noise sources is changed with noisy activities, entertainments, music, and transportation. The noise from vehicles has increased tremendously due to

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mushrooming number of various types of vehicles plying on the roads. The production of such high-level of noise from these vehicles can have impact on hearing of persons exposed.^[6]

AIM

The aim of the study was to study the incidence of NIHL in police constables and to study the effect of age, personal habits such as smoking/drinking and medical conditions such as diabetes and hypertension on hearing loss.

MATERIALS AND METHODS

A survey based cross-sectional study conducted in the Department of Ear Nose and Throat (ENT), Tuticorin Medical College Hospital. The subjects were 50 police personnel (43 - males and 7 - females). A detailed history was taken regarding the number of years of service, past ear disease, past medical conditions affecting hearing. All the subjects underwent routine ENT examination and pure tone audiometry to identify detectable hearing loss. All the subjects had normal hearing on recruitment. Diagnosis of NIHL was based on the history of occupational noise exposure, bilateral hearing loss, hearing loss >25 dB at 4 KHz in two consecutive audiograms, and no significant medical history is affecting hearing. The severity of NIHL was based on the WHO grading. Hearing within 0–25 dB or loss (better ear) is classified as normal hearing, 26–40 dB (better ear) as mild impairment, 41–60 dB (better ear) as moderate impairment, 61–80 dB (better ear) as severe impairment, and >80 dB (better ear) as profound impairment. These ranges of levels are categorized as such by averaging the hearing level at frequencies 500 Hz, 1000 Hz, and 4000 Hz in the better ear.

RESULTS

NIHL was present in 94% of subjects. The severity of NIHL was mild in 26% of subjects and 38% having moderate and severe in 36%. The degree of high-frequency hearing loss ranged from mild to moderate. The dip at 4 KHz was >40 dB in 38% of subjects in the age range of 40–49 years and 52% of the subjects in the age range of 50–59 years. 20% had 40 dB dip at 4 KHz sloping hearing loss (descending curve) was seen in 92% of the subjects unilaterally/bilaterally. Notched audiogram (4 KHz notch) was obtained in 12% of the subjects unilaterally/bilaterally. History of non-insulin dependent diabetes mellitus (NIDDM) was reported by

22% of the 50 people with severe NIHL compared to 78% with mild NIHL. 38% were the smoker for more than 20 years also having the sloping pattern in pure tone audiogram. However, there is no specific change in 12% of hypertensive individuals.

DISCUSSION

The WHO estimates that globally 16% of individuals have a moderate to a greater degree of hearing loss due to occupational noise exposure. Chronic exposure to traffic noise could be an important source of occupational hearing loss, especially in motorcycle police officers.^[7,8] The first signs of NIHL can be observed in the typical 4000-Hz “notch” observed on audiograms, indicating a loss of hearing ability in the middle of the frequency range of human voices.^[9] Many theories attempt to explain why the region around 4 KHz seems to be more susceptible to the broadband noise. The region of the cochlea associated with 4 KHz is more vulnerable to damage because of difference in cochlear mechanics, cochlear metabolism or blood supply and noise amplification by external ear in the 2–4 KHz region by the time noise reaches the inner ear. NIHL causes damage to hair cells starting in the basal turn of the cochlea. Outer hair cells are affected by the inner hair cells. Selective 4000 Hz hearing loss is characteristic of the onset of NIHL, selective 4000 Hz hearing loss is thought to indicate early or moderate NIHL and to be specific for hearing impairment, for this reason, making it an appropriate measurement for our study.^[9] Audiogram in NIHL shows a typical notch at 4 KHz both air and bone conduction. It is usually symmetrical on both sides. The patient may have tinnitus, difficulty in hearing in noisy surroundings in an early stage, later notch deepens and widens to involve lower and higher frequencies. Our result is similar to that of other studies showing that the prevalence of NIHL is directly proportional to increasing age and longer duration of service.^[10,11] NIHL has been reported in police personnel worldwide. A high incidence (94%) of NIHL is reported in the present study. This is similar to the findings of other studies where the prevalence of NIHL was found to be 28% in French police officers,^[2] 66.4% in traffic police personnel in Kathmandu city,^[1] 81.2% in Pune traffic police^[12] in India, and 84% in traffic police in Jalgaon urban center in India. The high prevalence may be attributed to longer duration of service (all the subjects in the present study had served for more than 20 years) and greater noise pollution in India. In the present study, 26% of the subjects had mild NIHL. This finding is similar to study conducted in the police force in Brunei Darussalam where 45.6% were found to have mild to severe NIHL. Of this the majority (93%) had mild NIHL, 3.5% had moderate NIHL, and

another 3.5% had severe NIHL. Further 21.7% of the subjects in the age range of 40–49 years and 29.6% of the subjects in the age range of 50–59 years had mild NIHL, increasing age and longer duration of service had an effect on NIHL.

CONCLUSION

NIHL is an incurable but preventable occupational condition. This study shows that increasing age, longer duration of service, and presence of NIDM are significant associated factors for NIHL. Preventative strategies such as the adequate provision of a hearing protective device, regular education and training for the employer and employees, implementation of a hearing conservation program at the workplace, and regular health surveillance (audiometry) for police personnel with exposure to excessive noise, can help address the problem. Persons who have to work at places where noise is above 85 dB should have pre-employment and then annual audiograms for early detection. Ear protectors should be used. Introduction of stringent legislations regarding usage of horns Organization of intensive public awareness campaigns regarding ill effects of noise, via print, and electronic media.

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Treatment of Vitiligo with 5-Fluorouracil after Microneedling of the Lesion

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Abstract

Background: Vitiligo is a chronic acquired disorder characterized by the development of depigmented macules which slowly enlarges with the concurrent appearance of new lesions.

Aim: The aim is to study the efficacy of treating vitiligo by microneedling followed by application of 5-fluorouracil on vitiligo patches.

Materials and Methods: This study was conducted in a tertiary hospital from March 2017 to August 2017. For this study, we selected about 50 patients in the age group of 10–50 years who had been taking treatment for vitiligo for 2–3 years without much improvement. We suggested them about needling with 5-fluorouracil application over vitiligo patches. The procedure was performed at a gap of 2 weeks on vitiligo patches of various patients for about 3 months.

Result: After about 1 month of this procedure, we noticed an improvement in about 40% of patients with some erythema and hyperpigmentation developing on the margins of vitiligo patches. Gradually more than 50% of patients had similar improvement by the end of 2 months. After 3 months, about 60% of patients had hyperpigmentation in the vitiligo lesions with almost complete pigmentation in very small patches; larger ones had less pigmentation and 40% did not have any pigmentation from the previous state.

Conclusion: 5-fluorouracil is a simple and effective method for treating small vitiligo patches (< 5 cm diameter generally) with no major side effects. It is a cost-effective procedure in treating a very resistant disease, i.e., vitiligo, especially for small lesions.

Key words: 5-fluorouracil, Microneedling, Pigmentation, Vitiligo

INTRODUCTION

Vitiligo is a common form of localized depigmentation. It is an acquired condition resulting from the progressive loss of melanocytes. It is characterized by milky white sharply demarcated macules. According to a recent Vitiligo Global Issues Consensus Conference, the term “vitiligo” can be used as an umbrella term for all non-segmental forms of vitiligo (including acrofacial, mucosal, generalized, universal, mixed, and rare variants of vitiligo).^[1]

It is stated that vitiligo affects 0.5–1 % of the world's population.

It can begin at any age, and the prevalence is probably the same in sexes.

Various theories have been suggested for the etiology of vitiligo; the autoimmune theory is currently the leading hypothesis and is supported by strong evidence. It is based on the clinical association of vitiligo with a number of disorders also considered to be autoimmune or autoinflammatory.^[1] Among autoimmune diseases, the strongest association is with thyroid disease.

Histochemical studies show a lack of dopa-positive melanocytes in the basal layer of the epidermis. Electron microscopic studies confirm the loss of melanocytes. In inflammatory vitiligo, where there is raised erythematous border, there is an infiltrate of lymphocytes and histiocytes.

Medical treatment is the primary mode of therapy to achieve repigmentation. However, in patients recalcitrant to medical treatment alone, various surgical therapies can be used either alone or in conjunction with medical treatment to achieve

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regimentation provided that the disease is stable. Needling followed by topical application of 5% 5-fluorouracil is a recent advancement to the treatment modality of vitiligo. In the present case series, we report some cases of vitiligo who had no or minimal regimentation of the achromic patches with conventional therapy and responded to addition of needling with the application of topical 5-fluorouracil treatment leading to significant repigmentation.

MATERIALS AND METHODS

This study was conducted at Baba Raghav Das Medical College, Gorakhpur, Uttar Pradesh, from March 2017 to August 2017.

For this study, we selected about 50 patients in the age group of 10–50 years who had been taking treatment for vitiligo for 2–3 years without much improvement. Some were taking NBUBV therapy also along with oral and topical medication. Their disease was stable for 3–4 months on an average. We suggested them about needling with 5-fluorouracil application over vitiligo patches. The procedure was performed at a gap of 2 weeks on vitiligo patches of various patients for about 3 months. They were explained about the side effects which might occur and asked to sign on the consent form for the procedure. We tried to take those patients only who had small patches of vitiligo to avoid discomfort and better assessment.

5-fluorouracil, available in cream form, is needed along with 26G needle and gloves. Under aseptic precautions, microneedling was done on the patch followed by application of 5-fluorouracil in minor operation theatre (OT). The patients were made to sit for 1 h after application so as to check for any side effects.

RESULT

After about 1 month of this procedure, we noticed an improvement in about 40% of patients (20) with some erythema and hyperpigmentation developing on the margins of vitiligo patches. Gradually more than 50% of patients (25) had similar improvement by the end of 2 months. After 3 months, about 60% of patients (30) had hyperpigmentation in the vitiligo lesions with almost complete pigmentation in very small patches; larger ones had less pigmentation and 40% (20) did not have any pigmentation from the previous state. We can see in Figure 1, a male patient having a small vitiligo patch on wrist has gradual hyperpigmentation after 2 months of treatment. Similarly a girl shown in Figure 2 had vitiligo patches on face that responded well to 5-fluorouracil application after 3 months of treatment

When these patients were followed up after 3 months, their pigmentation was still persistent and no progression of the disease was noted.

Duration of treatment (months)	Response in patients (%)
1	40 (20 patients)
2	50 (25 patients)
3	60 (30 patients)

DISCUSSION

More than 90% of patients had pain during the procedure; only a few had burning and erythema; no serious side effect was observed. This study shows that for small lesions of vitiligo, 5-fluorouracil application after needling is a cost-effective, safe, and easy method of treatment with minimal



Figure 1: Repigmentation in a small vitiligo patch on the wrist in a male patient after 2 months of treatment with 5-fluorouracil



Figure 2: Repigmentation in vitiligo patch over face in a girl after 3 months of 5-fluorouracil application

side effects although it is not reasonable for larger patches of vitiligo. It is comparable to a study by Sethi *et al.* in which dermabrasion was combined with 5- fluorouracil where erythema and serous discharge were noted in all patients.^[2]

A similar study was reported by Shashikiran *et al.* Efficacy of topical 5% fluorouracil needling in vitiligo. where more than 75% repigmentation was noted in 49% of the patches, 50–75% repigmentation was seen in 26% of the patches 25–50% repigmentation in 11% of the patches, whereas 14% of the patches responded poorly with less than 25% repigmentation^[4] (their study considered the number of patches and not the number of patients for assessment).

Application of 5-fluorouracil after therapeutic wounding, as a treatment for vitiligo, was introduced by Tsuji and Hamada in 1983.^[4,5]

A strong inflammatory reaction is seen after needling followed immediately by application of topical 5-fluorouracil. Due to this, there is local edema, which increases the intercellular spaces of the basal layer for a long time. Active melanocytes with frequently vacuolated cytoplasm are found migrating from the pigmented to the achromic epidermis through these enlarged intercellular spaces.

Further, the inflammatory mediators such as leukotrienes C4 and D4 are locally released, which would

stimulate melanocyte proliferation and migration. The metalloproteinase-2 synthesized by the keratinocytes during the epidermis remodeling process has been found to help in melanocyte migration. This favorable milieu, which persists for a long time, could explain the successful migration of melanocytes from the pigmented area to the achromic area.^[6]

In conclusion, we can say that 5-fluorouracil is a cost-effective way of treating vitiligo in patients with resistant patches of long duration.

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Study of Fasting and Postprandial Lipid Abnormality in Type 2 Diabetes Mellitus and Its Correlation with Vascular Complications of Diabetes

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Abstract

Introduction: High cardiovascular mortality which is associated with Type 2 diabetes mellitus (T2DM) is due to a prolonged, exaggerated postprandial (PP) state. The abnormal lipid profile in the PP state is more significant than that in the fasting state in causing atherosclerotic complications in T2DM.

Aims and Objectives: The objective of this study is to find fasting and postprandial lipid abnormality in T2DM patients and its correlation with vascular complications of T2DM.

Material and Methods: Fasting and PP lipids were measured in 150 T2DM patients. On the basis of normal and abnormal fasting lipid profiles, diabetic patients were divided into controls and cases, respectively, and evaluation for various complications was done and statistically analyzed.

Results: The result of this study showed a significant elevation in mean values of fasting blood glucose, serum cholesterol (SCH), low-density lipoproteins (LDL), very LDL, and triglycerides in the PP state in cases as compared to controls ($P < 0.05$). Waist-to-hip ratio in cases (mean 0.96 ± 0.02) was significantly higher ($P = 0.00$) as compared to that in controls (mean 0.93 ± 0.03). Microvascular complications such as retinopathy, nephropathy, and neuropathy were found significantly more in cases (46%, 55%, and 63%, respectively) as compared to controls ($P < 0.05$). Most common macrovascular complication observed in cases were IHD (24.6%) and least common were Peripheral Vascular Disease (10.6%). while there was no significant difference ($P > 0.05$) found in occurrence of macrovascular complications in between cases and controls.

Conclusion: Since we are in the PP phase for most of the day, it is important to estimate the PP lipid profile along with fasting lipid profile, as atherosclerosis is a PP phenomenon with respect to lipids, Thus correction in early phase can prevent complications. So in routine practice PP lipid profile along with fasting is warranted.

Key words: Type 2 diabetes mellitus, Lipid abnormality, Dyslipidaemia, Vascular complications of diabetes

INTRODUCTION

The growing incidence of Type 2 diabetes mellitus (T2DM) is a major problem in the modern world. DM is a group of metabolic diseases, which is characterized by chronic hyperglycemia, which results from the defects in the insulin secretion, insulin action, or both.^[1] Diabetic dyslipidemia

contributes to the excess morbidity and mortality in T2DM.^[2]

The abnormal lipid profile in the postprandial state is more significant than the abnormal lipid profile in the fasting state in causing atherosclerotic complications in Type 2 diabetics. The high cardiovascular mortality which is associated with T2DM is due to a prolonged, exaggerated, postprandial state.^[3] Persistent postprandial hypertriglyceridemia may result in proatherogenic environment leading to atherosclerosis and macrovascular disease in T2DM. It is being increasingly believed that atherosclerosis is a postprandial phenomenon as at least with respect to lipids, as we are in the postprandial phase for most of the day.^[4]

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It is not clearly known whether diabetic patients with macrovascular disease have greater abnormalities of postprandial lipid metabolism than those without. Hence, this study is being carried out to find the characteristics of postprandial lipid levels in patients with T2DM and its impact on vascular complications.

Aims and Objectives

The aims of this study are to find fasting and postprandial lipid abnormality in T2DM patients and to find the significance of postprandial dyslipidemia and its correlation with vascular complications of T2DM.

MATERIALS AND METHODS

The present study was carried out on 150 T2DM patients from the diabetic clinic or the indoor medicine wards in Government Medical College and Hospital, Jabalpur, M.P., India; on the basis of fasting lipids, we divided patients into cases and control. Cases were those with abnormal fasting lipid profile and controls were those with normal fasting lipid profile. Further evaluation for various complications was done according to protocol and statistically analyzed. The study was approved by the Institutional Ethics Committee before their participation; the patients and the volunteers were fully informed about the nature and the purpose of the study. Written consents were obtained from each of them.

Inclusion Criteria

Cases

All T2DM patients who were in the age group of 35–65 years on treatment with oral hypoglycemic agents (OHA) and were attending medicine Outpatient Department (OPD), diabetic clinic, and admitted in medicine wards with abnormal fasting lipid profiles were selected as cases.

Controls

All Type 2 diabetic mellitus patients which were in the age group of 35–65 years on treatment with OHA attending medicine OPD, diabetic clinic and admit in wards having normal fasting lipid profile were selected as controls.

Exclusion Criteria

The following criteria were excluded from the study:

- Type I DM patients
- Diabetic patient on hypolipemic drug
- Patients on insulin therapy
- Gestational diabetic patients
- Patients with thyroid disease
- Patient not willing for study.

Laboratory Assays

Under aseptic conditions, blood samples were drawn in the morning after an overnight (i.e., after 12 h) fast and 2 h after

meals. The serum was separated from the blood cells by centrifugation within 30 min of the collection of the blood. The separated serum was analyzed for lipid abnormalities.

Statistical Analysis

The data of the present study were recorded into the computers and after its proper validation, checked for errors and data were analyzed using the software SPSS 20 for windows. Appropriate univariate and bivariate analysis was carried out using the Student *t*-test for the continuous variable (age) and Chi-square (χ^2) test for categorical variables. All means are expressed as mean \pm standard deviation for continuous data, while qualitative information is expressed in proportion with a percentage. The critical levels of significance of the results were considered at 0.05 levels, i.e., $P < 0.05$ was considered statistically significant.

RESULTS

A total of 100 cases and 50 controls were included in the final analysis. Mean age of cases and controls were 53.9 ± 9.9 years and 51 ± 7.9 years respectively, on applying unpaired *t* test no significant difference was found ($P=0.073$). On applying unpaired *t*-test, there were significantly higher value of hemoglobinA1c (HbA1c) (8.70 ± 1.5 vs. 6.58 ± 1.1) and waist-to-hip ratio (WHR) (0.96 ± 0.02 vs. 0.93 ± 0.03) value found to be more in cases as compared to controls ($P < 0.05$). We observed a significant increase in both the fasting and the postprandial blood glucose levels in cases, as compared to those of their controls. Furthermore, the postprandial blood glucose level was significantly increased as compared to that in the fasting state in cases.

On applying paired *t*-test [Tables 1-3], there was a significant increase in SCH, low-density lipoproteins (LDL), very LDL (VLDL), and triglycerides (TG) postprandial state as compared to fasting state in both cases as well as controls ($P < 0.05$), there were significantly higher values of postprandial SCH, LDL, VLDL, and TGs in cases as compared to respective values in controls ($P < 0.05$), while high-density lipoproteins (HDL) was not found higher ($P > 0.05$).

On applying Chi-square test [Table 4], all three microvascular complications (peripheral neuropathy, diabetic retinopathy, and diabetic nephropathy) were found statistically more prevalent in cases as compared to controls ($P < 0.05$), while none of three macrovascular complications (ischemic heart disease [IHD], Peripheral vascular disease [PVD], and cerebrovascular accident [CVA]) in our study [Table 5] was not found statistically significant ($P > 0.05$).

Paired *t*-test was applied in between fasting and postprandial lipid profile of patients with various

Table 1: Comparison of mean postprandial lipid parameters

Parameters (mg/dl)	SCH	HDL	LDL	VLDL	TG
Cases (n=100)	215.30±55.01	39.53±9.50	129.52±37.68	42.02±16.8	207.87±70.32
Controls (n=50)	171.68±20.84	39.25±16.5	109.50±19.08	33.22±10.1	144.14±21.92
P value	<0.05	>0.05	<0.05	<0.05	<0.05

All values in mg/dl, mean±SD. SD: Standard deviation, SCH: Serum cholesterol, HDL: High-density lipoproteins, LDL: Low-density lipoprotein, VLDL: Very low-density lipoproteins, TG: Triglycerides

Table 2: Comparison of mean lipid parameters within cases (n=100)

Parameters (mg/dl)	SCH	HDL	LDL	VLDL	TG
Fasting	133.46±23.83	42.34±3.06	93.07±16.5	26.58±8.00	102.04±16.09
Postprandial	171.68±20.84	39.25±16.5	109.50±19.08	33.22±10.1	144.14±21.92
P value	<0.05	>0.05	<0.05	<0.05	<0.05

All values in mg/dl, mean±SD. SD: Standard deviation, SCH: Serum cholesterol, HDL: High-density lipoproteins, LDL: Low-density lipoprotein, VLDL: Very low-density lipoproteins, TG: Triglycerides

Table 3: Comparison of mean lipid parameters within controls (n=50)

Parameters (mg/dl)	SCH	HDL	LDL	VLDL	TG
Fasting	166.17±38.77	39.13±8.25	103.17±28.43	31.36±12.9	135.96±41.29
Postprandial	215.30±55.01	39.53±9.50	129.52±37.68	42.02±16.8	207.87±70.32
P value	<0.05	>0.05	<0.05	<0.05	<0.05

SCH: Serum cholesterol, HDL: High-density lipoproteins, LDL: Low-density lipoprotein, VLDL: Very low-density lipoproteins, TG: Triglycerides

Table 4: Comparison of fasting and postprandial lipid profile in patients with microvascular complications

Lipid parameters (mg/dl)	Peripheral neuropathy (n=75)			Diabetic retinopathy (n=60)			Diabetic nephropathy (n=70)		
	Fasting	PP	P	Fasting	PP	P	Fasting	PP	P
SCH	160.0±42.6	205.9±63.3	<0.05	159.5±42.6	204.0±54.0	<0.05	160.1±43.9	208.4±61.4	<0.05
HDL	39.9±6.9	40.1±11.0	>0.05	41.0±7.6	37.8±9.2	<0.05	40.3±7.5	40.7±16.5	>0.05
LDL	99.27±30.0	125.5±42.5	<0.05	100.8±30.3	124.2±41.6	<0.05	98.9±31.5	122.7±38.6	<0.05
TG	128.3±48.9	199.5±78.1	<0.05	124.6±45.4	192.8±79.1	<0.05	126.3±45.9	193.8±75.9	<0.05

All values in mg/dl, mean±SD. SD: Standard deviation, SCH: Serum cholesterol, HDL: High-density lipoproteins, LDL: Low-density lipoprotein, TG: Triglycerides

Table 5: Comparison of fasting and postprandial lipid profile with macrovascular complications among study group

Lipid parameters (mg/dl)	IHD (n=37)			PVD (n=16)			CVA (n=29)		
	Fasting	PP	P	Fasting	PP	P	Fasting	PP	P
SCH	149.0±42.6	199.3±54.0	<0.05	172.0±47.4	213.5±49.9	<0.05	171.1±36.7	218.8±55.6	<0.05
HDL	39.2±9.5	40.5±20.4	>0.05	39.3±6.7	39.2±7.1	>0.05	41.1±5.5	43.9±20.3	>0.05
LDL	96.1±28.6	123.4±39.1	<0.05	97.4±32.2	122.9±45.9	>0.05	111.7±29.2	134.2±30.5	<0.05
TG	118.0±42.4	183.4±69.7	<0.05	138.0±53.9	219.6±94.6	<0.05	132.6±53.7	192.9±65.2	<0.05

All values in mg/dl, mean±SD. SD: Standard deviation, SCH: Serum cholesterol, HDL: High-density lipoproteins, LDL: Low-density lipoprotein, TG: Triglycerides, IHD: Ischemic heart disease, PVD: Peripheral vascular disease, CVA: Cerebrovascular accident

complications [Table 6], and we observed that there were significant ($P < 0.05$) higher mean values of postprandial SCH, LDL, and TG as compared to fasting SCH, LDL, and TG, respectively, while HDL was observed not significant in patients with peripheral neuropathy and diabetic nephropathy ($P > 0.05$). There were significant higher mean values of postprandial SCH, LDL, and TG in patients with IHD and CVA as compared to their fasting SCH, LDL, and TG ($P < 0.05$), while LDL in peripheral vascular disease and HDL in all three macrovascular

complications (IHD, peripheral vascular disease, and CVA) was not significant ($P > 0.05$).

DISCUSSION

Diabetes is one of the leading health problems in modern world. Diabetic dyslipidemia contributes to excess morbidity and mortality in T2DM, and the abnormal lipid profile in postprandial state is more significant than lipid profile in fasting state as most in

Table 6: Comparison of various parameters with lipid profile

Parameters	Cases (Mean±SD)						Controls (Mean±SD)									
	Fasting (mg/dl)			Postprandial (mg/dl)			Fasting (mg/dl)			Postprandial (mg/dl)						
	SCH	HDL	LDL	TG	SCH	HDL	LDL	TG	SCH	HDL	LDL	TG	SCH	HDL	LDL	TG
Age (years)																
<50	157.9±34.1	37.5±7.5	96.4±21.3	133.1±41.2	212.9±59.6	39.3±9.7	123.1±34.0	218.7±86.6	131.3±18.2	41.9±1.7	88.7±11.8	99.9±13.4	172.1±20.4	39.8±21.2	109.6±20.1	149.2±17.8
>50	170.7±40.6	40.0±8.5	106.8±31.2	135.5±42.9	216.6±52.8	39.7±9.5	133.0±39.4	202.1±59.7	135.2±27.1	42.9±4.1	89.8±14.0	104.6±18.7	171.2±21.8	38.6±8.8	109.4±18.3	138.2±5.1
Sex																
M	155.0±27.5	49.1±74.0	94.5±26.5	133.4±42.5	209.2±50.1	37.0±7.8	126.2±37.1	211.2±76.1	132.4±20.8	42.4±2.3	90.2±11.0	101.0±19.1	172.3±21.6	36.9±7.3	113.0±20.7	144.7±23.8
F	177.0±44.8	39.4±8.5	111.5±28.0	136.0±42.1	221.1±59.3	42.0±10.4	132.7±38.3	204.7±64.9	133.9±24.8	42.3±3.7	88.1±14.5	103.2±12.4	171.0±20.5	41.8±22.6	105.7±16.7	143.5±20.2
Locality																
Rural	167.9±42.0	46.7±63.5	104.3±30.0	139.3±45.7	219.6±54.0	40.1±10.1	132.4±38.8	219.3±80.9	135.0±19.6	41.2±1.3	90.9±7.6	104.5±14.3	164.2±19.1	37.5±6.5	101.6±18.3±	142.3±23.4
Urban	162.7±31.4	38.9±6.5	100.9±25.2	125.6±32.5	206.6±56.8	38.3±8.2	123.7±35.2	184.7±31.2	132.4±23.8	42.8±3.3	88.6±14.1	101.2±16.8	174.3±21.0	39.9±18.9	112.3±18.8	144.8±21.7
Treatment history																
Regular	160.7±26.7	39.6±8.2	97.7±24.5	138.0±46.6	207.0±43.1	38.1±6.1	127.9±38.1	224.0±71.4	128.9±24.9	42.3±3.6	87.5±15.4	102.1±16.5	170.4±18.7	41.2±22.1	111.0±17.3	144.2±22.8
Irregular	168.4±42.7	39.0±8.3	105.4±29.8	133.4±40.4	218.7±59.1	40.1±10.6	130.2±37.8	201.3±69.3	137.2±19.6	42.5±2.4	90.9±9.4±	102.0±16.0	173.0±23.1	37.4±7.9	108.0±21.0	144.1±21.5
Duration of DM (years)																
<5	165.2±41.3	54.3±90.3	102.2±32.9	136.6±49.9	203.1±65.0	38.4±10.2	114.2±32.5	222.6±102.6	130.5±23.2	42.4±3.3	88.8±11.4	102.6±16.0	167.3±21.3	40.9±19.4	108.0±21.4	144.8±20.4
>5	166.7±37.8	39.1±6.7	103.6±26.2	133.8±38.2	221.3±48.8	40.1±9.2	137.1±38.0	200.6±46.4	138.6±21.0	42.4±2.4	90.1±15.6	100.8±16.7	180.9±17.1	35.8±6.4	112.7±12.9	142.7±25.6
HbA1C																
<6.5	183.1±41.9	39.3±6.6	101.3±37.6	161.7±55.8	201.5±89.9	42.5±11.0	117.2±38.5	236.2±111.4	130.5±23.6	42.0±2.1	91.7±8.6	106.7±12.7	165.3±21.8	35.3±6.0	108.0±18.0	143.1±25.0
>6.5	164.3±38.2	44.7±54.9	103.4±27.5	131.7±39.5	216.8±50.3	39.2±9.3	130.9±37.6	204.7±64.4	137.4±20.8	43.0±4.1	85.1±17.0	94.5±18.4	182.0±14.4	45.8±24.7	111.9±21.0	145.9±16.1
WHR																
<0.95	162.1±39.8	38.2±6.7	94.1±26.3	144.7±47.0	222.3±59.0	40.9±8.5	124.2±37.8	233.9±83.2	135.5±19.8	42.3±2.2	90.8±9.1	102.7±16.7	172.4±20.7	41.0±19.9	111.8±20.0	145.3±21.9
>0.95	168.5±38.3	47.4±64.9	108.3±28.5	129.0±38.3	211.4±52.7	38.8±10.0	132.5±37.6	193.3±57.6	128.8±27.0	42.5±4.2	86.4±17.4	100.8±15.3	170.3±21.6	36.1±6.9	105.4±17.2	142.1±22.5
SD: Standard deviation, SCH: Serum cholesterol, HDL: High-density lipoproteins, LDL: Low-density lipoprotein, TG: Triglycerides, DM: Diabetes mellitus, HbA1c: HemoglobinA1c, WHR: Waist-to-hip ratio																

SD: Standard deviation, SCH: Serum cholesterol, HDL: High-density lipoproteins, LDL: Low-density lipoprotein, TG: Triglycerides, DM: Diabetes mellitus, HbA1C: HemoglobinA1c, WHR: Waist-to-hip ratio

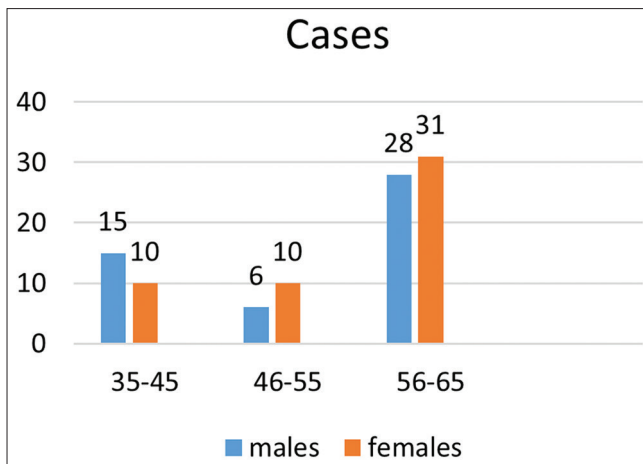


Chart 1: Distribution of cases according to age and sex

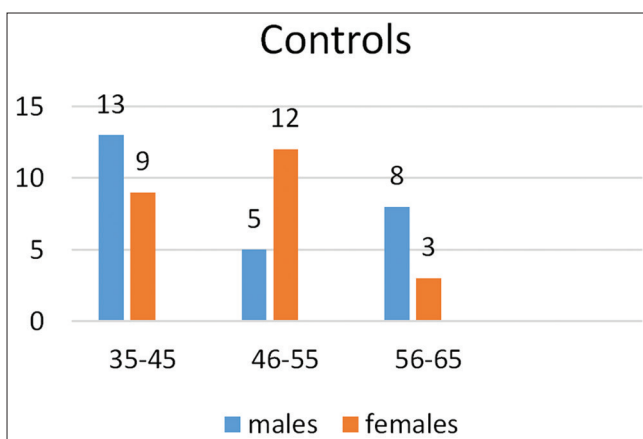


Chart 2: Distribution of controls according to age and sex

causing atherosclerotic complications. Atherosclerosis is a postprandial phenomenon with respect to lipids, as we are in the postprandial phase for most of the day, with an additional adverse effect of the meal-induced hyperglycemia.

In the present study, the postprandial lipid parameters (SCH, LDL, VLDL, and TG) were significantly increased in both cases as well as controls in comparison with their respective fasting parameters ($P < 0.05$). There were significantly increased postprandial lipid parameters (SCH, LDL, VLDL, and TG) of cases as compared to that of controls ($P < 0.05$). We also observed that there were significantly higher values of postprandial SCH, LDL, VLDL, and TG in patients with most of the various micro- as well as macro-vascular complications as compared to their respective fasting values ($P < 0.05$).

T2DM is metabolic disorder characterized by insulin resistance associated with proatherogenic cardiovascular risk profile which includes impaired glucose regulation, abdominal obesity, hypertension, atherogenic dyslipidemia,

and an increase in the microvascular and the macrovascular disease.^[5,6] As a result of the insulin resistance in the adipose tissue and obesity, the free fatty acid flux from the adipocytes is increased, which leads to an increased lipid synthesis in the hepatocytes. This is responsible for the dyslipidemia which is found in T2DM (elevated TGs, reduced HDL-cholesterol, and increased small dense LDL particles).^[7] The abnormal lipid profile in the postprandial state is more significant than the abnormal lipid profile in the fasting state in causing atherosclerotic complications in Type 2 diabetics.^[8] There are few studies that have reported that postprandial dyslipidemia is more important in the pathogenesis of the vascular changes and atherosclerosis and it increases the risk of the cardiovascular events.^[9-11]

The postprandial dysmetabolism and the associated oxidative stress may have a link with insulin resistance and T2DM, thereby increasing the incidence of cardiovascular disease disproportionately.^[12] Another study has proposed that cardiovascular disease morbidity and mortality associated with T2DM showed prolonged and exaggerated postprandial state.^[13]

CONCLUSION

In the present study, we found that there was very high occurrence of fasting and postprandial dyslipidemia in patients having diabetes, and when we compared postprandial dyslipidemia with fasting dyslipidemia in diabetic patients, we found that postprandial dyslipidemia was significantly higher than fasting dyslipidemia.

When we studied postprandial dyslipidemia in diabetic patients, we found a statistically significant association of postprandial dyslipidemia with increasing age, prolonged duration of disease, patients belonging to rural area, patients on irregular treatment, patients having other comorbid illness, and patients having higher HbA1c and increased WHR.

When we compared postprandial dyslipidemia and fasting dyslipidemia in diabetic patients having various vascular complication, we observed that there was a significant association between postprandial dyslipidemia and various complications including microvascular complications (peripheral neuropathy, diabetic retinopathy, and diabetic nephropathy) and macrovascular complications (IHD, CVA, and PVD). Hence, it can be concluded that postprandial dyslipidemia has the major contributory effect on various micro- and macro-vascular complications.

Hence, routine follow-up of postprandial dyslipidemia in diabetes may help in early diagnosis and prompt

management of various vascular complications which in turn can lead to improved quality of life.

Limitations of Study

1. Since our hospital being a tertiary center, more of the complicated diabetic patients were referred to medical college hospital so a community-based study might had given better idea about the prevalence of various complications.
2. We had included 150 diabetic patients which were a small number considering the high prevalence of diabetes in our society.
3. Since we had not included normal population as control group, it might had been the reason for variation in the findings observed in our study as compared to previous studies.
4. Fundus photography which is a gold standard for diagnosis of retinopathy was not available at our center.

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Comparative Evaluation of Intravenous Dexmedetomidine and Sublingual Nitroglycerin Spray to Attenuate Hemodynamic Response to Laryngoscopy and Intubation

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Abstract

Introduction: Laryngoscopy and intubation produce hemodynamic response due to increase in sympathetic and sympathoadrenal activity which manifest as increase in blood pressure and heart rate (HR).

Objective: This study was conducted to compare the effectiveness of intravenous (i.v) dexmedetomidine and sublingual nitroglycerin spray in attenuating the pressor response associated with laryngoscopy and intubation.

Materials and Methods: The study was carried out on 90 patients belonging to American Society of Anesthesiologists Grade I and II, aged 18–60 years, including either gender, scheduled for elective surgical procedure under general anesthesia.

Results: Systolic blood pressure, diastolic blood pressure, mean arterial pressure, and HR rise in all three groups. However, this rise was significantly less in dexmedetomidine group as compared to control and nitroglycerin group.

Conclusion: Dexmedetomidine (0.5 mcg/kg body weight i.v) is more effective for attenuation of hemodynamic response to laryngoscopy and intubation without undesired side effects and complications as compared to nitroglycerin spray.

Key words: Dexmedetomidine, Sublingual Nitroglycerin, Hemodynamic

INTRODUCTION

Laryngoscopy and intubation produce transient but marked sympathetic and sympathoadrenal response which manifest as increase in blood pressure and heart rate (HR).^[1-5] These can be tolerable in healthy patients, but in patients with cardiovascular compromise such as hypertension, ischemic heart disease, and cerebrovascular disease and in patients with intracranial aneurysms, even these transient changes in hemodynamic can result in potentially harmful effects

such as left ventricular failure, pulmonary edema, myocardial ischemia, ventricular dysrhythmias, and cerebral hemorrhage. Therefore, various drugs such as lidocaine spray, intravenous (i.v) fentanyl, i.v. magnesium sulfate, sublingual nifedipine, i.v. esmolol, and i.v. clonidine^[6-8] and procedures such as airway blocks (bilateral superior laryngeal nerve block and transtracheal recurrent laryngeal nerve block) have been tried to blunt this response, but none was found effective in completely attenuating this pressor response.

Dexmedetomidine is a potent and highly selective α -2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties. It produces hyperpolarization of noradrenergic neurons and suppression of neuronal firing in the locus coeruleus leads to decreased systemic noradrenaline release results in attenuation of sympathoadrenal responses and hemodynamic stability during laryngoscopy and tracheal intubation.

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Nitroglycerin is a nitrate and exerts its effect by being converted to nitric oxide in the body by mitochondrial aldehyde dehydrogenase. Nitric oxide is a potent vasodilator. Nitroglycerin produces dose-dependent relaxation of vascular smooth muscle. Therapeutic doses reduce systolic, diastolic, and mean arterial blood pressure (MAP), and in response to these effects, reflex tachycardia occurs.

Therefore, in search of a better agent, we compared dexmedetomidine, a newer α -2 agonist, 0.5 mcg/kg body weight with sublingual nitroglycerin spray 800 mcg for the attenuation hemodynamic response during laryngoscopy and intubation.

MATERIALS AND METHODS

The present study was carried out in the Department of Anaesthesiology, S.S. Medical College and associated S.G.M. and G.M. Hospitals, Rewa (M.P.) during July 2015–June 2016. After approval from the Institutional Ethical Committee, the study was conducted on 90 patients aged 18–60 years with American Society of Anesthesiologists Class I and II posted for elective surgery under general anesthesia. Patients with Mallampatti Grade III–IV, known hypersensitivity to dexmedetomidine or nitroglycerin, patients on antihypertensive drugs and cardiac disease, and patients having raised intracranial pressure were excluded from the study. The written and informed consent was obtained from the patients.

The patients fulfilling the selection criteria were randomly divided into three groups of 30 patients each depending on the drug given. Ninety patients were randomly divided into three groups of thirty patients each depending on the study drug given.

Group D: Received i.v. dexmedetomidine 0.5 mcg/kg diluted in 100 ml normal saline infused slowly over 10 min and 5 min before induction.

Group N: Received nitroglycerin 800 mcg sublingual spray 2 min before induction.

Group C: Received 100 ml normal saline i.v. 5 min before induction.

All patients were kept nil orally for at least 6 h before surgery. After shifting the patients to operation table, non-invasive blood pressure, electrocardiogram, and pulse oximeter were attached, and the parameters were recorded.

All the patients were uniformly premedicated with i.v. ondansetron 0.08 mg/kg and injection glycopyrrolate 0.04 mg/kg, 15 min before administration of the study drug.

The study drug was given as i.v. dexmedetomidine 0.5 mcg/kg diluted in 100 ml normal saline infused slowly over 10 min and 5 min before induction or nitroglycerin spray 800 mcg sublingually 2 min before induction.

Pre-oxygenation was done with 100% oxygen for 3 min. All patients were induced with injection propofol 2.5 mg/kg body weight, and muscle relaxation was facilitated with injection succinylcholine 1.5 mg/kg body weight. Laryngoscopy and intubation were performed 60 s after the administration of succinylcholine. The patients in which intubation cannot be performed within 20 s were excluded from the study. Anesthesia was maintained with 40% oxygen, 60% nitrous oxide, 1% sevoflurane, and intermittent doses of injection atracurium.

HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP were recorded just before induction, before intubation, and after intubation at 1, 3, 5, 7, 15, and 30 min.

More than 20% fall in MAP below baseline was considered as hypotension and was treated by decreasing sevoflurane and injection mephentermine 6 mg intravenously. More than 30% rise in MAP above baseline was considered hypertension. HR <60 bpm was considered bradycardia and HR <50 bpm was treated with injection atropine 0.6 mg intravenously. HR >100 bpm was considered tachycardia.

After completion of surgery, patients were reversed with injection glycopyrrolate 0.01 mg/kg and injection neostigmine 0.05 mg/kg and were extubated.

At the end of the study, the observations were tabulated and statistically analyzed using mean, standard deviation, *P* value, and student *t*-test. For comparison, $P \leq 0.05$ was taken to be statistically significant and <0.0001 was taken to be highly significant.

RESULTS

A total of 108 patients were assessed for eligibility, of which 15 refused and 3 did not meet the inclusion criteria. All the patients in three groups were comparable to each other with respect to age, weight, and sex [Table 1].

Baseline HR was comparable in all three groups. After giving study drug, there was a significant increase in HR in Group N from baseline, while significant decrease in HR was observed in Group D. At 1, 3, and 5 min after intubation, there was a rise in HR in all three groups from baseline. However, the rise in HR was significantly higher in Group N as compared to Group D and Group C.

Among Group C and D, this rise was significantly higher in Group C as compared to Group D. In Group D, rise in HR was slight after intubation and returned to baseline at 3 min after intubation. At 7 min after intubation, mean HR reached near baseline value in Groups C and N [Figure 1].

There was an increase in MAP, SBP, and DBP after laryngoscopy and intubation in all groups, but it was significantly higher in Group C as compared to Groups D and N and it was also significantly higher in Group N as compared to Group D at 1, 3, and 5 min after intubation. In Group D, this rise at 1 min was non-significant and returned to baseline at 3 min after intubation. At 7 min after intubation, these values reached near baseline value in Groups C and N also [Figures 2-4].

Hypotension was observed in 5 patients of Group N. Hypertension was found in 20 patients in Group C, not in any patient in Group D, and 2 patients in Group N. Tachycardia was seen in 13 patients in Group C, 1 patient in Group D, and 25 patients in Group N. Bradycardia was not observed in any patients [Table 2].

DISCUSSION

In our study, we found that injection dexmedetomidine given preoperatively was associated with significantly lesser increase in HR after laryngoscopy and intubation compared to control and nitroglycerine spray.

Similarly, there was an increase in MAP, SBP, and DBP after laryngoscopy and intubation in all groups, but this increase was significantly less in Group D as compared to Group C and Group N and it was also significantly less in Group N as compared to Group C at different time intervals [Figures 2-4].

Similar results were found by Scheinin *et al.*^[9] in their study “dexmedetomidine attenuates sympathoadrenal responses

to tracheal intubation” in which they found that the maximal average increase (vs. baseline) was 1% and 21% in systolic, 23% and 46% in diastolic arterial pressure, and 6% and 29% in HR in the dexmedetomidine and saline groups, respectively, just after intubation.

Reddy *et al.*^[7] found that the mean HR, SBP, DBP, and MAP levels in dexmedetomidine group were significantly lower than esmolol group and control group immediately after intubation. In our study, we also found lower mean HR, SBP, DBP, and MAP level in dexmedetomidine

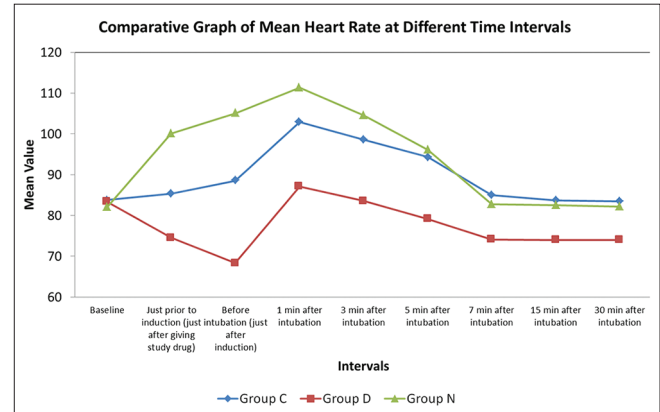


Figure 1

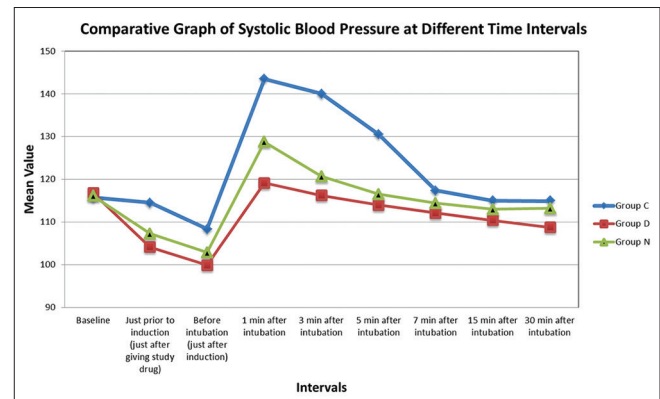


Figure 2

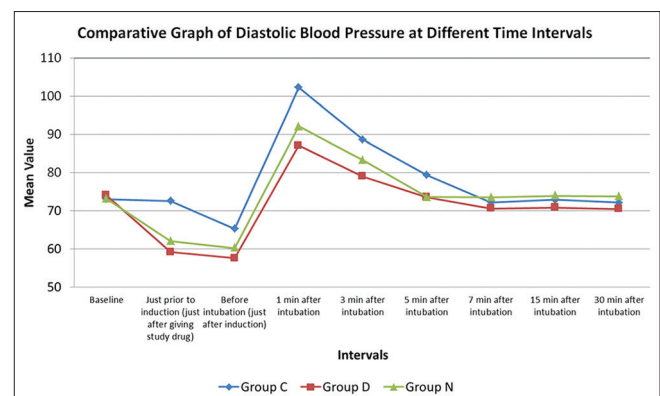


Figure 3

Table 1: Patient characteristics

Characteristics	Group D	Group N	Group C	P value
Age	35.4±12.6	39.36±11.93	39.93±10.86	0.27
Weight	55.7±5.50	54.5±5.64	55.1±6.01	0.72
Sex - male	20	11	11	0.17
Female	10	19	19	0.27

Table 2: Incidence of complications

Complications	Group C	Group D	Group N
Hypotension	0	0	5
Hypertension	20	0	2
Bradycardia	0	0	0
Tachycardia	13	1	25

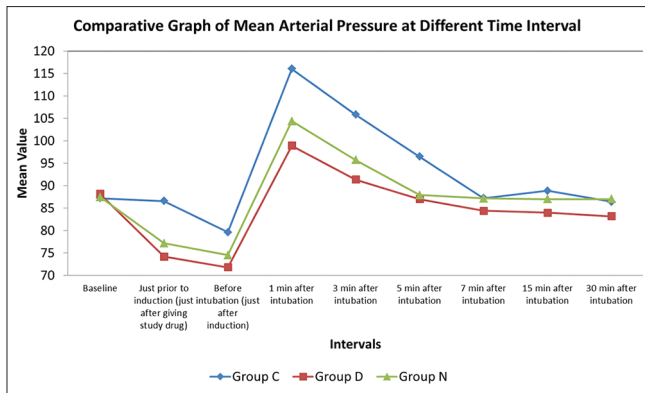


Figure 4

group in comparison with nitroglycerin and control group immediately after intubation.

Sarkar *et al.*^[8-12] studied i.v clonidine 3 mcg/kg body weight and dexmedetomidine 0.5 mcg/kg body weight for blunting pressor response during laryngoscopy and intubation. They found that the mean MAP, SBP, DBP, and HR was significantly lower after intubation in both dexmedetomidine and clonidine group as compared to control group. Similarly, we also observed significantly lower mean SBP after intubation in dexmedetomidine group as compared to control group.

Hypotension was observed in 5 patients of Group N. Hypertension was found in 20 patients in Group C, not in any patient in Group D, and 2 patients in Group N. Tachycardia was seen in 13 patients in Group C, 1 patient in Group D, and 25 patients in Group N. Bradycardia was not observed in any patient.

This dexmedetomidine-induced hemodynamic profile can be attributed to the known sympatholytic effects of α_2 -agonists. The α_2 -receptors are involved in regulating the autonomic and cardiovascular systems. Alpha-2 receptors are located on blood vessels, where they mediate vasoconstriction, and on sympathetic terminals, where they inhibit norepinephrine release. The decrease in HR by dexmedetomidine is due to a centrally mediated decrease in sympathetic tone and an increase in vagal activity. It seems that postsynaptic alpha-2 adrenoceptors and imidazoline receptors in the brainstem are involved.

The hemodynamic effect of nitroglycerin can be attributed to its vasodilatory action on vascular smooth muscle. Systemic arterial pressure may fall slightly in lower doses. Higher doses cause further venous pooling and may

decrease arteriolar resistance as well, thereby decreasing systolic and DBP and cardiac output and causing tachycardia by activation of compensatory sympathetic reflexes.

CONCLUSION

Dexmedetomidine (0.5 mcg/kg body weight i.v) is more effective for attenuation of hemodynamic response to laryngoscopy and intubation without undesired side effects and complications.

Nitroglycerin (800 mcg sublingual spray) also attenuates blood pressure response (less than dexmedetomidine) during laryngoscopy and intubation, but it produces reflex tachycardia which is undesirable.

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To Know the Diagnostic Accuracy of Ultrasonography for Major Salivary Gland Masses and Its Correlation with Histopathological Examination

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Abstract

Introduction: Major salivary gland pathologies are a significant source of morbidity in general population. The role of ultrasonography (USG) in the evaluation of salivary gland masses is become increasingly important due to the availability of high-frequency probe which permit visualization of more subtle anatomical and pathological details.

Aims and Objectives: The aim of this study is to know the reliability of USG as a diagnostic tool for the assessment of masses of major salivary gland.

Materials and Methods: The study was conducted in the Department of Radiodiagnosis, Gajra Raja Medical College and J.A. Group of Hospitals, Gwalior (Madhya Pradesh), in USG Machine SSD4000SV (Aloka Trivitron) from August 2011 to October 2012. A total 124 patients was enrolled in study after taking detailed history and relevant clinical examination. Subsequently, the patient was subjected to high-resolution USG followed by histopathological examination (HPE).

Results: According to the study, non-neoplastic pathologies 78 (62.9%) were more common than neoplastic salivary gland pathologies 46 (37.1%). Of 46 neoplastic pathologies, benign tumors 32 (69.57%) were more common than malignant 14 (30.43%). The age distribution of the patients with salivary gland neoplasm ranged from 1-80 years and Majority of belongs to the 30-70 years age group. Benign tumors were more common in 30-40 years age group. Malignant tumors were more common after 50 years of age. Male:female ratio for malignant tumors is 6:1 and equal in benign tumors. Parotid gland was the most common site accounting for 91.30% followed by submandibular gland (8.7%) of all salivary gland tumors. On USG examination, all tumors were hypoechoic. Most benign tumors (87.5%) had well-defined borders, but 12.5% of malignant tumors also had well-defined (sharp) borders. The internal structure of tumor was not a relevant indicator of malignancy. According to the study, the most common tumors were pleomorphic adenoma which accounted for 60.87% of all cases followed by mucoepidermoid carcinoma (17.4%) of all cases confirmed by HPE.

Conclusion: In our study, an excellent correlation was seen in the diagnosis of salivary gland masses between sonography (grayscale and color Doppler sonography [CDS]) and histopathology. Sonography (grayscale and color Doppler together) was found to be highly sensitive and specific in the diagnosis of salivary gland masses; however, it is more sensitive for detecting benign tumors and more specific for malignant tumors.

Key words: Adenocarcinoma, Color Doppler, Neoplasm, Pleomorphic adenoma, Salivary glands, Ultrasonography

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INTRODUCTION

Major salivary glands (parotid, submandibular, and sublingual) pathologies are a significant source of morbidity in general population. Salivary gland masses are commonly encountered by surgeon and radiologist in daily practice. Clinical examination is alone often insufficient to identify

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the origin and nature of lesion. Imaging is required in the vast majority of cases. Sonography is first imaging modality after clinical examination.^[1,2] Ultrasound is used to identify focal salivary gland mass, whether it is intraglandular or extraglandular.^[3] Color Doppler may help in diagnosing malignancy when there is disorganized internal color flow. The accuracy can be further enhanced by fine-needle aspiration cytology (FNAC) under ultrasound guidance.^[4] Computed tomography (CT) and magnetic resonance imaging (MRI) are best diagnostic aid, but both are highly expensive and not universally available.^[5-7] So we can say that Sonography, being a real-time, non-invasive, painless, relatively inexpensive and radiation free imaging modalities for the assessment of masses of major salivary gland.

Aims and Objectives

The aim of this study is to know the reliability of ultrasonography (USG) as a diagnostic tool for the assessment of masses of major salivary gland (benign/malignant neoplasm).

MATERIALS AND METHODS

The present study was conducted in the Department of Radiodiagnosis, G.R. Medical College and J.A. Group of Hospitals, Gwalior (Madhya Pradesh), in USG Machine SSD4000SV from August 2011 to October 2012. The informed consent and detailed history were taken, and relevant clinical examination was done. Subsequently, the patients were subjected to sonography.

The following sonographic parameters were studied in each case:

1. Size
2. Echogenicity
3. Echotexture
4. Vascularity
5. Ductal system of salivary gland
6. Bilateral cervical region for evidence of cervical lymphadenopathy.

FNAC/histopathology was done to confirm the sonographic diagnosis.

Inclusion Criteria

A total of 124 patients of all age groups attending the various outdoor and indoor departments of hospital with signs and symptoms related to salivary gland masses were included in the study.

Equipment

All the ultrasound examination was performed with real-time sonography equipment SSD4000SV (Aloka Trivivron

Pvt. Ltd., Tokyo Japan) using linear array transducer of frequency 7–12 MHz. As and when required 3.5 transducer was also used for adequate penetration, particularly in case of large salivary gland swelling.

Statistical Analysis

The SPSS software package was used for the analysis. Statistical significance was defined as a $p < 0.05$. Student's *t*-test and Chi-square test were used to calculate the significance between the variables.

OBSERVATIONS

A total of 124 patients with clinical symptoms pertaining to the salivary gland pathologies were assessed by high-resolution ultrasound and results showed that majority of 96 (77.4%) patients with salivary gland diseases belonged to ≤ 50 years of age. Male to female ratio is 1.3:1 [Table 1].

In sonographic findings, non-neoplastic salivary gland pathologies were more common 78 (62.9%) than neoplastic salivary gland pathologies 46 (37.1%) [Table 2]. Of 46 neoplastic pathologies, benign tumors were 32 (69.57%) and malignant tumors were 14 (30.43%) [Table 3]. Majority of the tumor in this study occurred between the ages from fourth to sixth decades. Benign tumors were more common in 30–40 years age group patients, whereas malignant tumors were common after 50 years. Male:female ratio 1:1 for benign tumors and 6:1 for malignant tumors were observed [Table 4].

In the study Parotid gland was the most common site accounting for 42/46 (91.30%) followed by submandibular gland 4/46 (8.7%) of all salivary gland tumors. All of 42 parotid tumours 30 (71.4%) were benign and 12 (28.5%) were malignant. where's in submandibular gland 50% were benign and 50% were malignant tumors (Table 5). All patients presented with swelling. Features of rapid growth, pain, and associated facial paralysis were considered as signs of malignancy. Ten of 46 patients presented with pain in swelling, all are malignant. Pain occurred in 71.4% of malignant tumors. Two patients with malignant tumor presented with facial nerve palsy accounting for 4.3%. Deep lobe involvement was seen in 2 patients presenting as parapharyngeal masses, in malignant tumour accounting for 4.3% of all tumors. 4 patients with malignant tumor presented as lymph node swelling in the cervical region 8.7% of all tumors [Table 6]. All tumors were hypoechogenic compared with the surrounding parenchyma. Most benign tumors (87.5%) had well-defined borders, but 12.5% of malignant tumors also had well-defined (sharp) borders. The internal structure of tumor was not a relevant indicator of malignancy. The color Doppler sonography (CDS) examination revealed that 68.7% of benign and 28.7%

Table 1: Distribution of patients according to age and sex

Age in years	n (%)		
	Male	Female	Total
1–10	6 (4.84)	8 (6.45)	14 (11.29)
11–20	12 (9.68)	8 (6.45)	20 (16.13)
21–30	14 (11.29)	14 (11.29)	28 (22.58)
31–40	12 (9.68)	8 (6.45)	20 (16.13)
41–50	10 (8.06)	4 (3.23)	14 (11.29)
51–60	6 (4.84)	10 (8.06)	16 (12.90)
61–70	8 (6.45)	2 (1.61)	10 (8.06)
71–80	2 (1.61)	0 (0.00)	2 (1.61)
Total	70 (56.45)	54 (43.55)	124 (100)

Table 2: Distribution of cases according to pathology

Salivary gland pathology	No. of cases (%)
Non-neoplastic	78 (62.9)
Neoplastic	46 (37.1)

Table 3: Relative frequency of benign and malignant major salivary gland tumor

Type of tumor	Number of cases (%)
Benign	32 (69.57)
Malignant	14 (30.43)
Total	46 (100)

Table 4: Age distribution of patients with salivary gland neoplasm

Age in years	n (%)		
	Benign	Malignant	Total
0–10	2 (4.35)	0 (0.00)	2 (4.35)
10–20	2 (4.35)	0 (0.00)	2 (4.35)
21–30	2 (4.35)	0 (0.00)	2 (4.35)
31–40	14 (30.43)	2 (4.35)	16 (34.78)
41–50	6 (13.04)	2 (4.35)	8 (17.39)
51–60	4 (8.70)	2 (4.35)	6 (13.04)
61–70	2 (4.35)	6 (13.04)	8 (17.39)
71–80	0 (0.00)	2 (4.35)	2 (4.35)
Total	32 (69.57)	14 (30.43)	46 (100.00)

Table 5: Site distribution of salivary gland neoplasm

Salivary gland	Benign	Malignant	Total (%)
Parotid	30	12	42 (91.30)
Submandibular	2	2	4 (8.7)
Sublingual	0	0	0 (0)
Total	32	14	46 (100)

of malignant tumors were poorly vascularized [Table 7]. In this study, all neoplastic USG diagnosis confirmed by histopathological examination (HPE) and found that the

Table 6: Mode of presenting symptoms of salivary gland tumors

Symptoms	Number of patients (%)
Swelling	46 (100)
Pain	10 (21.7)
Facial palsy	2 (4.34)
Cervical node swelling	4 (8.7)
Parapharyngeal mass	2 (4.34)

Table 7: Ultrasonographic features of benign and malignant salivary gland tumor histological diagnosis

Parameter	n (%)	
	Benign tumor (n=32)	Malignant tumor (n=14)
Shape		
Lobulated	14 (43.75)	2 (14.29)
Ovoid	10 (31.25)	0 (0.00)
Irregular	8 (25.00)	12 (100.00)
Margin		
Well defined (sharp)	28 (87.50)	2 (14.29)
Ill defined	4 (12.50)	12 (85.71)
Echogenicity		
Anechoic	0 (0)	0 (0.00)
Hypoechoic	32 (100)	14 (100.00)
Isoechoic	0 (0)	0 (0.00)
Hyperechoic	0 (0)	0 (0.00)
Echotexture		
Homogeneous	12 (37.5)	0 (0.00)
Non-homogeneous	20 (62.50)	14 (100.00)
Calcifications	10 (31.25)	4 (28.57)
Cystic areas	4 (12.50)	4 (28.57)
Vascularization		
Absent	2 (6.25)	0 (0.00)
Poorly vascularized	22 (68.75)	4 (28.57)
Well vascularized	8 (25.00)	10 (71.43)

pleomorphic adenoma was most common which accounted for 60.4% followed by mucoepidermoid carcinoma [Figure 1] was commonest which accounted 60.4% followed by mucoepidermoid carcinoma [Figure 2]), 17.4% and accounting for Adenocarcinoma 4.35% [Figure 3] of all cases [Table 8]. Overall in our study, USG showed a sensitivity of 100% and specificity of 87.5% for benign tumors and 87.5% sensitivity and 100% specificity malignant tumors.

DISCUSSION

The present study was undertaken to evaluate the role of high-frequency USG and CDS in the evaluation of salivary gland pathology.

Distribution of Salivary Gland Diseases by Age and Sex

A total of 124 patients with clinical symptoms pertaining to the salivary gland pathologies were assessed by high-resolution ultrasound and results showed that majority of

Table 8: The distribution of benign and malignant tumors, according to histological type

Diagnosis	Sonographic diagnosis	Histopathological examination
Benign	34	32
Malignant	12	14
Salivary gland tumor Cases n=46 (%)		
Benign		
Pleomorphic adenoma	28 (60.87)	
Warthin's tumor	2 (4.35)	
Hemangioma	2 (4.35)	
Malignant		
Mucoepidermoid carcinoma	8 (17.39)	
Adenoid cystic carcinoma	2 (4.35)	
Adenocarcinoma	2 (4.35)	
Pleomorphic ex carcinoma	2 (4.35)	

96 (77.4%) patients with salivary gland diseases belonged to <50 years of age. Male-to-female ratio is 1.3:1.

In sonographic findings, non-neoplastic salivary gland pathologies were more common 78 (62.9%) than neoplastic salivary gland pathologies 46 (37.1%). Of 46 neoplastic pathologies, benign tumors were 32 (69.57%) and malignant tumors were 14 (30.43%). Majority of the tumor in this study occurred between the age from fourth to sixth decades. Benign tumors were more common in 30–40 years age group patients, whereas malignant tumors were common after 50 years. Male:female ratio 1:1 for benign tumors and 6:1 for malignant tumors were observed.

Silvers *et al.*,^[8] Renehan *et al.*,^[9] and Ellis *et al.*^[10] found that pleomorphic adenoma occurred in the fourth and fifth decades of life but may arise at any age. Renehan *et al.*^[9] described a slight predominance in women.

Two patients with Warthin's tumor and two patients with hemangioma were seen in the 61–70 and 1–10 years of age group, respectively, and both were males.

Renehan *et al.*^[9] and Ellis *et al.*^[10] reported that Warthin's tumor was the most common in elderly males in the fifth and sixth decades of life. Baker *et al.*^[11] described that infantile hemangioma was the most common vascular lesion in infancy and childhood.^[11]

Malignant salivary gland tumors were observed in 14 (11.3%) patients comprised of 12 (9.7%) males and 2 (1.6%) females. Musani *et al.*^[12] also reported that malignant tumors were more common in males.

Sonographic Features of Salivary Gland Disease

Sonography can be used to visualize all of the submandibular and sublingual salivary glands and the entire parotid gland,

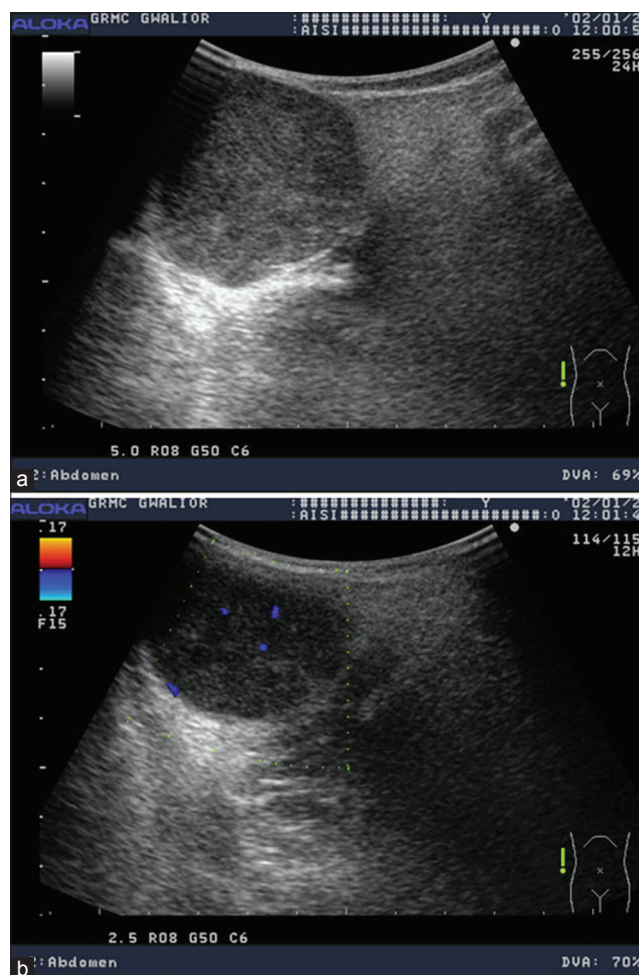


Figure 1: (a and b) Grayscale and color Doppler ultrasonography image of pleomorphic adenoma of right parotid gland

except for the portion obscured by the acoustic shadow of the mandible.

Neoplasm

Tumors were diagnosed by sonography in 46 patients, 42 were seen in the parotid gland, and 4 were seen in the submandibular gland. All palpable lesions were shown sonographically. Hence, in our study, the sensitivity of sonography in the detection of salivary gland tumors was 100%.

Of these 46 patients with salivary gland neoplasm, the final pathological diagnosis included 14 malignant tumors and 32 benign masses. The presumed sonographic diagnoses showed 34 cases as benign and probably benign masses, on pathological diagnosis; 2 cases were confirmed malignant and 32 cases benign, while 12 cases were diagnosed as probably malignant and malignant masses, and all cases were confirmed malignant on pathologic diagnosis.

Of 32 cases of benign tumor, pleomorphic adenoma was seen in 28 cases, and Warthin's tumor and hemangioma

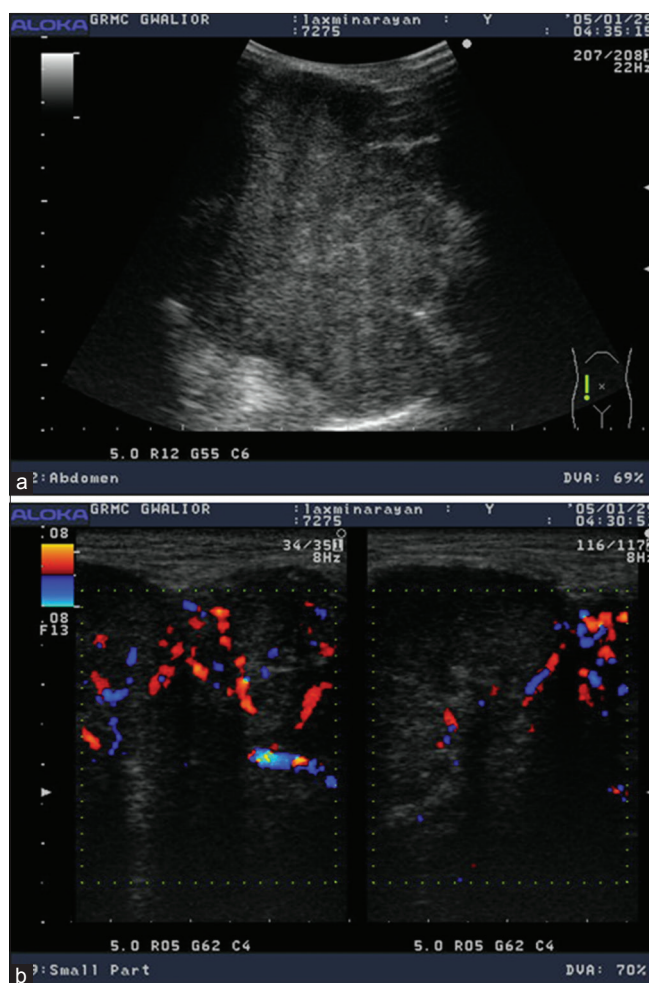


Figure 2: (a and b) Grayscale and color Doppler ultrasonography image of adenocarcinoma of right parotid gland

were seen in 2 cases each. Of 14 cases of malignant tumor, mucoepidermoid carcinoma was seen in 8 cases followed by adenoid cystic carcinoma, pleomorphic ex carcinoma, and adenocarcinoma with 2 cases each. The most common benign parotid tumor was pleomorphic adenoma and the most frequent malignant tumor was mucoepidermoid carcinoma.

All tumors were hypoechoogenic compared with the surrounding parenchyma. Gitzmann^[13] also described the similar finding.

Dumitriu *et al.*^[14] described that most benign tumors (87.8%) had sharp borders, but 39.9% of malignant tumors also presented sharp borders. In our study, most benign tumors (87.5%) had well-defined margin, but 12.5% of malignant tumors also presented well-defined (sharp) margin.

Margin of tumor was the most significant criteria for differentiating between benign and malignant tumor.

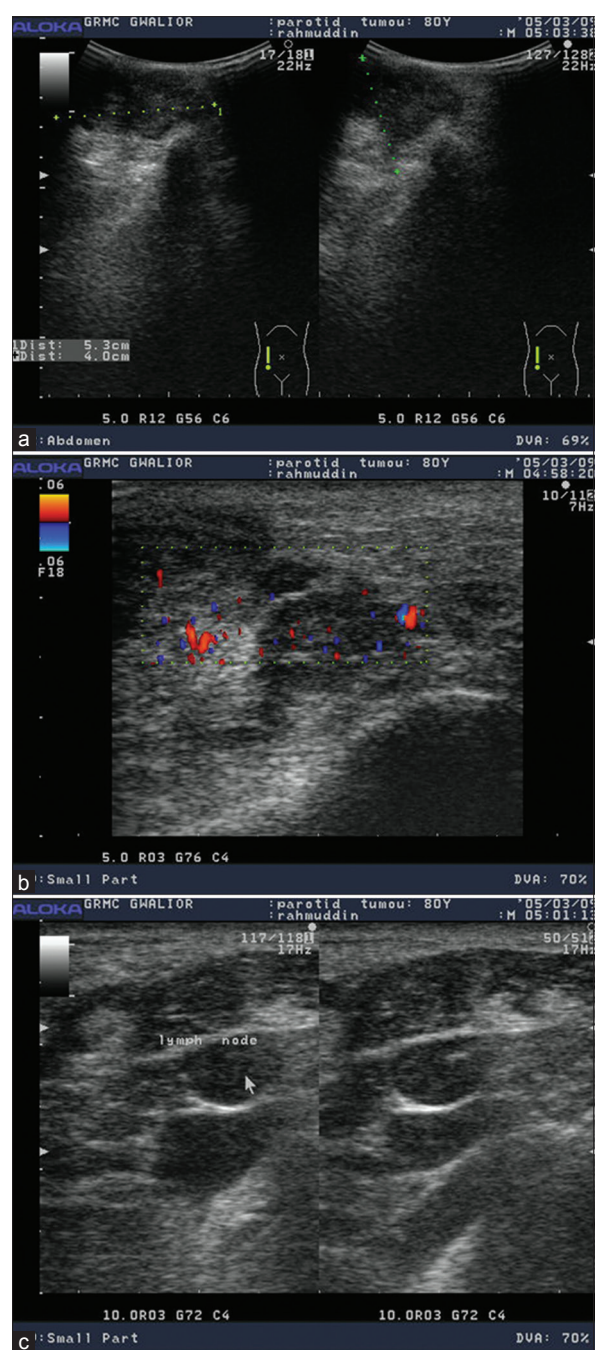


Figure 3: (a-c) Grayscale and color Doppler ultrasonography image of mucoepidermoid of right parotid gland with cervical lymphadenopathy

However, if this criterion alone is considered, it becomes obvious that almost 12.5% of malignant tumors would be diagnosed as benign. Out of the 4 benign tumors with ill-defined margin, 2 were hemangiomas. It was presented as heterogeneous structure. This aspect is consistent with the commonly accepted pattern for hemangiomas.

Other ultrasound features such as shape of tumor, echotexture, and vascularity were also considered in this study.

In our study, most (75%) benign tumors had either lobulated or ovoid shape, while 25% benign tumor had irregular shape. Most (85.7%) malignant tumors had irregular shape.

Dumitriu *et al.*^[14] found that 51.50% benign tumor were homogenous and 48.5% were non-homogenous in echotexture. In case of malignancy, 50% were homogenous and 50% were non-homogenous.

Wu *et al.*^[15] found 9.6% of benign tumors were homogenous and 91.2% were heterogeneous (non-homogeneous). Among malignant tumors, 16.7% were homogenous and 83.3% were heterogeneous.

In our study, 37.5% of benign tumor had homogenous echotexture, while 62.5% had non-homogeneous echotexture. All malignant tumor had non-homogeneous echotexture.

Calcification was seen in 10 benign and 4 malignant tumors. Cystic areas were seen in equal number of benign and malignant tumor, i.e. 2 cases each.

Above findings suggest that echotexture of the tumor was not a relevant indicator for differentiating between benign and malignant tumor.

Dumitriu *et al.*^[14] found that the on CDS examination 60.6% of benign and 55.5% of malignant tumors were poorly vascularized, while 30.30% of benign and 38.8% malignant tumors were well vascularized.

In our study, 68.75% benign tumor were poorly vascularized, 25% were well vascularized, and absence of vascularization was seen in 6.25% of patient. Among malignant tumor, 10 (71.4%) were well vascularized, and 4 (28.53%) were poorly vascularized.

Ultimately, all of these numbers confirm the fact that vessel density, as appreciated by CDS, is a reliable factor in the differential diagnosis between benign and malignant tumors, although the number of patients in the study was less. This is not consistent with other studies, which state that CDS is not enough, but that the measurement of peak flow velocity, and particularly, that of the resistance index and pulsatility index could be more useful by Bradley *et al.*

Ultrasound is also very useful for detecting regional cervical lymphadenopathy associated with salivary gland tumor.

In our study, 10 of 14, i.e., 71% of patients with malignant salivary gland neoplasm showed associated cervical

lymphadenopathy. Cervical lymphadenopathy was not seen in any case with benign salivary gland neoplasm.

All the above findings show that ultrasound is very useful in the description of many features of a salivary gland tumor such as its exact location, size, shape, borders, and structure. CDS can provide accurate information about the density of vessels in the mass.

In our study in the Department of Radiodiagnosis, all cases of malignant tumor were in advanced stage, and hence, it was possible to differentiate between benign and malignant cases by 2D and color Doppler sonography; however, the accuracy was not 100% as 2 sonographically diagnosed case of benign tumor turn out to be malignant on HPE.

CONCLUSIONS

The present study concluded that high-resolution sonography along with color Doppler should be used as first-line imaging modality in the evaluation of salivary gland masses. Sonography is a valuable primary evaluation for the visualization of salivary gland tumors. There was an excellent correlation seen in the diagnosis of salivary gland masses between sonography (grayscale and CDS) and histopathology. Sonography (grayscale and color Doppler together) was found to be highly sensitive and specific in the diagnosis of salivary gland masses; however, it is more sensitive for detecting benign tumors and more specific for malignant tumors. When a tumor cannot be delineated completely by means of sonography, CT or MRI should be performed.

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Comparative Study between the Effects of 4% Lignocaine Solution through Endotracheal Tube Cuff and 1.5 mg/kg of Intravenous 2% Lignocaine on Coughing and Hemodynamics During Extubation in Neurosurgical Patients

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Abstract

Aim: A prospective, randomized, double-blind trial was performed to compare the effects of 4% endotracheal tube cuff lignocaine and 1.5 mg/kg intravenous lignocaine on coughing and hemodynamics during extubation in patients undergoing neurosurgical procedures.

Methods: Group A ($n = 50$) patients received 4% lignocaine into endotracheal tube cuff after intubation and Group B ($n = 50$) patients received intravenous lignocaine 2% at 1.5 mg/kg before extubation. Coughing was assessed by the scale of 3 at the time of extubation, 0–2 min, 2–4 min, and 4–8 min post-extubation. Hemodynamic parameters were recorded at 1 min, 2 min, 5 min, and 10 min and were compared with baseline values.

Results: Comparison of hemodynamic variables, incidence, and severity of cough at emergence was analyzed using unpaired *t*-test. The incidence and severity of cough were less in Group A when compared to Group B. There was no significant difference in hemodynamic variables in between the groups.

Conclusion: Intracuff 4% lignocaine was found to be superior to 2% intravenous lignocaine in suppressing cough during emergence.

Key words: Cough reflex, Endotracheal tube cuff, Hemodynamic response, Intravenous, Lignocaine

INTRODUCTION

Tracheal intubation with an endotracheal tube is necessary during general anesthesia. After intubation, inflating the cuff around the endotracheal tube maintains a seal. Smooth Emergence from general anesthesia is frequently complicated by coughing induced by stimuli from the

endotracheal tube.^[1] Irritant or stretch stimuli in the trachea caused by the tube and its cuff are presumed mechanisms in inducing cough. Rapidly acting receptors which are found throughout the trachea are thought to be the irritant receptors involved in the cough reflex. These nociceptive stimuli can be blocked by topically applied anesthetics.^[2] Coughing during emergence can result in hypertension, tachycardia, raised intraocular and intracranial pressures, myocardial ischemia, bronchospasm, and surgical bleeding.^[3] This can be of particular relevance in neurosurgical, ophthalmic, and vascular procedures.

2% preservative-free lignocaine solution can be given intravenously in a dose of 1.5 mg/kg to attenuate stress response during intubation as well as extubation.^[4] Many

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studies proved its efficacy in attenuating stress response during emergence, but prior studies failed to prove that it effectively suppresses a cough during emergence.^[5] Whereas 4% lignocaine hydrochloride containing 40 mg/mL given in a dose of 1–5 mL (40–200 mg) or 0.6–3 mg/kg anesthetizes mucus membranes. It can be used as spray/cotton applicator/packs/instilled into cavities.^[6] 4% intracuff lignocaine diffuses across the endotracheal tube in a fashion that may enable the cuff to serve a potentially useful role as a reservoir for local anesthetic.^[7]

Hence, it anesthetizes the tracheal mucosa surrounding the endotracheal tube cuff and may reduce the incidence of coughing during emergence. In this study, we evaluated its efficacy in reducing cough during emergence compared to intravenous lignocaine.

METHODS

After Institutional Ethics Committee approval and written informed consent, 100 patients of ASA Grades 1 and 2 were included in this randomized, prospective clinical study.

Inclusion Criteria

- Age: 16–56 years
- Sex: Both genders
- Neurosurgical procedures.

Exclusion Criteria

- Known H/o reactive airway disease
- H/o altered sensorium
- Signs of raised intracranial pressure
- Upper airway infection
- Known H/o smoking
- Airway pathology
- H/o anticipated difficult intubation
- Any contraindication to the study drug.

Group Allocation

A total of 100 patients were randomly allocated into two groups of 50 each by computer-generated random numbers into Groups A and B.

- Group A: Received 4% lignocaine solution into endotracheal tube cuff, volume according to minimal occlusion volume technique during cuff inflation.
- Group B: Received preservative-free 2% lignocaine (loxicard) at a dose of 1.5 mg/kg intravenously before extubation.

In the pre-operative period, after selection of the patients who met the inclusion criteria, all the routine laboratory investigations were done. On the day of surgery, patient's baseline parameters of HR, NIBP, SpO₂, and RR were noted. In the operating room, two 18 gauge IV cannulas were

secured. Monitoring devices such as SpO₂, electrocardiogram (ECG), NIBP, and temperature were connected to all the patients. General anesthesia was induced using a standard regimen in all the patients of both groups. Premedication was done with injection glycopyrrolate 5 µg/kg IV and injection fentanyl 2 µg/kg IV, just before induction.

After preoxygenation for 5 min, all the patients were induced with injection thiopentone sodium 5 mg/kg IV and intubation was done using suxamethonium 2 mg/kg IV with appropriate sized polyvinyl chloride (PVC) cuffed endotracheal tube, and then, the tube was secured after checking for bilateral air entry at the angle of the mouth to the desired length.

Group A endotracheal tube cuff was inflated with 4% lignocaine solution, the volume decided by the minimum occlusion volume technique. Group B endotracheal tube cuff was inflated with 0.9% saline solution, the volume according to minimal occlusion volume technique in the same manner as in Group A. Precautions taken while inflating the cuff are slow inflation than usual to prevent damage to tracheal mucosa and to see that no air bubble enters the cuff while inflating with 4% lignocaine.

Anesthesia gas mixture was administered through closed circuit of an anesthesia workstation with N₂O, O₂, and sevoflurane in a concentration of 66.6%, 33.3%, and 0.5% (1–1.5%), respectively. Neuromuscular blockade was maintained with vecuronium in a dose of 0.08 mg/kg. Neuromuscular blockade was antagonized with neostigmine in a dose of 70 µg/kg and glycopyrrolate 5 µg/kg IV at the end of the surgical procedure.

In Group B, just before extubation, 2% lignocaine (preservative-free) was given intravenously. At the same time in Group A, the same amount of normal saline was administered intravenously to ensure blinding. Three anesthesiologists were involved in this study, namely, principal investigator, Observer A and B. The solutions to be injected into the inflatable cuffs of endotracheal tube were loaded by the Principal investigator who was aware of the group allocation. They were supplied to the operating room in sealed envelopes. The intravenous solutions are given just before extubating the patients were also loaded by the principal investigator, and they were also supplied in sealed envelopes. The sealed envelopes were labeled according to their route of administration and were opened just before administration of drugs. The observer anesthesiologist A administered all the study drugs according to their route. The principal investigator went out of the operating room after administering the drugs. Just before extubation, the observer anesthesiologist A administered IV drugs according to the group allocation. The observer anesthesiologist B

monitored all the patients throughout the surgery and made the following observations.

Continuous monitoring was done in all the patients with pulse oximetry, ECG, systolic blood pressure (SBP), and diastolic blood pressure (DBP) every 1 min for the first 15 min, followed by every 5 min till the end of surgery.

During extubation, hemodynamic monitoring was done at 1 min, 2 min, 5 min, and 10 min immediately following extubation.

All the patients were assessed for incidence of coughing and its severity at the time of emergence.

Three category scale for scoring severity of cough^[8] during emergence was used in this study.

- Mild - single episode
- Moderate - 1 episode of unsustained cough for <5 s
- Severe - sustained bouts of coughing for >5 s.

All the data were statistically analyzed. Demographic data were analyzed using Fischer exact test. Comparison of hemodynamic variables, incidence, and severity of coughing at emergence was analyzed using unpaired *t*-test. $P < 0.05$ was considered statistically significant. Data were expressed as mean, standard deviation, and percentage.

RESULTS

A total of 100 ASA I/II patients were included in this randomized prospective study. All the patients completed the study.

The patients of both the groups were comparable with respect to demographic characteristics such as age, gender, weight, ASA grading, and duration of surgery. $P > 0.05$ was statistically not significant [Table 1].

The hemodynamic parameters such as heart rate, SBP, and DBP in our study were monitored at extubation, 1 min, 2 min, 5 min, and 10 min post-extubation and compared between 2 groups and found that they were not significant statistically, ($P > 0.05$).

The mean heart rate was higher at the time of extubation and subsequently lower at 1 min, 2 min, 5 min, and 10 min after extubation in both the groups. The attenuation of heart rate was comparable between the groups, ($P > 0.05$), not significant [Table 2].

The mean SBP was higher at the time of extubation and gradually decreased at 1 min, 2 min, 5 min, and 10 min post-extubation, in both the groups. The attenuation of

mean SBP was comparable between the groups, $P > 0.05$, not significant [Table 3].

The mean DBP was higher at the time of extubation and gradually decreased at 1 min, 2 min, 5 min, and 10 min post-extubation in both the groups. The attenuation of mean DBP was comparable between the groups. The hemodynamic data and SpO₂ were similar for both the groups [Table 4].

The incidence of coughing was compared between the two groups at extubation within first few minutes [Table 5 and Graph 1].

For initial 2 min after extubation, the incidence of coughing was significantly higher in the 2% IV lignocaine group than 4% cuff lignocaine group (A vs. B: 16% vs. 38%) ($P = 0.05$), statistically significant.

Table 1: Demographic characteristics of the studied patients

Data	Mean±SD (n=50)		P value
	Group A	Group B	
Age (years)	32.64±9.26	33.26±9.21	0.73
Weight (kg)	64.86±7.76	65.12±8.14	0.87
Sex (%)			
Male	27 (54)	31 (62)	
Female	23 (46)	19 (38)	
ASA (I/II)	31+19	28+22	
Duration of surgery (in min)	78.40±50.12	82.10±47.28	0.70

Values are expressed as mean±SD or ratio or absolute numbers. Student *t*-test, *Fischer's exact test, †Chi-square test. $P < 0.05$ statistically significant. SD: Standard deviation

Table 2: Heart rate of the patients in the two groups at different intervals.

Time interval	Mean±SD n=50		P value
	Group A	Group B	
HR 1 st min after extubation	80.60±6.38	80.34±5.83	0.83
HR 2 nd min after extubation	81.32±7.35	81.48±6.78	0.91
HR 5 th min after extubation	82.32±7.13	81.24±5.64	0.40
HR 10 th min after extubation	81.64±7.13	81.44±7.12	0.88

Values are expressed as mean±SD or ratio or absolute numbers. Student *t*-test, $P < 0.05$ statistically significant. SD: Standard deviation

Table 3: Systolic blood pressure of the patients in the two groups at different intervals

Time interval	Mean±SD n=50		P value
	Group A	Group B	
SBP 1 st min after extubation	117.20±8.93	120.04±8.86	0.11
SBP 2 nd min after extubation	119.28±10.66	120.16±8.91	0.65
SBP 5 th min after extubation	119.96±8.75	120.32±9.30	0.84
SBP 10 th min after extubation	120.16±8.91	120.92±8.57	0.66

Values are expressed as mean±SD or ratio or absolute numbers. Student *t*-test, $P < 0.05$ statistically significant. SD: Standard deviation

The incidence of coughing at 2–4 min after extubation was also significantly higher in 2% IV lignocaine group than 4% cuff lignocaine group (A vs. B: 11% vs. 36%) $P < 0.05$, statistically highly significant.

At 4–8 min after extubation, 2% IV lignocaine group had 34% incidence of coughing while none of the patients in 4% cuff lignocaine group had coughing after 4 min ($P < 0.05$), statistically highly significant.

The severity of cough was compared between two groups. The incidence of mild cough was significantly higher in 2% IV lignocaine group when compared to 4% cuff lignocaine group (A vs. B: 15% vs. 40%) $P < 0.05$, statistically significant [Table 6 and Graph 2].

The incidence of moderate cough was also significantly higher in the 2% IV lignocaine group when compared to 4% cuff lignocaine group ($P < 0.05$), statistically significant.

28% of patients in 2% IV lignocaine group had severe cough while none of the patients in 4% cuff lignocaine group had severe cough. $P < 0.05$, statistically significant.

Table 4: Diastolic blood pressure of the patients in the two groups at different intervals

Time interval	Mean±SD n=50		P value
	Group A	Group B	
DBP 1 st min after extubation	79.90±5.21	80.20±5.38	0.77
DBP 2 nd min after extubation	76.88±5.30	79.82±6.24	0.01
DBP 5 th min after extubation	78.28±6.29	78.26±8.12	0.98
DBP 10 th min after extubation	79.96±5.67	79.88±6.22	0.94

Values are expressed as mean±SD or ratio or absolute numbers. Student *t*-test, $P < 0.05$ statistically significant. SD: Standard deviation

Table 5: Incidence of cough after extubation in the two groups

Time interval (min)	Number of patients (%)	
	Group A (n=50)	Group B (n=50)
0–2	9 (18)	15 (30)
2–4	6 (12)	14 (28)
4–8	3 (6)	12 (24)

Data expressed as % and absolute numbers

Table 6: Severity of cough after extubation in two groups

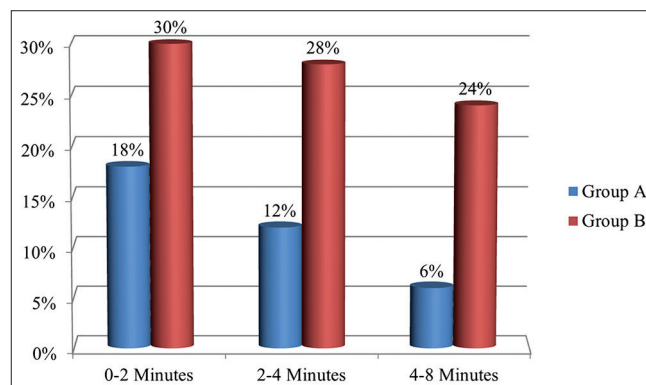
Grade	Number of patients (%)	
	Group A (n=50)	Group B (n=50)
Mild	10 (20)	17 (34)
Moderate	8 (16)	14 (28)
Severe	1 (2)	10 (20)

Data expressed as % and absolute numbers

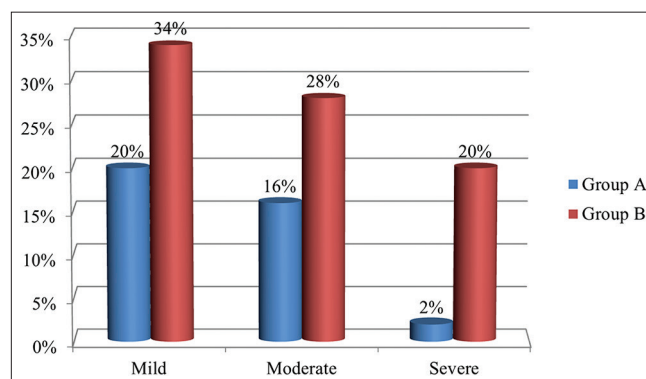
DISCUSSION

A technique that would allow patients from anesthesia to tolerate an endotracheal tube while also affording airway protection with intact supraglottic reflexes would be desirable in a selected group of surgical patients. Various methods have been employed to attenuate hemodynamic responses and also to decrease the incidence of coughing which include extubation in deep plane of anesthesia and administering intravenous agents like lignocaine, opioids like fentanyl, α -agonists such as dexmedetomidine and topical or intracuff application of lignocaine 4%, and IV lignocaine 2% have been a traditional method which is employed in various clinical trials as a control.^[9] Although IV lignocaine has shown to suppress both mechanically and chemically induced airway reflexes, it is not very much effective against cough during emergence which was proved in many clinical studies.^[10] The effects of 4% intracuff lignocaine were studied and compared with 2% IV lignocaine as control in this study. In this study, intracuff lignocaine has demonstrated success in attenuating hemodynamic responses and decreasing the incidence and severity of cough during emergence when compared to IV lignocaine.

Lignocaine instilled in the endotracheal tube cuff diffuses slowly across the cuff membrane. The cuff acts as a reservoir for lignocaine, allowing diffusion and subsequent



Graph 1: Incidence of cough minutes after extubation



Graph 2: Incidence of severity of cough after extubation

anesthesia of tracheal mucosa in contact with the cuff. This method reduces emergence phenomena including post-operative coughing and sore throat.

Various *in vitro* studies demonstrated that lignocaine diffused across the membrane of the cuff of the endotracheal tube, the diffusion of which depended on various factors such as the non-ionized fraction of local anesthetic, alkalinization, temperature, duration of procedure, and concentration of local anesthetic.^[11,12]

The mean volume which was inflated into ET tube cuff was 7 ± 2 mL, but no sign of lignocaine toxicity was observed during the intra-operative and post-operative period in our study. The deflated volumes were always less than the inflated volumes, in the study group; the deflated volumes amounted to 6.2 ± 1.5 mL.

The protective cough reflexes above the tube cuff and of the vocal cords should remain intact. However, if cuff damage may occur, there is always the risk of leakage and systemic absorption of local anesthetic with its consequences.^[13]

It was observed that none of the patients in this study had signs of lignocaine toxicity and all the cuffs of ET tubes were found intact after extubation. The cuffs of ET-tubes being intact, the concern for lignocaine toxicity was negligible because the amount of drug diffused among the ET tube cuff would be very less.

One limitation of this study was, plasma levels of lignocaine were not measured unlike in the other studies, due to lack of feasibility to this investigation in our institution.

The plasma levels required to suppress coughing during emergence were found to be around $3 \mu\text{g/mL}$ of lignocaine in previous studies.

Venkatesan and Korula conducted a similar randomized clinical trial comparing the effects of 4% ET cuff lignocaine versus IV lignocaine on coughing and hemodynamics on extubation in patients undergoing elective craniotomies and reported that there were no significant differences in terms of hemodynamic responses and also coughing during extubation.^[14] Our study differs from this study with respect to incidence and severity of coughing as there was significant attenuation of coughing in cuff lignocaine group in our study.

Fagan *et al.* suggested that local anesthetic lignocaine instilled into the ET cuff might cause anesthesia of the trachea by diffusing across the PVC membrane, anesthesia confining to the mucosa in contact with the cuff and protective cough reflexes above the tube cuff and below the cords

would remain intact.^[15] The preservation of cough reflexes in post-extubation period can be explained by the above.

Wetzel *et al.* suggested similar results in intracuff lignocaine group compared with the saline group, but they did the study in smokers.^[16]

Navarro *et al.* compared alkalized intracuff 2% lignocaine with intracuff saline and concluded that intracuff lignocaine was superior to saline in decreasing incidence of emergence coughing and sore throat during the post-operative period in smokers.^[17]

George *et al.* compared IV 2% lignocaine versus 2% lignocaine spray down the ET tube versus placebo for extubation response in neurosurgical patients. They concluded that the effectiveness of IV lignocaine versus lignocaine spray to attenuate extubation response was comparable. Lignocaine spray instilled into the ET tube was not superior to IV lignocaine in their study because the installation of 2% lignocaine spray was done 20–30 min before extubation which was in contrast to our study where we have administered intracuff lignocaine at the time of intubation so that there is adequate time for cuff lignocaine to be absorbed into tracheal mucosa and cause anesthetic effect.^[18]

Snigdha *et al.* compared the installation of 4% lignocaine into ET cuff versus air and concluded that cuff lignocaine has significantly reduced post-extubation coughing, nausea, vomiting, dysphonia, hoarseness, and sore throat compared to air.^[19]

The above studies were correlating to the observations of our study with few differences in the methodology, study drugs and time of administration.

Our study concluded that both intracuff 4% lignocaine and IV were similar in attenuating hemodynamic responses during extubation and intracuff 4% lignocaine has been superior to 2% IV lignocaine in suppressing cough during emergence.

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Evaluation of Success Rate of Brachial Plexus Block by Selective Cord Stimulation

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Abstract

Aims and Objectives: The aim is to study and compare the success rate of brachial plexus block achieved by stimulation of individual cord, that is, medial, lateral, and posterior cord.

Introduction: Infraclavicular block is indicated for surgery of the forearm, wrist, and hand. It is performed by localizing one cord of the brachial plexus and injecting the local anesthetic solution at that location. In this study, we compare the success rate of brachial block achieved by stimulating individual cord, that is, posterior, medial and anterior. The approach used with the help of nerve stimulator at a stimulator current of 0.4 mA or less infraclavicular vertical brachial plexus block approach.

Materials and Methods: A total of 108 patients who were planned to undergo forearm or hand surgeries were divided into three groups. Infraclavicular brachial plexus block (ICPB) was performed using 50-mm insulated nerve stimulator needle and B. Braun Stimuplex RC nerve stimulator with an initial stimulator current of 1.0 mA with 2 Hz frequency. The patients belonging to the respective groups would receive ICPB after attaining the evoked muscle response.

Result: After prospective, randomized comparative study which was carried out in 108 patients, result achieved was that in comparison to the lateral and medial cord, posterior cord blockade was associated with rapid onset of motor block and sensory block with selective cord stimulation and this also decreased the incidence of block failure.

Key words: Infraclavicular brachial plexus block, Lateral cord, Medial cord, Nerve stimulator, Posterior cord

INTRODUCTION

Anesthesia began with “rag and bottle”. Whether the rag was the sponge that Morton used, or the folded pocket handkerchief used by Simpson to turn a liquid into a vapor by draining it from a bottle into a “rag.” This was the first method of inhalational anesthesia. Then, there was the era of unending endeavors to control pain, The “Fifth Vital Sign”! The efforts to manage pain have evolved from the simple topical application of cocaine, through the use of sedation analgesia - the “twilight sleep” and techniques of neuraxial blockade, to the development of nerve blocks

that are still in use today, in one form or another and with one eponymous name or another.

Regional anesthesia is preferred to avoid the complications of general anesthesia. However, supraclavicular and axillary routes of brachial plexus block have presented with various complications and unpredictable cases of failure bringing back the use of the infraclavicular route. Thus, despite being not so common in use, the infraclavicular block has its own advantages to offer.^[1]

In this study, we evaluate the success rate of brachial plexus block by selective cord stimulation through infraclavicular approach.

Aims and Objectives

Focused aims of the study

1. Time taken for onset of complete motor and sensory block
2. Duration of sensory block

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3. Duration of analgesia
4. To study and compare the success rate of brachial plexus block achieved by stimulation of individual cord, that is, medial cord, lateral cord, and posterior cord.

Primary objectives

- To assess and compare the success rate of block by evaluating
- The extent of block (as assessed by the motor block in the number of nerves)
- The effectiveness of sensory block in each group.

Secondary objectives

1. To observe hemodynamic changes (if any)
2. To look for side effects (if any).

MATERIALS AND METHODS

The present study was undertaken in indoor patients admitted in Orthopaedics Ward in NSCB Medical College and Hospital, Jabalpur, Madhya Pradesh.

Sample Size

The adequate required sample size was estimated using following formula

$$n = z^2pq/d^2$$

Where

n = sample size

z = 1.96 (considering 0.05 alpha, 95% confidence limits, and 80% beta)

q = 1-p

d = marginal error (precession)

To calculate the adequate required sample size, we have taken assumption suggested by previous literature review that 15–45% (15% relative precision) difference between the groups would be observed.

Sample size is 36 from the above formula. Therefore, minimum 36 subjects in each group will be adequate in number. Therefore, minimum 36 subjects in each group will be adequate numbers.

Sampling Method

Considering the best of the patients by reviewing the previous records of this health facility to achieve the maximum sample size, we will screen all the patients who fulfill the inclusion and exclusion criteria and ready to give the written informed consent.

Selection of Cases

After obtaining institutional and ethics committee approval and written informed consent, 108 patients of

both sexes in the age group of 15 years–65 years, body weight between 45 and 75 kg belonging to Class 1 and 2 of ASA classification posted for elective surgeries on the forearm, hand, and wrist were enrolled for the study. A detailed history, thorough physical examination, routine investigation, or any special investigation if required were done for the study.

Exclusion Criteria

- Patient refusal
- Local infection at needle insertion site.
- Patient using anticoagulants drugs.
- Patient with hypertension, pregnancy, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus I and II, or pre-existing neuropathy involving the surgical limb.

Study Design

This was a prospective, randomized, double-blinded, comparative study.

For the purpose of the study, the patients were randomly allocated by random number table into three groups of 36 patients each.

Group L: Stimulation of lateral cord of brachial plexus was inferred by the motion of muscles supplied by the median nerve.

Group M: Stimulation of medial cord of brachial plexus was inferred by the motion of muscles supplied by the ulnar nerve.

Group P: Stimulation of posterior cord of brachial plexus was inferred by the motion of muscles supplied by the radial nerve.

Equipments in material and methods [Figure 1]

- Sterile tray
- Sterile towel
- Sterile swabs
- Sponge holding forceps
- Betadine solution and spirit
- 2 ml and 10 ml syringe
- B Braun Stimuplex nerve stimulator
- Braun Stimuplex insulated needle.

Drugs

Injection ropivacaine 0.75% (plain)

Patients received 0.75% ropivacaine (plain) as the drug for the infraclavicular block. The quantity of the drug depended on patient's body weight (0.5 ml/kg). Maximum 30 ml of the drug was injected.

In Case of any Emergency or Complications

- Emergency drugs
- Intubation kit
- Resuscitation equipment.

Technique

The patient was placed on the operation table in supine position. Before starting the procedure, all the monitoring equipment (NIBP cuff, pulse oximetry probe, and electrocardiogram) were attached to the patient and baseline value of blood pressure (BP), heart rate, SpO₂, and respiration rates (RR) were recorded, and an IV cannula 18 G was inserted. Pre-medication of any kind was not given.

Technique for Vertical Infraclavicular Block

- Under all aseptic precautions, after painting and draping, the infraclavicular brachial plexus block (ICPB) was performed using 50-mm insulated nerve stimulator needle and B. Braun Stimuplex RC nerve stimulator with an initial stimulator current of 1.0 mA with 2 Hz frequency.
- The patient was placed in supine position with the head rotated away from the site to be blocked. The arm was rested on the side with the wrist supinated if possible. The main landmarks for this block were as follows:
 1. Middle of the sternal notch
 2. Puncture site
 3. Coracoid process
 4. Head of humerus
 5. Anterior part of acromia.

The puncture site is halfway between the middle of the sternal notch and the anterior part of acromion.

Figure 2 shows the landmarks for vertical infraclavicular brachial plexus block

A skin wheal was raised just above the puncture site with 2 ml of 2% lignocaine with a 24 G needle.

- Insulated needle was inserted just above the puncture site in a vertical direction to maximum depth not more than 4 cm. Figure 3 shows the technique of vertical infraclavicular brachial plexus block.
- The needle was advanced until an evoked motor response of the hand muscles

Group L

Stimulation of lateral cord of brachial plexus was inferred by the motion of muscles supplied by the median nerve, especially,

- Flexor carpi radialis (abduction and flexion of wrist joints and of flexor pollicis longus (flexion of thumb)
- Lateral two lumbricals - flexion at metacarpophalangeal joints of index and middle fingers and extension of interphalangeal joint



Figure 1: Equipments used

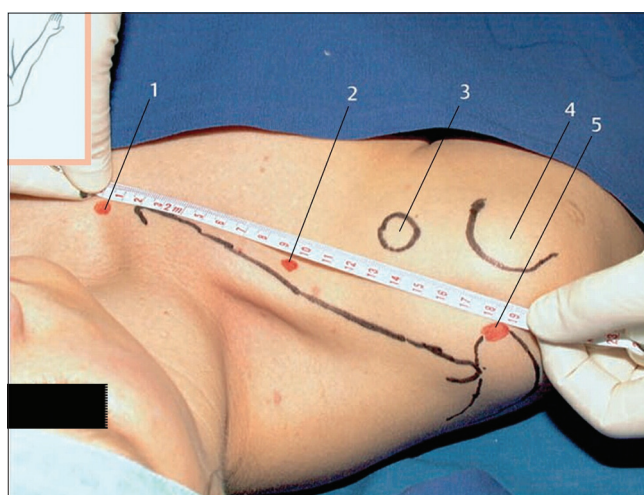


Figure 2: Landmarks of the Vertical Infraclavicular block



Figure 3: Technique of vertical infraclavicular brachial plexus block

- Adductor pollicis brevis (thumb abduction)
- Flexor pollicis brevis (flexes metacarpophalangeal joints of thumb)
- Opponens pollicis (opposes thumb toward fingers).

Group M

Stimulation of medial cord of brachial plexus was inferred by the motion of muscles supplied by the ulnar nerve, especially

- Flexor carpi ulnaris, that is, wrist flexion and adduction
- Medial two lumbricals flexion of metacarpophalangeal joint of ring and little finger and extension of interphalangeal joint
- Adductor pollicis (thumb adduction)
- Interossei of hand
- Abductor digiti minimi (abducts little finger)
- Flexor digiti minimi (flexes little finger).

Group P

Stimulation of posterior cord of brachial plexus will be inferred by action of triceps, extensor carpi radialis, that is, elbow extension and wrist extension.

- Once the desirable evoked motor response was obtained, the needle was stabilized, negative aspiration for blood or air was done and the calculated drug volume was injected
- After complete injection of drug, the observation was made by another observer to make the study double-blinded
- Immediately after injection of local anesthetic, the patient was observed for signs of local anesthetic toxicity and intravascular injection
- Time of administration of drug was noted.

Evaluation

- Onset of sensory and motor block was assessed every 5 min after injection up to 30 min using below-mentioned scale.

Motor Block Evaluation

- Musculocutaneous nerve - elbow flexion
- Median nerve - thumb and index finger opposition
- Radial nerve - wrist extension
- Ulnar nerve - little finger flexion

Scale

- Normal motor function - 0
- Decreased motor strength - 1
- Complete block - 2

Sensory block assessment was done by cold sensation loss to ice cube application at the region of sensory supply of each nerve.

Sensory Block Evaluation

- Musculocutaneous nerve - lateral aspect of forearm
- Median nerve - Thenar eminence
- Radial nerve - Dorsum of hand (web between thumb and index finger)
- Ulnar nerve - Palmer and dorsal aspect of little finger.

Scale

- Sensation in response to cold - 0
- Lesser degree of cold compared to that on contralateral side - 1
- No recorded cold sensation - 2
- The block was considered failed if the patient complains pain during surgical intervention
- Time to achieve onset of sensory block was defined as the time interval between the administration of drug and sensation absent to cold
- Time to achieve complete motor block was defined as the time interval between administration of the drug and complete loss of muscle function
- Surgery was permitted only when block was complete; general anesthesia was instituted whenever block was inadequate
- Duration of sensory block was defined as the time interval between onset of complete sensory blockade to return of normal sensation to cold
- Duration of motor block was defined as the time interval between onset of complete motor blockade to recovery of normal muscle function
- Duration of analgesia was defined as the time interval between the onset of the complete sensory block to the post-operative visual analog scale (VAS) score >4.

VAS

Pain intensity was evaluated using 10-cm visual scale where 0 represents no pain and 10 represents worst possible pain. Rescue analgesia with intramuscular diclofenac injection 75 mg was given if VAS was >4. VAS score was recorded post-operatively at 0, 4, 8, 12, 12.30, 13, 13.30, 14, 14.30, 15, and 16 h.

16 h analgesic consumption was also noted.

Complications

- Fatal arrhythmias
- Convulsion
- Vascular puncture
- Pneumothorax
- Nausea/vomiting.

Monitoring

Throughout the procedure, BP, RR, and pulse rate was monitored continuously. Vital signs were recorded at 0, 10 min, 20 min, 30 min, 60 min, 2 h, 4 h, 6 h, 12 h, and 24 h.

Observations

Table 1 shows the mean age of patients (in years) in three groups which were almost comparable ($P > 0.05$). Table 2 shows the sex-wise distribution of all the patients in various groups. Majority of patients were male in all the groups as compared to females. However, the distribution

of both males and females in each group was comparable ($P > 0.05$).

Table 3 shows the mean weight of patients (in kg) in various groups. All the groups were comparable ($P > 0.05$). Table 4 shows the number of sensory nerves blocked in three groups

In Group P, 32 (88.88%) patients out of 36 got all four nerves blocked when compared to Group L were 24 (66.66%) and Group M were 23 (63.88%) patients got all four nerves blocked.

In Group P, the effectiveness of block was significantly higher when compared to Group L ($P = 0.024$) and Group M ($P = 0.013$), respectively.

Table 5 shows number of motor nerves blocked in three groups.

In Group P, 29 (80.55%) patients had all the four nerves blocked when compared to Group L, where 19 (52.77%) and Group M, where 17 (47.22%) patients had all the four motor nerves blocked.

The extent of block was significantly higher in Group P when compared to Group L ($P = 0.012$) and Group M ($P = 0.003$), respectively.

Table 6 shows the mean time taken (in min) to achieve complete sensory block in Groups L, M, and P which was 15.96 ± 0.69 min, 16 ± 0.60 min, and 12.09 ± 0.73 min, respectively.

Table 1: Mean age of the patients in the study group

Group	L	M	P
Mean value (years)±SD	31.39±12.03	40.67±16.66	36.03±13.16

SD: Standard deviation

Table 2: Sex-wise distribution of patients in the study groups

Group	L	M	P
Male (%)	28 (77.78)	29 (88.56)	26 (72.22)
Female (%)	8 (22.22)	7 (19.44)	10 (27.78)
Total	36	36	36

Table 3: Mean weight of patients in the study groups

Group	L	M	P
Mean value (kg)±SD	54.58±7.78	59.83±10.19	63.22±9.70

SD: Standard deviation

Time to achieve complete sensory block was significantly less in Group P, (12.09 min) than in Group L, (15.96 min) and Group M, (16 min).

On statistical analysis, the difference in time taken to achieve complete sensory block in between Groups L and P and Group M and P was found to be highly significant ($P < 0.0001$) and ($P < 0.0001$), respectively.

Thus, it affirms that the onset of complete sensory block was fast in Group P when compared to Group L and M in order of $P > L > M$.

The mean time difference in onset of complete sensory block between Group P and L was 3.87 min and Group P and Group M and P was 3.91 min.

Table 7 shows the meantime (in min) to achieve complete motor block in Groups L, M, and P, which was 20.95 ± 0.71 min, 22 ± 0.71 min, and 17.83 ± 0.66 min, respectively.

Time to achieve complete motor block was significantly less in Group P, (17.83 min) than in Group L, (20.95 min) and Group M, (22 min).

On statistical analysis, the difference in time to achieve complete motor block in Groups L, M, and P was found to be highly significant ($P < 0.0001$) and ($P < 0.0001$), respectively.

Table 4: Effectiveness of block (assessed by all four sensory nerves blocked)

Number of nerves blocked	L (%)	M (%)	P (%)
0	2 (5.55)	2 (5.55)	0
1	2 (5.55)	4 (11.11)	1 (2.77)
2	3 (8.33)	3 (8.33)	1 (2.77)
3	5 (13.88)	4 (11.11)	2 (5.55)
4	24 (66.66)	23 (63.88)	32 (88.88)

Table 5: Extent of motor block (assessed by all four motor nerves blocked)

Number of nerves blocked	L (%)	M (%)	P (%)
0	2 (5.55)	2 (5.55)	0
1	2 (5.55)	4 (11.11)	1 (2.77)
2	5 (13.88)	6 (11.11)	2 (5.55)
3	8 (22.22)	7 (19.44)	4 (11.11)
4	19 (52.77)	17 (47.22)	29 (80.55)

Table 6: Time taken to achieve complete sensory block

Groups	L	M	P
Mean value±SD (in min)	15.96±0.69	16±0.60	12.09±0.73

SD: Standard deviation

Thus, it affirms the onset of complete motor block was fast in Group P than in Group L and M in order of $P > L > M$.

The mean time difference between Group P and L was 3.12 min and between Group P and M was 4.17 min.

Table 8 shows the mean \pm standard deviation (in min) duration of analgesia in three Groups L, M, and P, which was 772.5 ± 36.74 min, 774.78 ± 35.79 min, and 772.5 ± 36.54 min respectively.

On statistical analysis, there was no significant difference in duration of analgesia in between three Groups L, M, and P.

Table 9 shows the median VAS score at 4th, 8th, 12th, 12.5th, 13th, 13.5th, 14th, 14.5th, 15th, and 16th h post-operatively in all three groups.

At 13th h post-operatively, the median VAS score was <4 and was comparable in all three groups.

At 13.5th h post-operatively, there was an increase in VAS score to 5 in all three groups.

There were no statistically significant differences in VAS score post-operatively in three groups.

DISCUSSION

The present study was conducted to evaluate the success rate of brachial plexus block by selective cord stimulation through infraclavicular approach. Our intention was to find out whether localizing the posterior cord during a single injection infraclavicular block would place the needle centrally within the infraclavicular portion of the brachial plexus and allow a uniform spread of the local anaesthetic, thereby selective cord stimulation would affect the overall time of onset of sensory and motor blockade in that respective group.

We found that the success rate was significantly higher when the injection was performed on a radial type response (80.5%) compared with the median (52.6%) or ulnar nerve (47.2%) distal motor type response as evaluated by the extent of block assessed by the motor block of all the 4 nerves within 30 min of the injection of the local anesthetic.

Our result reaffirms the outcome of the study conducted by Lecamwasam *et al.*, where they reportedly found, on the basis of complete motor block, that posterior cord stimulation has a greater success rate (73.5%) when compared to stimulation of lateral (63.5%) or medial cord (53.3%), respectively.

Table 7: Time taken to achieve complete motor block

Groups	L	M	P
Mean \pm SD (in min)	20.95 \pm 0.71	22 \pm 0.71	17.83 \pm 0.66

SD: Standard deviation

Table 8: Duration of analgesia

Groups	L	M	P
Mean \pm SD (in min)	772.5 \pm 36.74	774.78 \pm 35.79	772.5 \pm 36.54

SD: Standard deviation

Table 9: Median VAS score

Groups (h)	L	M	P
VAS AT 4	0	0	0
VAS AT 8	0	0	0
VAS AT 12	3	0	0
VAS AT 12.5	3	2	0
VAS AT 13	3	3	0
VAS AT 13.5	5	5	5
VAS AT 14	5	5	5
VAS AT 14.5	5	5	5
VAS AT 15	6	6	6
VAS AT 16	6	6	6

VAS: Visual analog scale

The effectiveness of the block as assessed by the sensory block of all the 4 nerves was found to be 66.6%, 63.8%, 88.8% in Groups L, M, and P, respectively, in our study.

Besides this, success rates vary a lot between the studies ranging from 44 to 100%.^[2-7] This may be due to single or multiple neurostimulation, field of surgery, approach or technique used or the definition of successful block being used, which varies from complete (motor and sensory) involvement of all the five nerves below the elbow^[2,4-6,8] to the completion of surgery without requiring any form of supplementation.^[9,10] However, in our study, success rate among the three groups was evaluated by the extent and effectiveness of the block defined by the complete motor block (all the four nerves) and complete sensory block, respectively.

Distal motor response (flexion of the wrist or fingers) is an important predictor for better results irrespective of the approach.^[2-8,11] Borgate *et al.* reported a success rate of 44% when the proximal response was accepted for local anesthetic injection, compared to 97% when distal motor response was accepted.

It has been previously proposed that proximal response of biceps can be due to stimulation of musculocutaneous nerve, which often leaves the lateral cord at or above the level of infraclavicular region,^[2,5] while, when the distal

response is obtained, the needle is more centrally placed, resulting in even diffusion of local anesthetic.^[4,9,12]

Borgeat *et al.*^[16] reported a 97% rate of IC block success when nerve stimulation elicited a distal response consistent with central placement. Porter *et al.* visualized the block needle besides visualizing the LA spread in ultrasound-guided coracoid ICPB, and they suggested that block failure in the proximal muscle stimulation group was due to LA spread between the pectoral muscle and axillary artery.

There are some studies emphasizing that double or multiple stimulations^[5,10,13] improve the success rate of ICPB, whereas some studies suggest that stimulation of median nerve,^[11] posterior cord,^[9] or all three cords^[6] cause less chances of failure.

Sebastien Bloc obtained a significantly higher success rate with single injection ICPB when performed on a radial nerve-type response (90%) compared with the median (74%) or ulnar (68%) nerve distal motor-type response by neurostimulation. Li *et al.* found that neurostimulation of the posterior cord with Wilson's approach provided complete blockade in 78.9% and stimulating the lateral cord provided complete blockade in 53.1%.^[14]

Similar observations have been made with ultrasound-guided blocks also. Bowens *et al.* observed a significantly higher success rate of block when the drug was placed centrally^[15] with ultrasound and neurostimulation-guided techniques.

The rationale behind our study is that when the infraclavicular portion of the plexus is viewed from the angle taken by the needle, the posterior cord appears to lie central to both the lateral and medial cords; hence, LA injection at the posterior cord is more likely to reach all the three cords.

However, recent studies have shown that septa in the infraclavicular region result in inadequate spread of the Local anaesthetic.^[16] Besides, Sala Blanch *et al.* have proposed that as the cords twist around the axillary artery,^[18] their relative positions change. These might be the reasons for the observed cases of failed blocks in our study.

The onset time of sensory and motor block was faster in nerve distribution in Group P than Groups L and M. These findings are in corroboration with the findings of Lecamwasam *et al.* and Gaertner *et al.*^[6,9] Lecamwasam *et al.*^[9] observed that posterior cord stimulation resulted in less cases of block failure and rapid onset of motor block in more nerves. Gaertner *et al.*^[6] found a faster onset time of sensory and motor block in each nerve distribution with

multiple nerve stimulation when compared to single nerve stimulation. We propose that the onset time of the block may be influenced by the type of nerve stimulation used for the performance of block.

Associated complications with eliciting the distal muscle response are vascular puncture, pneumothorax, and discomfort to patients.^[12] However, in our study, no such complications were encountered. This may be attributed to the careful use of the neurostimulation technique and infraclavicular approach which has been reported to avoid neurovascular structures of the neck and diminish the possibilities of pulmonary complications and pneumothorax.

CONCLUSION

Hence, this study concludes that selective cord stimulation of posterior cord is associated with a greater effectiveness and extent of the infraclavicular block.

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Prevalence of Silent Ischemic Heart Disease in Patients of Rheumatoid Arthritis

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Abstract

Background: Almost half of the deaths in patients of rheumatoid arthritis (RA) are due to cardiovascular diseases. Many studies have shown that patients of RA are at increased risk of mortality and morbidity from ischemic heart disease (IHD). In half of the RA patients with confirmed IHD, the disease was clinically silent. Hence, early detection of the silent IHD is important to reduce the morbidity and mortality in patients of RA.

Objectives: The objectives of this study were to determine the prevalence of silent IHD in RA patients, to identify the predictors of silent IHD in patients with RA and to study the correlation between silent IHD and RA disease activity.

Methods: A total of 50 patients with a diagnosis of RA, attending the Medicine Outpatient Department and admitted in medicine wards of N.S.C.B. Medical College and Hospital, Jabalpur (M.P), were taken into the study determining the prevalence of silent IHD in RA. All patients fulfilled the 2010 ACR/EULAR classification criteria for RA.

Results: Prevalence of silent IHD in RA patients in this study is 10%. There is significantly increased the incidence of silent IHD among patients with increased duration of RA, increased disease activity, and increased total cholesterol and erythrocyte sedimentation rate.

Conclusions: There is a quite common prevalence of silent IHD in patients with RA. The predictors for silent IHD are prolonged disease duration, high disease activity, hypercholesterolemia, and presence of high activity markers.

Key words: Ischemic heart disease, Rheumatoid arthritis, Silent

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder of unknown etiology marked by a symmetric, peripheral polyarthritis, and various systemic manifestations. RA patients are more prone to heart conditions such as the thickening of the artery walls (atherosclerosis) and heart attacks.^[1]

The most common cause of death in RA is cardiovascular disease, accounting for more than 50% of the mortality.^[2]

The risk for myocardial infarction in female RA patients is twice that of women without RA, and in long-standing disease of at least 10 years, the risk is 3 times higher. The most likely explanation is that the inflammation associated with RA has an impact on the vasculature.^[3]

The pathogenic mechanisms involved in accelerated cardiovascular complications in RA appear to be complex and multifactorial. Both traditional and non-traditional risk factors potentially contribute to the increased cardiovascular risk. There is a need for heightened awareness of the increased risk for silent ischemia, early myocardial infarction, and sudden death.^[4]

The underlying cause of ischemic heart disease (IHD) appears to be accelerated in patients with RA. The reason for this may be related to clustering of classical cardiac risk factors such as dyslipidemia, a prothrombotic state, and other processes.

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However, classical risk factors, though important, do not appear to be sufficient to explain the accelerated atherosclerosis associated with RA.^[5] This is possibly due to the systemic inflammation associated with RA, which may make RA itself (like diabetes) an independent risk factor for the development of IHD.^[6]

MATERIALS AND METHODS

- A total of 50 patients with a diagnosis of RA, attending the Medicine Outpatient Department (OPD) and admitted in medicine wards of N.S.C.B. Medical College and Hospital, Jabalpur (M.P), were recruited into the study, determining the prevalence of silent IHD in RA.
- All patients fulfilled the 2010 ACR/EULAR classification criteria for RA.

Criteria for Selection of Patients

Inclusion criteria

Include cases of RA.

A case of RA is defined on the basis of 2010 ACR/EULAR classification criteria for RA.

Exclusion criteria

Include patients known to have

- IHD
 - Family history of IHD (defined as a male or female first degree relative sustaining any ischemic cardiovascular disease)
 - History of chronic smoking
 - Diabetes mellitus (DM) (defined as fasting blood sugar (FBS) >126 mg/dl and/or symptoms of DM and random blood sugar >200 mg/dl)
 - Hypertension (defined by JNC 7 criteria as systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) >90 mmHg)
 - Patients with disabilities which may interfere with stress electrocardiogram (ECG) test as orthopedic or neurological disabilities.
 - All patients were subjected to full history taking including age, sex, smoking, family history of IHD, family history of RA or diabetes, RA disease duration, and presence of complications.
 - Following investigations were included in the study:
1. Complete blood count with erythrocyte sedimentation rate (ESR)
 2. B. urea, S. creatinine
 3. Fasting lipid profile - low-density lipoprotein (LDL), high-density lipoprotein, very LDL, triglycerides, cholesterol
 4. FBS, postprandial blood sugar

5. CRP, RA factor
6. ECG
7. 2D echo
8. Treadmill test (TMT)

Disease activity in RA was measured by DAS28 score.

Exercise TMT

- All patients were subjected to exercise treadmill stress ECG using the modified Bruce protocol.
- Heart rate, blood pressure, and a 12-lead ECG were obtained at baseline and at each stage of the exercise protocol (every 3 min)
- Target heart rate was calculated as $220 - \text{age}$.
- Exercise endpoints included:

Physical exhaustion, significant arrhythmia, severe hypertension (SBP >240 mmHg or DBP >110 mmHg), or severe hypotensive response (decrease >20 mmHg in SBP from baseline).

Positive exercise ECG was defined as

- ST-segment depression of ≥ 1 mm which was horizontal or downsloping, lasting at least for 80 ms
- Development of sharply pointed, symmetrical, arrowhead inverted T waves
- Inversion of U waves developing after exercise
- Failure to increase or actual decrease in Q wave amplitude with exercise
- Development of LBBB with exercise.
- Lengthening of QTc interval with exercise
- Development of multiform ventricular ectopics
- Development of uniform ventricular ectopics, especially
 - If they are occurring in showers
 - If they give rise to bigeminal rhythm
 - If occurring in patient of age 40 years or more
 - If persisting for several minutes or longer
 - Silent ischemia was defined as ischemia on stress test in the absence of angina and/or ECG changes of either a bundle branch block or ST segment abnormality consistent with IHD.

RESULTS

- Prevalence of silent IHD in RA patients in this study is 10% as shown in pie chart below [Figure 1].
- Prevalence of silent IHD in RA patients is increased with increase in disease activity [Figure 2].
- There is significant association between increased duration of RA and occurrence of silent IHD in RA patients [Figure 3].
- There is significantly increased prevalence of silent ischemic heart disease among patients with increased ESR [Figure 4].

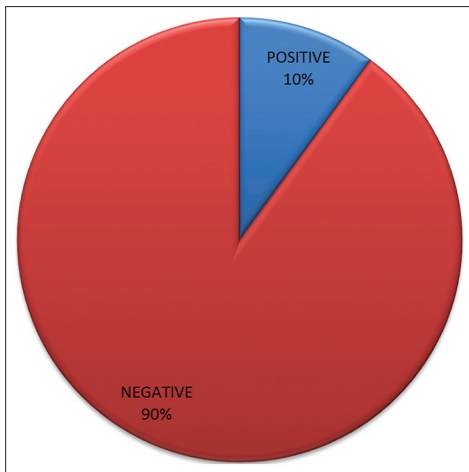


Figure 1: Silent ischemic heart disease in rheumatoid arthritis patients

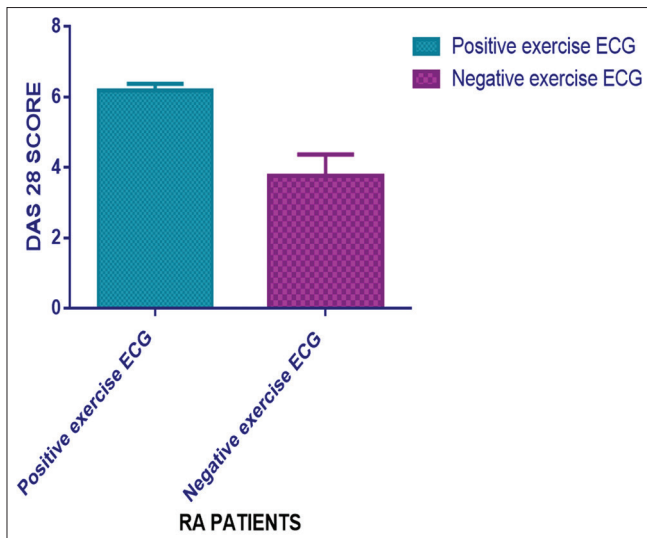


Figure 2: DAS28 score and positive exercise electrocardiogram relation

- Prevalence of silent IHD in RA patients is increased in patients with high total cholesterol.

There was no significant correlation of silent IHD in RA patients with LDL, HDL or triglycerides [Figure 5].

DISCUSSION

- In the current study, we studied a total of 50 patients who were diagnosed as cases of RA. These patients were attending the medicine OPD and were admitted in medicine wards of N.S.C.B. Medical College and Hospital, Jabalpur (M.P) [Table 1]
- In all 50 patients studied, we did not find any evidence of IHD on ECG and 2D echo
- All these patients were subjected to undergo TMT to detect silent IHD.

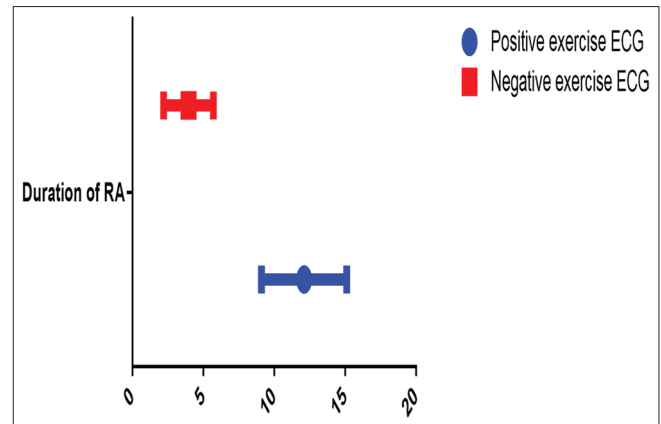


Figure 3: Duration of rheumatoid arthritis and positive exercise electrocardiogram relation

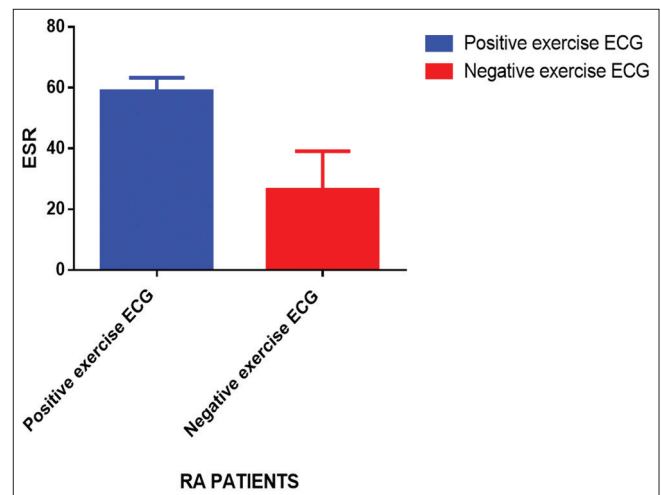


Figure 4: Erythrocyte sedimentation rate and positive exercise electrocardiogram relation

- In 5 patients, we found the TMT to be abnormal. In 4 patients, we found multifocal VPCs, and in 1 patient, we found significant ST depression. Of 5 patients who showed abnormal TMT, 4 were females and 1 was male
- Hence, in our study, we found silent IHD in 10% of the patients. These were consistent with the results of Dala *et al.*, 2012 [Figure 6].^[7] They had found silent IHD in 10.6% of the patients. Maradit-Kremers *et al.*, 2005,^[8] concluded that patients with RA have a significantly higher risk of CHD when compared with non-RA subjects. RA patients are less likely to report symptoms of angina and more likely to experience unrecognized MI and sudden cardiac death. RA has a greater burden of coronary atherosclerosis at their first angiogram that is independent of traditional CV risk factors. This may be due, at least in part, to the expansion of number of classic CD4+ T cells that have previously been implicated in the pathogenesis of IHD^[9]
- In the present study, the frequency of stable IHD (SIHD) increased in RA patients with prolonged

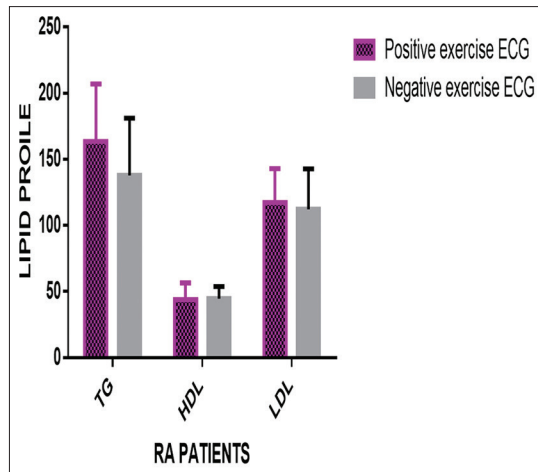


Figure 5: LIPID profile and positive exercise electrocardiogram relation

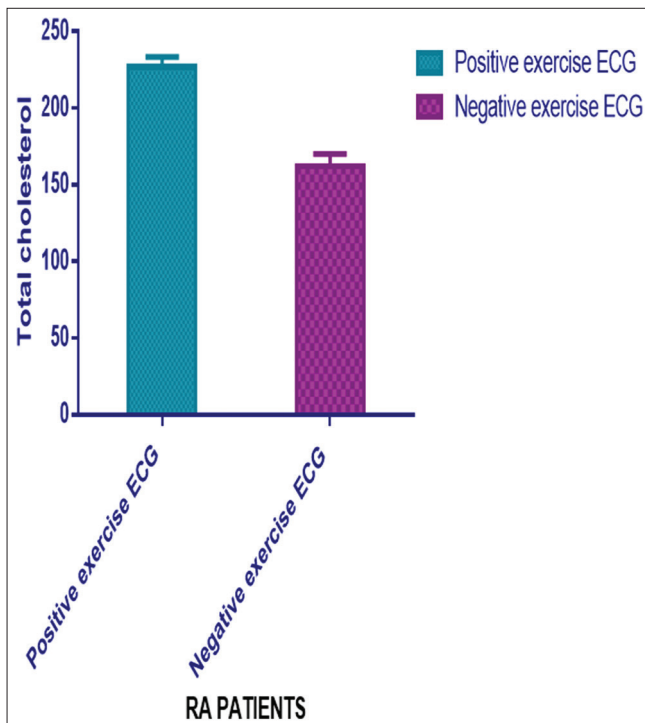


Figure 6: Total cholesterol and positive exercise electrocardiogram relation

duration, and this goes hand-to-hand with the study of Fietta *et al.*, 2009,^[10] who reported that atherosclerosis is an early and common finding in RA patients, positively correlating to the disease duration and severity. This was also consistent with Dala *et al.*, 2012, Menoufiya University Hospitals, Egypt^[7]

- We also found that the occurrence of SIHD is significantly increased in patients with RA in association with the high markers of inflammation and activity as high ESR and this agrees with other studies as that of Dala *et al.*, 2012.^[7] It is also consistent with Chung *et al.*,

Table 1: Comparison between ischemic and non-ischemic group regarding history, clinical and laboratory data in RA patients

Data	Mean±SD		P value
	Positive exercise ECG	Negative exercise ECG	
Age	56.6±14.95	47.82±9.87	0.079
Hemoglobin	10.32±2.65	11.84±1.98	0.121
ESR	58.8±4.54	26.4±12.79	0.000
RA duration	12.1±6.74	3.97±1.76	0.000
Das 28 score	6.18±0.20	3.76±0.61	0.000
Total cholesterol	226.8±6.57	161.84±8.35	0.001
Triglycerides	163.4±43.49	137.82±43.32	0.217
HDL	43.98±12.48	44.71±9.05	0.869
LDL	117.42±25.62	112.14±30.60	0.713

ECG: Electrocardiogram, SD: Standard deviation, ESR: Erythrocyte sedimentation rate, RA: Rheumatoid arthritis, HDL: High-density lipoprotein

2005, who reported that the prevalence and severity of coronary calcification is increased in established RA and is related, in part, to elevated inflammatory markers.^[11] Galiutina and Bychak, 2011, also found that silent myocardial ischemia in patients with the RA was associated with high activity of inflammatory process. CV morbidity and mortality strongly correlate with disease activity, whereas the successful pharmacological control of the chronic inflammation decreases the risk of CV complications^[12]

- Myasoedova *et al.*, 2011, also reported that their findings underscore the importance of systemic inflammation as a key player in the development of CVD in RA by demonstrating independent associations of ESR and CRP with cardiovascular outcomes and mortality. This is concordant with the concept of acceleration of cardiovascular risk and mortality with increasing inflammatory burden and suggests the need for minimization of cumulative inflammation in RA^[13]
- In our study, age was found not to have significant association with SIHD in patients with RA. This is inconsistent with the results of Chung *et al.*, 2006,^[14] and Dala *et al.*, 2012^[7]
- We also found that the occurrence of silent IHD is significantly increased in patients with RA in association with the high disease activity. We had measured disease activity using DAS 28 score.
- In our study, we found the incidence of silent IHD is increased in patients with hypercholesterolemia. This finding was consistent with findings of Dala *et al.*, 2012,^[7] who also showed significant association between increased silent IHD in RA patients and increased cholesterol.

Limitations of the Study

- RA factor and CRP are also important markers of systemic inflammation. We did not find their

Table 2: Comparison between ischemic and non-ischemic group regarding gender, seropositivity and CRP in RA patients

Data	Gender		RF		CRP	
	Male (%)	Female (%)	Positive (%)	Negative (%)	Positive (%)	Negative (%)
Positive exercise ECG	1 (20)	4 (80)	5 (100)	0 (0)	5 (100)	0 (0)
Negative exercise ECG	24 (53.3)	21 (46.7)	39 (86.7)	6 (13.3)	40 (88.9)	5 (11.1)
Total	25 (50)	25 (50)	44 (88)	6 (12)	45 (90)	5 (10)
Fisher's exact	0.349		1.000		1.000	

ECG: Electrocardiogram, SD: Standard deviation, ESR: Erythrocyte sedimentation rate, RA: Rheumatoid arthritis, HDL: High-density lipoprotein

significant association with silent IHD in patients with RA [Table 2]. Because we recorded only qualitative measurements of RA factor and CRP. Their quantitative measurements were not available at our study center.

- Study sample is small constituting 50 patients total because patients who had developed disabilities that interfered with walking and running on treadmill machine were excluded from the study.

CONCLUSIONS

- Silent IHD is a quite common incidence in RA patients (10%).
- The predictors for SIHD are prolonged disease duration, high disease activity, hyperlipidemia, and presence of high activity markers.

“Targeting these risk factors in RA patients could help in lowering incidence of IHD and its complications.”

Recommendation

TMT is recommended as a good screening method for silent IHD, especially in the presence of its predictors in patients with RA.

ACKNOWLEDGMENTS

We gratefully acknowledge the help rendered by Mr. M. P. Singh for his statistical expertise. We also like to express our gratitude to Mr. Dubey for providing technical assistance during TMT.

We bow in reverence to all our patients who in spite of their pain and suffering have cheerfully cooperated.

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Assessment of Atherosclerosis by Carotid Intima-media Thickness in Patients with Rheumatoid Arthritis

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology marked by a symmetric peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. Atherosclerosis is emerging as an important complication of RA, with coronary artery disease being the major cause of mortality in these patients.

Materials and Methods: Study includes 65 RA patients and 65 normal healthy controls. Ultrasound examinations of the carotids were carried out both in cases and controls by SIEMENS ACUSON X300 diagnostic ultrasound system.

Results: Mean carotid intima-media thickness (CMT) in RA patient was statistically significant more than controls. In this study, the prevalence of asymptomatic (subclinical) atherosclerosis in RA patients was 32.3%. In RA patients age, duration of RA and serum triglyceride level demonstrated significant univariate correlation with CMT ($P < 0.05$). On multivariate linear regression analysis duration of RA and serum triglyceride level were found to have a significant correlation with CMT ($P < 0.05$).

Conclusion: Patients with RA had higher mean CMT. Prevalence of asymptomatic (subclinical) atherosclerosis is more in RA patients as compared to normal healthy people.

Key words: Rheumatoid arthritis, CMT, IMT, CAD, Atherosclerosis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology marked by a symmetric peripheral polyarthritis.^[1] It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. It affects the synovial tissue and underlying cartilage and bone. The pathological hallmarks of RA are synovial inflammation and proliferation, focal bone erosions, and thinning of articular cartilage. Atherosclerosis is emerging as an important complication of RA, with coronary artery disease being the major cause of mortality in these

patients.^[2] The inflammatory events in RA patients play an important role in acceleration of atherosclerosis process. Asian Indians as an ethnic group are predisposed to higher incidence of insulin resistance (metabolic syndrome), obesity and premature atherosclerosis.^[3,4] Atherosclerotic changes at the carotid bifurcation are a well-known cause of cerebrovascular disease ranging from thromboembolic transient ischemic attacks due to small emboli of fatty debris and platelet aggregates to completed strokes due to carotid thrombosis and secondary embolism.^[5] B-mode ultrasound allows for direct visualization of both the vessel wall and the lumen and, subsequently, for detection of early atherosclerosis, indicated by intima-media thickening (IMT). Increases in carotid IMT are directly associated with an increased risk of cardiovascular disease.^[6,7] Carotid intimo-medial thickness is a widely accepted surrogate marker of atherosclerosis. It is a reliable, simple and noninvasive marker of subclinical atherosclerosis.^[8]

Aims and Objectives

The aims are to determine the prevalence of subclinical (asymptomatic) atherosclerosis in patients with rheumatoid arthritis (RA).

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To study the determination of disease activity in RA and correlation with CIMT and determination of FLP in RA and correlation with CIMT.

MATERIALS AND METHODS

The study was conducted in the Department of Medicine (Medicine ward and OPD), Netaji Subhash Chandra Bose Medical College, Jabalpur (M.P.), India. Hospital based cross-sectional study was from March 2015 to August 2016. The study includes 65 RA patients and 65 normal healthy controls.

Exclusion Criteria

Patients and control subjects exhibiting traditional risk factors such as hypertension (blood pressure >140/90 mmHg), smoking, diabetes mellitus, and clinically manifest atherosclerosis by way of CAD, peripheral vascular disease, and cerebrovascular disease were excluded from the study. Similarly, patients and controls are known to have dyslipidemia and on treatment for the same were excluded. Patients with disease onset below 18 years, disease duration <5 years, and RA overlap with other rheumatic diseases were excluded from the study. Patients are not willing to be a part of the study.

Methods

All patients were subjected to full history taking including age, sex, duration of RA, presenting complaints, history, treatment history, and addiction history, family history of RA, and presence of associated comorbidities.

Following investigations were included in the study:

- Complete blood count with erythrocyte sedimentation rate.
- Blood urea, serum creatinine, and serum electrolytes.
- Fasting lipid profile- low-density lipoprotein (LDL), high-density lipoprotein (HDL), very LDL (VLDL), triglycerides, and cholesterol.
- Fasting blood sugar and postprandial blood sugar.
- C-reactive protein and RA factor.

Measurement of CIMT

Ultrasound examination of the carotids was carried out both in cases and controls by SIEMENS ACUSON X300 diagnostic ultrasound system. Ultrasound examination of the carotids carried out for detection of CIMT. The carotid wall is seen as two parallel echogenic lines separated by a hypo-echoic line. The inner hypoechoic line is the lumen-media interface, and the outer line is the media-adventitia interface. The distance between the two lines is the combined intimo-medial thickness. Measurements were made bilaterally at the carotid bulb, 2 cm proximal to

the bulb over the common carotid artery (CCA) near its origin. The mean of the six readings was used to calculate the CIMT. The CIMT, defined as the thickness, measured in the far wall of the CCA, from the media-adventitia interface to the intima-lumen interface (with a threshold value for subclinical vascular damage >0.9 mm).

Data Analysis

The data were fed into an excel spreadsheet and then tabulated. Data were statistically analyzed using *t*-test, Chi-square test, Fisher's exact test, and Karl Pearson's correlation using SPSS version 20 and Microsoft excel *P* < 0.05 was considered to be statistically significant.

RESULTS

The present study included a total of 65 RA patients and 65 healthy controls. Majority of cases (41.5%) and controls (43.1%) were in the age group of 40–49 years. Dyslipidemia was defined by high value of National Cholesterol Education Programme-Adult Treatment Panel III (NCEP ATP III) guidelines, that is (total cholesterol >200 mg/dL, LDL cholesterol >100 mg/dL, HDL cholesterol <40 mg/dL, and triglycerides >150 mg/dL).

In this study, 35.38% of patients have high cholesterol level, 67.69% of patients have high triglyceride level, 15.38% of patients have high LDL, and 35.38% of patients have low HDL level [Table 1].

Compared to cases in control group 12.3% of patients high cholesterol level, 38.46% of patients had high triglyceride level, 9.23% of patients had high LDL level, and 15.38% of patients had low HDL level.

In this study total cholesterol, LDL cholesterol, VLDL cholesterol, and serum triglyceride were higher in patients as compared to controls and HDL cholesterol level lower in cases as compared to controls total cholesterol 192.83 ± 41.242 versus 167.22 ± 28.777 mg/dL ($P < 0.05$), LDL cholesterol 103.474 ± 23.7529 versus 96.491 ± 20.2395 mg/dL ($P = 0.074$), VLDL cholesterol 33.169 ± 26.2932 versus 28.844 ± 15.0451 mg/dL ($P = 0.252$), serum triglyceride 190.78 ± 74.269 versus 141.74 ± 28.423 mg/dl ($P < 0.05$), and HDL cholesterol 44.869 ± 9.4617 versus 56.365 ± 16.9516 mg/dL ($P < 0.05$) [Table 2].

In this study, there was the statistically significant difference in the total cholesterol, serum triglyceride, and HDL cholesterol of the patients and controls group. In this study, mean \pm SD of CIMT in patients (0.7546 ± 0.193 mm) was significantly ($P = 0.000$) greater than controls (0.6385 ± 0.16672 mm) [Table 3].

Table 1: Profile of dyslipidemia in patients with RA and normal controls

Variable	Cutoff value as per NCEP ATP III GUIDELINES NO.	Patients with RA n=65 (%)	Normal controls n=65 (%)
High cholesterol (mg/dL)	>200	23 (35.38)	8 (12.3)
High triglyceride (mg/dL)	>150	44 (67.69)	25 (38.46)
High LDL (mg/dL)	>100	10 (15.38)	6 (9.23)
Low LDL (mg/dL)	<40	23 (35.38)	10 (15.38)

Proportion of dyslipidemia is more in cases as compared to controls. RA: Rheumatoid arthritis, LDL: Low-density lipoprotein

- 21 patients (32.3%) with RA had a higher mean CIMT (>0.9 mm).
- 4 normal healthy controls 6.15% are associated with higher mean CIMT (>0.9 mm).
- In this study, the prevalence of subclinical (asymptomatic) atherosclerosis in patients with RA is 32.3%.

The various continuous variables in patients of RA with CIMT >0.9 mm and <0.9 mm were compared using the median values of each continuous variable. The Pearson's Chi-square was applied to these variables [Table 4].

21 RA patients had mean CIMT >0.9 mm.

In RA patients age ($P = 0.007$), duration of RA ($P = 0.000$), and total triglyceride level ($P = 0.046$) were significantly associated with CIMT >0.9 mm.

RA patient with mean CIMT >0.9 mm had higher mean age (50.14 ± 6.747 years), longer mean disease duration (96.00 ± 14.199 months), and lower mean serum triglyceride level (164.33 ± 61.17 mg/dL).

Pearson's univariate coefficients of age 0.328 (0.004), duration of RA 0.393 ($P = 0.001$), and serum triglyceride level -0.229 ($P = 0.033$) demonstrated significant univariate correlation with CIMT [Table 5].

On applying multivariate linear regression analysis with age, duration of RA and total triglyceride level as the independent variables and CIMT as the dependent variable, only duration of RA and total triglyceride level were found to have a significant correlation with CIMT.

Utilizing the above regression model an equation to predict CIMT was derived $=0.396 + 0.004 \times (\text{disease duration in months}) - 0.001 \times (\text{serum triglyceride level})$.

The value of R for this model was 0.497, signifying that the correlation between the observed values of CIMT and those predicted by this model was 0.497. The value of R^2 (goodness of fit measure/coefficient of determination) for this model was 0.247 signifying that this model of regression explained 24.7% of the variation in CIMT.

Table 2: Demographic and lipid profile of patients and controls

Variables	RA (n=65)	Control (n=65)	P value
Age (years)	45.829±0.026	43.86±9.033	NS
Total cholesterol (mg/dL)	192.83±41.242	167.22±28.777	0.000
HDL- cholesterol (mg/dL)	44.869±9.4617	56.365±16.9516	0.000
LDL-Cholesterol (mg/dL)	103.4742±3.7529	96.491±20.2395	NS
VLDL-cholesterol (mg/dL)	33.1692±6.2932	28.8441±5.0451	NS
TGs (mg/dL)	190.787±4.269	141.742±8.423	0.000

In this study systolic BP, diastolic BP, total cholesterol, HDL cholesterol, and triglycerides level were found to be statistically significant ($P < 0.05$) as compared to cases. RA: Rheumatoid arthritis, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, TGs: Triglycerides

Table 3: Comparison of CIMT among cases and controls

Variables	Mean±SD		P value
	Case	Control	
Rt mean CIMT (mm)	0.777±0.173	0.637±0.1746	$P < 0.000$
Lt mean CIMT (mm)	0.746±0.2032	0.64±0.173	$P < 0.002$
Total mean CIMT (mm)	0.7546±0.193	0.6385±0.166	$P < 0.000$

Total mean CIMT value was found to be statistically significant in cases as compared to controls ($P < 0.05$), CIMT: Carotid intima-media thickness, SD: Standard deviation

Table 4: Comparison of variables affecting CIMT

Variables	CIMT<0.9 n=44 (%)	CIMT>0.9 n=21 (%)	P value
Age	43.5±9.304	50.14±6.747	0.007*
BMI	22.839±3.10	22.905±3.346	0.938
Disease duration	81.82±13.515	96.00±14.199	0.000*
Systolic BP	120.73±6.264	123.71±6.820	0.086
Diastolic BP	76.61±4.205	77.14±4.498	0.644
Total cholesterol	189.45±34.060	199.90±53.583	0.343
HDL cholesterol	45.00±8.572	44.595±11.32	0.873
LDL cholesterol	103.155±23.111	104.143±25.61	0.877
VLDL cholesterol	35.459±30.955	28.371±10.787	0.313
Total triglyceride	203.409±77.22	164.33±61.17	0.046*

Age, disease duration, and serum triglyceride level ($P < 0.05$) significantly associated with CIMT>0.9 cm, CIMT: Carotid intima-media thickness, SD: Standard deviation, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

In this study based on DAS 28. Disease activity scores each group studied as Group A (DAS <2.6, remission),

Table 5: Univariate correlation coefficients of various factors affecting CIMT

Variables	Pearson's univariate correlation coefficient (P)	Multivariate regression analysis (SE)	P
Age	0.328 (0.004)*	0.003 (0.002)	0.157
Disease duration	0.393 (0.001)*	0.004 (0.001)	0.007*
Triglycerides	-0.229 (0.033)*	-0.001 (0.000)	0.033*
Total cholesterol	0.064 (0.306)		
HDL cholesterol	0.082 (0.257)		
LDL cholesterol	0.054 (0.334)		
VLDL cholesterol	-0.053 (0.339)		

CIMT: Carotid intima-media thickness, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein

Group B (2.6–3.2, low), Group C (>3.2–5.1, moderate), and Group D (>5.1, high) in these groups the relationship of activity of RA with CIMT was studied.

In Group C (>3.2–5.1) the value of CIMT was found to be maximum mean \pm SD 0.8361 \pm 0.16323 mm [Table 6]. Patients with RA duration <7 years mean \pm SD of CIMT was (0.7188 \pm 0.1496).

Patients with RA duration 7–8 years mean \pm SD of CIMT was (0.8429 \pm 0.186 mm). Patients with RA duration >8 years mean \pm SD of CIMT was (0.8591 \pm 0.157 mm).

Patients with RA duration >8 years had more mean CIMT value [Table 7].

DISCUSSION

The patients with RA have a 2 to 5 times increased the risk of developing a premature cardiovascular disease that shortens life expectancy by 5–10 years. Thus, in patients with active RA, the majority of cardiovascular deaths result from accelerated atherosclerosis.^[9]

The inflammatory events in RA patients play an important role in the acceleration of atherosclerosis process. Atherosclerosis, previously thought to be a passive disease of lipid accumulation, is now widely acknowledged as a dynamic inflammatory process beginning with endothelial activation, leukocyte recruitment, lipid oxidation, and culminating with plaque destabilization, and thrombosis. In RA although the primary site of inflammation is the synovial tissue, cytokines such as tumor necrosis factor α , interleukin (IL1 β), and IL 6 are released into systemic circulation. These circulating cytokines alter the function of distant tissues, including adipose tissue, skeletal muscle, and liver which leads to dyslipidemia.^[10]

Atherosclerotic changes at the carotid bifurcation are a well-known cause of cerebrovascular disease ranging from thromboembolic transient ischemic attacks due to small emboli of fatty debris and platelet aggregates to completed strokes due to carotid thrombosis and secondary

Table 6: Correlation of DAS 28 with mean CIMT

DAS	Number	Mean CIMT \pm SD (mm)
<2.6	19	0.7342 \pm 0.160
2.6–3.2	21	0.7476 \pm 0.168
>3.2–5.1	18	0.8361 \pm 0.163
>5.1	7	0.7571 \pm 0.200

RA patients with DAS28>3.2–5.1 had maximum value of mean CIMT 0.8361 \pm 0.0163, CIMT: Carotid intima-media thickness, SD: Standard deviation

Table 7: Comparison of duration of RA with mean CIMT

Duration of RA	Number of RA patients	CIMT (mean \pm SD) (mm)
<7 years	40	0.7188 \pm 0.1496
7–8 years	14	0.8429 \pm 0.186
>8 years	11	0.8591 \pm 0.157
Total	65	0.7692 \pm 0.16972

Mean CIMT value higher in RA patients with duration>8 years, CIMT: Carotid intima-media thickness, SD: Standard deviation, RA: Rheumatoid arthritis

embolism. In this study, the prevalence of asymptomatic (subclinical) atherosclerosis in RA patients was 32.3%. In RA patients age, duration of RA and serum triglyceride level demonstrated significant univariate correlation with CIMT (<0.05). On multivariate linear regression analysis duration of RA and serum triglyceride level were found to have a significant correlation with CIMT ($P < 0.05$).

CONCLUSION

Patients with RA had higher mean CIMT.

Prevalence of asymptomatic (subclinical) atherosclerosis is more in RA patients as compared to normal healthy people.

Duration of RA and total triglyceride level were found to have a significant correlation with CIMT.

Increased duration of RA was associated with the higher value of CIMT.

Limitations of Study

Some patients with RA were taking corticosteroids and methotrexate, and since both of these drugs are known to

be having atherogenic effects, this can be a confounding factor in our study.

Since our sample size was small due to a lesser number of patients attending OPD, this was insufficient to estimate the exact prevalence of atherosclerosis in patients with RA.

ABBREVIATIONS

- FLP – fasting lipid profile
- CAD – coronary artery disease
- IL 1 β - interleukin 1 β
- IL 6 - interleukin 6
- OPD – outpatient department
- CIMT – carotid intimo-medial thickness
- IMT - intimo-medial thickness
- RA – rheumatoid arthritis

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A Study on Imaging Modalities in Primary Hyperparathyroidism

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Abstract

Background: Hyperparathyroidism (HPT) is the third most common endocrine disease. The rate of incidence is increasing with the more extensive availability of early screening methods including levels of serum parathyroid hormone (PTH) and calcium. Primary HPT (PHPT) results from unregulated overproduction of the PTH, usually due to a parathyroid adenoma or hyperplasia. With the advent of minimally invasive parathyroid surgeries, the need to differentiate between the two has arisen in clinical practice.

Materials and Methods: A total of 32 cases of PHPT were studied. Pre-operative localization was done using ultrasonography (8-12 MHz linear transducer probe), magnetic resonance imaging (1.5 Tesla), and technetium 99 m-methoxyisobutyl isonitrile (Tc^{99m} Sesta MIBI) scan. Parathyroidectomy was performed, and histological analysis was done to confirm the clinical diagnosis. The expression of Ki-67 and p53 was analyzed in the tumor tissue in 22 patients.

Results: It was found that double imaging modality had higher sensitivity and specificity for adenomas as compared to either individual scan. Immunohistochemical analysis showed increased uptake of Ki67 in adenomas and hyperplasia as compared to normal tissue. P53 uptake was seen on both adenomas and hyperplasia.

Conclusion: Double imaging modality is better than using single imaging modality in the identification of HPT.

Key words: Hyperparathyroidism, Ki67, p53, Parathyroid adenoma, Parathyroid hyperplasia, SESTAMIBI scan, Ultrasound

INTRODUCTION

Primary hyperparathyroidism (PHPT) is the inappropriate or unregulated overproduction of parathyroid hormone (PTH) resulting in an abnormality of calcium and phosphorus metabolism. The incidence of HPT, the third most common cause of endocrine disease, is increasing. Routine screening and yearly checkups are making early detection a possibility, promoting prompt intervention. It has been found that, while the incidence and prevalence globally are similar to that of the US, but presentation varies greatly. In the US and Europe, most (80%) patients present with asymptomatic disease, but

in resource-poor nations, most (>80%) patients present with symptoms.^[1]

PHPT is a relatively common disorder affecting 1 in 500 women and 1 in 2000 men over 40 years of age. The best estimate of incidence is 22/100,000/year, and prevalence is approximately 1/1000.^[2] Over 80% of patients with PHPT have solitary adenomas, the remaining having multiple adenomas, hyperplasia, or carcinomas.

Studies have suggested three different mechanisms for parathyroid gland dysfunction in PHPT: (1) A defect in calcium recognition, (2) a monoclonal tumor from overexpression of a growth stimulator, or (3) a monoclonal tumor from inactivation of a growth inhibitor.^[3]

p53 mutations have been found to play a role in the development of many common human malignancies.^[4] Ki-67 gene is present in all proliferating cells, and there is great interest in its role as a marker of proliferation.^[5] Recently, gene array techniques have revealed the Ki-67

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gene's role in several "proliferation signatures," showing that a set of genes with increased expression patterns is correlated with a tumor cell.

At present, PHPT, whether caused by an adenoma or hyperplasia, can be cured surgically with a high rate of success. With the advent of more advanced surgical techniques including minimally invasive parathyroidectomy, the need for more accurate pre-operative localization of lesion is gaining importance. It has been found that with optimized pre-operative mapping, the success rate of less invasive techniques equals that of the traditional bilateral approach.^[6-11]

The commonly used non-invasive imaging techniques are sonography, scintigraphy, computed tomography, and magnetic resonance imaging (MRI). Our study has compared the sensitivity and specificity of these modalities and compared the results of each. We also examine the efficacy of using multiple modalities. Sonography and 99 mTc-SESTAMIBI scintigraphy have emerged as dominant, and potentially complementary, techniques in the pre-operative evaluation of PHPT.

MATERIALS AND METHODS

The study sample included 32 cases of PHPT (as documented by elevated serum PTH and calcium levels), 9 male and 23 female, of a mean age group of 44.66 years with a standard deviation (SD) of 11.406. The mean pre-operative PTH value was 638.47 (range), and the mean pre-operative serum calcium level was 12.32 mg/dL. Pre-operative localization was done using ultrasonography (USG) (8-12 MHz linear transducer probe), MRI (1.5 Tesla) and 99 m-methoxyisobutyl isonitrile (^{99m}Tc Sesta MIBI) scan. Parathyroidectomy was performed, and histological analysis was done to confirm the clinical diagnosis.

Histology

After surgical excision, the specimens were fixed and buffered in formalin, embedded in paraffin, sectioned, stained with hematoxylin and eosin, and classified as adenomas according to the Ghandur-Mnaymneh and Kimura classification.

Immunohistochemical (IHC) analysis

Paraffin slides were xylene washed, rinsed twice with alcohol (18:1:1 100% ethanol:100% ethanol:100% isopropanol) and several times with deionized water. The slides were incubated 5 times at room temperature. Counterstaining and visualization of nuclear staining were done. Semiquantitative analysis was done for scoring the IHC staining. The staining pattern for Ki-67 was taken as, 0 = no staining; 1 = faint reaction; 2 = moderate reaction; and 3 = strong reaction.

The expression of Ki-67 and p53 was analyzed in the tumor tissue in 22 patients only and subsequently discontinued as it did not have any diagnostic value.

RESULTS

The mean age group was found to be 44.6, with a SD of 11.406, with maximum clustering seen between 50 and 60 years. A clear female preponderance was observed (28.1% male: 71.9% female.) The most common clinical presentation was found to be body pain, followed by urolithiasis, as a part of a master health check-up, abdominal pain, and neck swelling, in that order.

A marked decline in serum PTH levels were observed post-operative, and serum calcium levels came back to normal ($P < 0.001$).

When comparing imaging modalities, it was found that USG was found to have give a false negative result in 56.3% and true positive in 43.8%. MRI and SESTAMIBI scan both were found to have a true positive rate of 93.8% and false negative rate of 6.2%. 13 patients were subject to MRI as well as SESTAMIBI scan. On using this double imaging modality, it was found that sensitivity was 83% and positive predictive value was 71.4%.

IHC analysis showed, out of 22 samples of parathyroid adenoma, positive uptake of Ki67 in 14 samples. 8 samples did not show any uptake. It was found that Ki67 uptake in normal parathyroid tissue was seen in 3 out of 8 specimens.

p53 staining was positive in 21 specimens of parathyroid adenoma out of a total of 22, while 7 out of 8 normal parathyroid tissue showed positivity for the same.

DISCUSSION

Parathyroid lesions in our study were found to be common in the 5th decade. The mean age was 46.86 years, which was found to be comparable to the mean age in the study, done by Afshin *et al.* (52.2) but did not correlate with the study done by Gopal *et al.* (33.5).

In our study, the male to female ratio is 1:1.75, which was comparable to the study done by Gopal *et al.* (1:2), does not correlate with the study done by Afshin *et al.* The incidence of parathyroid lesions was higher in females in our study but not as high as the study done by Afshin *et al.* (1: 4)

Polyuria, polydipsia, and weakness accompanied with skeletal abnormality, nephrocalcinosis, nephrolithiasis,

peptic ulcer disease, and psychiatric disorder are the most common clinical manifestation of HPT.

Nearly 45.4% of our patients presented with bone pain and 40.1% of patients presented with urolithiasis comparable to the most of the studies. The mean pre-operative PTH value was found to be 611.18, found to be comparable to that of study done by Afshin *et al.* mean serum intact PTH level was 584, while study done by Gopal *et al.* had elevated mean PTH value of 866. The mean pre-operative serum calcium was found to be 12.43, found to be comparable to that of study done by Gopal *et al.* (12.55).

A total of 13 patients underwent ultrasound neck (38.5%). Lesion was localized in 5 patients. Lesion could not be localized in 8 patients. Whereas in the study done by Afshin *et al.* USG revealed 34 lesions out of 36 patients (94.4%). In study done by Gopal *et al.* USG revealed 44 lesion out of 79 patients (55.6%).

Our study did not correlate with either of them.

Of the 22 study patients, 20 patients were localized preoperatively by Sesamibi scan. Whereas in study done by Afshin *et al.* ($n = 36$) MIBI scan showed 26 parathyroid lesion in patients with PHPT. In study was done by Saengsuda MIBI scintigraphy correctly laterized and localized 17 of 19 abnormal parathyroid glands with sensitivity 90%, specificity 100%, and positive predictive value (PPV) 100%.

In our study (on using combined modality), 13 patients were subject to USG and SESTAMIBI scan. USG and SESTAMIBI scan were found to have 46% sensitivity, 100% specificity with a positive predictive value of 100% and negative predictive value of 25%.

In our study $n = 22$ with PHPT, 14 patients had solitary adenomas and 8 patients had parathyroid hyperplasia. In study done by Gopal *et al.*, 69 patients diagnosed to have adenoma and 10 patients had parathyroid hyperplasia. In our study p53, immunostaining had 100% positivity for adenomas and 87.5% positivity in normal tissue not

comparable any of the other studies. Ki 67 had 64.2% positivity to adenomas which were comparable to study done by Ricci *et al.* (57.2%). Ki 67 positivity (37.5%) was seen in normal tissue which did not correlate with other studies.

CONCLUSION

Using double imaging modality increases the diagnostic accuracy of HPT than using a single modality, and hence, it is strongly recommended. Ki67 and p53 assays in the specimens did not prove to be of any beneficial value. It probably needs a larger cohort to arrive at a meaningful value of these assays.

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Comparative Study of Mental Stress Score between Various Surgical Modalities for Treatment of 10–20 mm Renal Calculi

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Abstract

Introduction: The treatment of renal calculi has undergone a paradigm change in the past two decades. The ultimate aim in treating these stones will be to achieve a complete clearance with minimal morbidity. The risk of recurrence or incomplete clearance or need for ancillary procedures would significantly affect patients' mental health.

Purpose: The purpose of this study is to compare mental stress experienced by the patient on the completion of the treatment using Kessler Psychological Distress Scale (K10) for each modality in the management of renal and upper ureteric calculi 10–20 mm size.

Materials and Methods: This was a prospective study on patients with renal calculi. Following the procedure, patients were asked to fill up and complete the questionnaire at 2 and 6 weeks. The K10 questionnaire contained 10 questions with each of them having 5 outcomes. Based on the total score, the degrees of mental distress due to the procedure were graded as mild, moderate, and severe.

Results: When assessing patients' psychological status using Kessler's scale at 2 weeks, a majority of patients had a score of <20. However, one-fifth of patients in the retrograde intrarenal surgery group and about one-sixth of patients in percutaneous nephrolithotomy (PCNL) group had a mild distress score. When assessing patients' psychological status using Kessler's scale at 6 weeks following primary procedure, most patients are <20 score, and hence, not statistically significant. But when the Shock wave lithotripsy (SWL) group was analyzed, 2.5% of patients had a significant psychological stress.

Conclusion: All three procedures have a good acceptance rate among the patients. PCNL, though more invasive than the other two procedures, has a better acceptance rate in view of achieving complete clearance in one sitting. On the other hand, extracorporeal SWL (ESWL), despite being so non-invasive, has a significant psychological impact in view of the need for multiple sittings and associated complications.

Key words: Lithotripsy, nephrolithotomy, questionnaire, renal calculi

INTRODUCTION

The primary goal while treating renal calculi and upper ureteric calculi is to achieve maximum clearance of stone with minimal morbidity. The various minimally invasive modalities described for treatment of such

stones are shockwave lithotripsy (SWL), percutaneous nephrolithotomy (PCNL), and retrograde intrarenal surgery (RIRS).^[1,2] The same authors had earlier published their study comparing success rate, retreatment rate, need for auxiliary procedure, complication rate, mean procedure time, and mean hospital stay between the above three modalities. As a part of that study, we also had assessed the mental stress score following the surgical treatment received using Kessler Psychological Distress Scale (K10). Kessler Psychological Distress Scale (K10) is used to assess the patients' mental stress, which was proposed by Kessler R, Professor of health care policy, Harvard Medical School, Boston, USA. This K 10 test is a patient's self-report measure to assess their current condition about anxiety and depression following

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a procedure.^[3] The 10-item Kessler Psychological Distress Scale (K10) is a short measure of non-specific psychological distress, which has been shown to be a sensitive screen for the Diagnostic and Statistical Manual of Mental Disorders criteria for anxiety and mood disorders.^[4]

The three surgical procedures taken for consideration in our study are all very well established and widely accepted modalities of treatment. For a stone smaller than 10 mm, initial treatment option has always been extracorporeal SWL. For a large stone above 20 mm, PCNL is the accepted modality of treatment. For stones in the interim range, the options are plenty. The level of acceptance of these procedures also varies from one procedure to the other. The purpose of this study is to identify if any of the above-mentioned procedures have any impact on the ultimate psychological status that might alter the final outcome in such patients.

Aim

The aim of this study is to compare mental stress experienced by the patient on the completion of the treatment using Kessler Psychological Distress Scale (K10) for each modality in the management of renal and upper ureteric calculi 10–20 mm size.

MATERIALS AND METHODS

This was a prospective observational comparative study conducted in a teaching institution over 1 year period from November 2013 to October 2014. A total of 287 cases renal and upper ureteric calculi of 10–20 mm size were included in our study. All patients underwent PCNL, RIRS, or SWL. The study model was presented to the Institutional Ethical Committee and approval was obtained. Following the procedure, patients were asked to fill up and complete the questionnaire at 2 and 6 weeks. The K10 questionnaire contained 10 questions with each of them having 5 outcomes. The outcomes were numbered and rated from 1 to 5.

Table 1 describes the details of the K 10 questionnaire circulated among the patients at 2 and 6 weeks after

treatment. Based on the total score, the degrees of mental distress due to the procedure were graded as follows:

Score <20, where patients are likely to be well without any mental illness.

Score 20–24, where patients are likely to have mild mental disorder.

Score 25–29, where patients are likely to have moderate mental disorder.

Score >29, where patients are likely to have serious mental disorder.

Inclusion and Exclusion Criteria

All patients presenting with calculi of 10–20 mm in otherwise normal renal pelvicalyceal system, pelviureteric junction, or proximal ureter up to L3 transverse process were included in our study. Those patients in whom the stone was below L3 transverse process, multiple renal calculi with second calculi size more than 4 mm, abnormal upper urinary tract anatomy such as duplex system, horseshoe kidney, ectopic kidney, and pelviureteric junction obstruction, and patients with axial skeletal abnormality such as scoliosis and kyphosis or bleeding diathesis were all excluded from the study.

The choice of treatment modality for the management of the upper urinary tract calculi of 10–20 mm calculi is largely determined by the individual surgeon taking into consideration the patient's anatomy, comorbid conditions, urinary tract anatomy, stone density, and location as well as patients' preference.

Statistical Analysis

Descriptive statistical analysis was carried out in the present study. To describe about the data frequency analysis, percentage analysis was used for categorical variables, and for continuous variables, the mean and standard deviation were used. For the multivariate analysis, the Kruskal–Wallis test and ANOVA were used, and for trivariate and bivariate analysis, Mann–Whitney test was used. To find the significance in categorical data, Chi-square test was used. In both the above statistical tools, the probability value of <0.05 is considered as significant level. The statistical

Table 1: K 10 test questionnaire given to patients at 2 and 6 weeks after treatment

Questionnaire	Scoring points				
During the past 15 days, about how often did you feel tired out of no good reason?	1	2	3	4	5
During the past 15 days, about how often did you feel nervous?	1	2	3	4	5
During the past 15 days, about how often did you feel so nervous that nothing could calm you down?	1	2	3	4	5
During the past 15 days, about how often did you feel hopeless?	1	2	3	4	5
During the past 15 days, about how often did you feel restless and fidgety?	1	2	3	4	5
During the past 15 days, about how often did you feel so restless you could not sit still?	1	2	3	4	5
During the past 15 days, about how often did you feel depressed?	1	2	3	4	5
During the past 15 days, about how often did you feel everything was an effort?	1	2	3	4	5
During the past 15 days, about how often did you feel so sad that nothing could cheer you up?	1	2	3	4	5
During the past 15 days, about how often did you feel worthless?	1	2	3	4	5

1 - None of the time, 2 - A little of the time, 3 - Some of the time, 4 - Most of the time, 5 - All the time

software SPSS 16.0 version was used for the analysis of the data, and Microsoft Word and Excel have been used to generate graphs and tables.

Observations

Table 2 and Figure 1 illustrates the Kessler's distress scale at 2 weeks after intervention. When assessing patients' psychological status using Kessler's scale at 2 weeks, a majority of patients had a score of <20. However, one-fifth of patients in the RIRS group and about one-sixth of patients in PCNL group had a mild distress score. None of the patients in RIRS group had moderate or severe distress scores.

Table 3 and Figure 2 illustrates the Kessler's distress scale at 6 weeks after intervention. When assessing patients' psychological status using Kessler's scale at 6 weeks following primary procedure, most patients are <20 score and hence not statistical significant. But when the Shock wave lithotripsy (SWL) group was analyzed, 2.5% of patients had a significant psychological stress. Following PCNL as the primary treatment at the end of the study at 6 weeks, all patients are stone free and without mental distress. In RIRS group, the mental distress at the end of 6 weeks is within the comfort zone. In SWL group, the mental distress at the end of 6 weeks is within the comfort zone in almost all patients with 2 patients having mild distress at 6 weeks in view of prolonged need of completion of stone management.

DISCUSSION

Renal calculus and the bothersome symptoms increase the need for multiple visits to hospitals and also cause significant psychological impact on patients.^[5] Moreover, continuous usage of medication, need for recurrent

surgical procedures, limitation in physical activity, and loss of working hours and associated financial burden are found to be associated with many psychological disturbances. Among these, anxiety has been identified as the more prevalent entity and is associated with poor patient compliance toward management and even progress to depression in many patients.^[6,7]

In the treatment of renal stones, the type of anesthesia, need for an inpatient admission, success and failure rate of the procedure, complications, need for the auxiliary procedure, and affordability to the procedures all play a role in influencing patients' anxiety status.

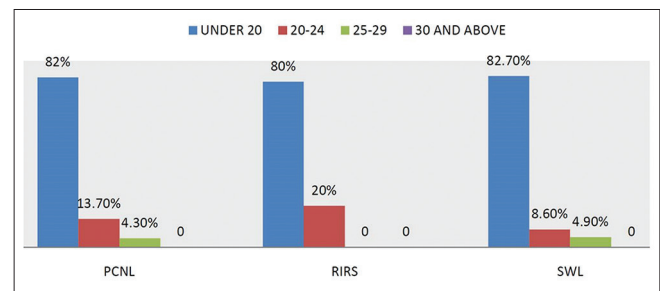


Figure 1: Kessler psychological distress scale at 2 weeks

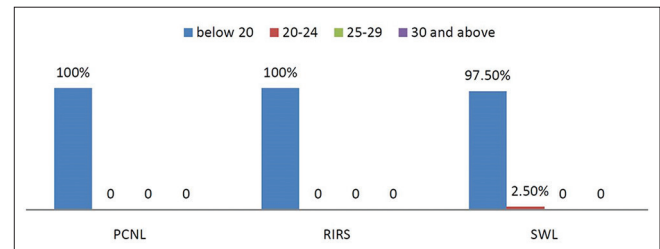


Figure 2: Kessler psychological distress scale at 6 weeks

Table 2: Kessler psychological distress scale at 2 weeks

Distress score	Group, n (%)				Chi-square	P value
	PCNL	RIRS	ESWL	Total		
Below 20	132 (82)	36 (80)	67 (82.7)	235 (81.9)	7.535	0.110
20–24	22 (13.7)	9 (20)	7 (8.6)	38 (13.2)		
25–29	7 (4.3)	0	7 (8.6)	14 (4.9)		
30 and above	0	0	0	0		

PCNL: Percutaneous nephrolithotomy, RIRS: Retrograde intrarenal surgery, ESWL: Extracorporeal shockwave lithotripsy

Table 3: Kessler psychological distress scale at 6 weeks

Distress score	Group, n (%)				Chi-square	P value
	PCNL	RIRS	ESWL	Total		
Below 20	161 (100)	45 (100)	79 (97.5)	285 (99.3)	5.122	0.077
20–24	0	0	2 (2.5)	2 (0.7)		
25–29	0	0	0	0		
30 and above	0	0	0	0		

PCNL: Percutaneous nephrolithotomy, RIRS: Retrograde intrarenal surgery, ESWL: Extracorporeal shockwave lithotripsy

In our earlier study when assessing the failure rates of these procedures, SWL recorded the maximum failure (17.3%), with 19.8% of patients needing auxiliary procedure.^[8] On the other hand, PCNL and RIRS (5.6% and 11.1%, respectively) had the least number of cases needing an auxiliary procedure.^[8]

The degrees of mental distress due to the procedure were graded based on Andrew's study.^[9] The work done by Brown *et al.* assessed patients' anxiety before and after different surgical procedures for renal calculus and to identify various factors that can attribute to pre- and post-operative anxiousness.^[10] The measurement of palmar sweat (evaporimeter) for quantifying stress and bipolar visual analog scale and the Spielberger State Anxiety Questionnaire were used before and after the procedures. The study concluded highly significant reduction in the palmar sweat production and score obtained following open surgery, but no changes in patients undergoing PCNL or lithotripsy before and after treatment. Pre-operatively, fear of a general anesthetic, and post-operatively, pain were identified as cause for patients' anxiety.

State and Trait Anxiety Inventory scale was used to assess the anxiety status of 128 patients following SWL. It showed that the residual fragments after SWL procedure made patients more anxious as additional procedures were needed for clearing the left out stones. The study also concluded that detailed information should be provided to patients with respect to procedure and possible complications, and potential need for additional treatment may reduce the anxiety.^[11]

A study done by Brown *et al.* with 24 patients undergoing extracorporeal piezolithotripsy with continuous assessment of anxiety by measurement of palmar sweat during the procedure itself found with 50% of patients showed increased levels of palmar sweat throughout treatment, with a return to pre-treatment levels after the procedure. 8 patients attributed pain as their cause for anxiety. Patient education before the procedure may help in reducing anxiety.^[12]

Extracorporeal SWL (ESWL) seems to be safe and simple and being done as an outpatient procedure. It does not require any anesthesia and patient can go back home the same day. All of these factors support the fact that it will not have any impact on the psychological status of the patients, but it was not so in our study. This study underlines the fact that the patient anxiety depends not only on the severity of the procedure but also on the sequelae of the procedure, such as incomplete clearance, complications of the procedure, need for multiple admissions, and ancillary procedures.

Limitations of this Study

The sample size is small and associated with difficulty in performing stratified analysis. The study was unable to exclude many of the other confounding factors which may have influenced some of the outcomes analyzed which is beyond the scope and purview of this study.

CONCLUSION

All three procedures have a good acceptance rate among the patients. PCNL, though more invasive than the other two procedures, has a better acceptance rate in view of achieving complete clearance in one sitting. On the other hand, ESWL, despite being so non-invasive, has a significant psychological impact in view of the need for multiple sittings and associated complications.

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Chronic Inflammatory Gingival Enlargement: A Case Report

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Abstract

Gingival enlargement also known as gingival overgrowth is defined as increase in the size of gingiva. Gingival enlargement can be caused by a wide variety of etiologies. Gingival enlargement may result from acute or chronic inflammatory changes; chronic changes are much more common. Chronic inflammatory gingival enlargement (CIGE) is caused by prolonged exposure to dental plaque. Plaque-induced inflammation can be the sole cause of gingival enlargement or can be the secondary cause. Gingival enlargement can be a functional and esthetic disparity so in all patients therapy to control gingival enlargement is essential. This report aims to highlight the importance of patient motivation and patient compliance in treatment planning of CIGE.

Key words: Chronic inflammatory enlargement, Gingival disease, Gingival enlargement

INTRODUCTION

Gingival enlargement, a common feature of gingival diseases, is defined as an increase in the size of the gingiva. Gingival overgrowth varies from mild enlargement of isolated interdental papilla to segmental or uniform and marked enlargements affecting one or both the jaws with diverse etiopathogenesis.^[1] It is a multifactorial condition that develops as interactions between host and environment or in response to various stimuli.^[2] It may be plaque-induced or associated with systemic hormonal disturbances. It also occurs as a manifestation associated with several blood dyscrasias such as leukemia and thrombocytopenia. Based on the extent and severity, these enlargements may lead to functional disturbances such as altered speech, difficulty in mastication, and esthetic and psychological problems.^[1] Ingles *et al.* summarized different methods and presented their clinical index to measure the degree of gingival enlargements.^[3]

Inflammatory gingival enlargement may be categorized as acute or chronic; wherein chronic changes are

much more common.^[4] Chronic inflammatory gingival enlargement (CIGE) is caused by prolonged exposure to plaque accumulation. Plaque-induced inflammatory gingival enlargements resolve with debridement of plaque and calculus and improved oral hygiene, where the gingival tissue is fibrotic resolution may not occur, resulting in persistence of periodontal pocket such that oral hygiene is impeded.^[5] This may lead to more inflammation and further plaque accumulation perpetuating this vicious cycle.

The therapeutic approaches related to gingival enlargement are based on the underlying etiology and the subsequent changes it manifests on the tissues. The prime treatment modalities involve obtaining a detailed medical history and nonsurgical periodontal therapy, followed by surgical excision to retain esthetical, and functional demands.

This case report presents a clinical presentation and treatment of CIGE.

CASE REPORT

A 25-year-old female reported to the Department of Periodontics of Nair Hospital Dental College, Mumbai, with a chief complaint of swollen gums, bleeding from gums, and bad breath.

The patient complained of swelling of the upper and lower gums. The patient had noticed the swelling 2 years prior and

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reported that it had increased in size since then. She also complained of bleeding from the gums while brushing and bad breath. She also complained of spacing between upper front teeth which increased gradually to present state. There was no other relevant medical, dental, or family history.

On clinical examination, marginal and papillary and attached gingiva appeared red and enlarged in the maxillary and mandibular arches, which were more prominent in the labial and buccal aspect as compared to palatal and lingual aspect. Gingiva appeared to friable and soft with smooth and shiny surface [Figure 1]. Further assessment revealed pathologic migration between 11 and 21, bleeding on probing on all teeth, and generalized pockets.

A treatment plan consisted of initial periodontal therapy followed by a curettage procedure which was followed by surgical therapy to improve esthetics and function. The initial periodontal therapy comprising supragingival and subgingival scaling was performed quadrant wise. Oral hygiene instructions were given and the use of chlorhexidine mouthwash (hexidine) twice a day for 1 week was advised. At the next visit, the gingival enlargement showed a slight reduction in size. Full mouth intraoral periapical radiographs were taken and hematological investigations were carried out which included complete blood count, bleeding time, and clotting time.

IOPA showed generalized horizontal bone loss and blood investigations were noncontributory. At next visit, quadrant wise curettage was performed. Oral hygiene instructions were reinforced and the patient was recalled after 15 days. At next visit, there was a considerable reduction in gingival enlargement, but the tissues appeared to be firm in consistency [Figure 2].

Sextant wise internal bevel gingivectomy was performed. Thinning of the flap was done with initial incision. The flap was reflected with periosteal elevator. Complete debridement was done. The flap was sutured back and periodontal pack was placed. Antibiotics and analgesics were prescribed. The excised tissue was sent for the histopathological examination.

Microscopic examination revealed hyperparakeratinized stratified squamous epithelium. The underlying dense fibrous connective tissue stroma showed severe chronic inflammatory cell infiltrate consisting of lymphocytes and plasma cells and a moderate number of endothelial-lined blood vessels suggestive of chronic inflammatory fibrous hyperplasia.^[6] A histopathological diagnosis suggestive of inflammatory fibrous hyperplasia was given.



Figure 1: Pre-operative



Figure 2: Post-curettage



Figure 3: Post surgery

1 month later, the patient reported back to the clinic. Intraoral examination revealed that the surgical site had healed satisfactorily [Figure 3]. Oral hygiene instructions were reinforced. The patient was also counseled regarding

the importance of follow-up and maintenance with special emphasis on motivation. The patient was followed next 6 months at an interval of 1 month.

DISCUSSION

Chronic inflammatory changes are common cause of gingival enlargement. CIGE is caused by prolonged exposure to dental plaque.

Factors that favor plaque accumulation and retention include poor oral hygiene, abnormal relationships of adjacent/opposing teeth, lack of tooth function, improper restorations, orthodontic therapy, and habits. Treatment of gingival enlargement is based on an understanding of the cause of the enlargement and the underlying pathologic changes.

Here, we report a case of CIGE. These enlargements are often associated with a long-standing bacterial plaque accumulation. Regular professional oral prophylaxis and good patient compliance are required in the management of such cases.

Enlargement resulting from inflammation alone can be treated successfully with local procedures and fastidious oral hygiene prevents recurrence. CIGE, which is soft and discolored and is caused principally by edema and cellular infiltration is treated by scaling and curettage procedures provided the size does not interfere in complete removal of deposits.

Chronic inflammatory enlargement which includes a significant fibrotic component surgical removal is the treatment of choice. Two techniques - gingivectomy and flap operation.

Recurrence after treatment is a most common problem. Recurrence of CIGE: (a) After treatment immediately - incomplete removal of irritants, (b) after

healing - inadequate plaque control by the patient most common cause.

One of the most important determinants of treatment outcomes is patient compliance. The willingness to perform adequate oral hygiene measures and receive timely periodic recalls and treatment is essential for a successful outcome.

CONCLUSION

CIGE in our case was due to poor oral hygiene as there was more of inflammatory component there was drastic reduction in enlargement after SRP and curettage, and the residual was corrected by internal bevel gingivectomy surgery.

Thus, understanding cause and pathogenesis and planning treatment based on it is important.^[7]

This report helps to highlight the importance of patient motivation and patient compliance in treatment planning. Oral hygiene education supplemented with positive motivation should be started at the initial stages of the treatment strategy to obtain predictable outcomes.

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Diagnostic Dilemma and Challenges in Management in a Case of Immune Thrombocytopenic Purpura in Pregnancy and Review of Literature

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Abstract

Thrombocytopenia is encountered in as many as 10% pregnancies, and the causes of thrombocytopenia in pregnancy are manifold. Failure to identify the correct cause can lead to unnecessary platelet transfusions in certain conditions while it (thrombocytopenia) could be corrected by appropriate drug therapy. Furthermore, consideration has to be given to the effect of drug therapy on the fetus. Here, we present a case where a pregnant patient of immune thrombocytopenic purpura showed no improvement in platelet count despite having received multiple platelet transfusions and intravenous methylprednisolone but in the end, responded to intravenous immunoglobulin.

Key words: Immune thrombocytopenic purpura, Intravenous immunoglobulin, Methylprednisolone, Pregnancy, Transfusion

INTRODUCTION

Incidence of thrombocytopenia in pregnancy is 8–10%.^[1] The causes of thrombocytopenia in pregnancy are manifold; some are seen to be associated only with pregnancy, whereas others occur in non-pregnant patients as well. Management options become fewer during pregnancy as many drugs can prove to be toxic to the fetus. Immune thrombocytopenic purpura (ITP) is an autoimmune disorder in which platelets are destroyed due to the binding of antiplatelet antibodies. It is one of the most common autoimmune disorders seen nowadays. Although it can present at any age, it has a predilection for young women.^[2] We report a pregnant patient with ITP who posed a therapeutic challenge.

CASE DESCRIPTION AND RESULT

A 28-year-old woman, G₃P₂₀₀₂, was admitted to our department at 36 weeks gestation with complaints of pain in abdomen and vaginal bleeding for 1 day. Her medical history was unremarkable, with no previous history of bleeding from any other site. Her blood pressure was 116/78 mmHg, and pulse rate was 88/min. She did not have pallor, icterus, or lymphadenopathy. Abdominal examination revealed that her fundal height was corresponding to the period of gestation, with a longitudinal lie and cephalic presentation and the fetal heart rate was 140 beats/min. Uterus was relaxed. Pelvic examination revealed no bleeding with the closed external os. Investigations revealed hemoglobin of 10 g/dL, white blood cell count of 7800/ μ L and platelet count of 20,000/ μ L. Her total bilirubin was 1.3 mg/dL with indirect bilirubin of 0.9 mg/dL. Renal function tests were normal. C-reactive protein level was 6 mg/L. Ultrasonography of the abdomen revealed mild hepatosplenomegaly along with single live fetus with the fundal placenta. Anti-nuclear antibody was negative. Urine examination was unremarkable. Peripheral smear examination showed

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moderate anisocytosis, occasional macrocytes, and normocytic normochromic red cells with severely reduced platelets. Dengue serology was negative and prothrombin time and activated partial thromboplastin time were normal. Human immunodeficiency virus, hepatitis B surface antigen and anti-hepatitis C were negative. Blood culture showed no growth. The patient was transfused 24 units random donor platelets in 3 days, but her platelet count kept on decreasing, reaching a nadir of 10,000/ μ L. Again, she was transfused 16 units of random donor platelets. Bone marrow aspiration was done which showed the normal maturation of myeloid and erythroid series with megakaryocytes. Diagnosis of immune thrombocytopenia was made. Again, her platelet count dropped down to 12,000/ μ L. Intravenous methylprednisolone therapy was started. Meanwhile, she went into labor. 12 unit random donor platelets were transfused during the intrapartum phase. She delivered a healthy baby weighing 2.5 kg. She had atonic postpartum hemorrhage which was managed by Bakri balloon intrauterine insertion and transfusion of 14 more random donor platelets along with 2 units of packed red cells. Due to the failure of rise in platelet counts, intravenous immunoglobulin (IVIG) was started, after which her platelet count increased to 44,000/ μ L. During the course of treatment, she received total 50 units of random platelets. The baby's platelet count was 2.01 lac/ μ L. Mother and baby were discharged in good condition on day 16 postpartum.

DISCUSSION

The incidence of ITP in pregnancy is estimated at 0.1–1/1000.^[3] Primary ITP is a diagnosis of exclusion. It has to be differentiated from both non-immune causes of thrombocytopenia and secondary immune thrombocytopenia. Accurate diagnosis is essential for appropriate treatment. Immune thrombocytopenia can be secondary to an autoimmune condition, a lymphoproliferative disease, a chronic infection or medication.^[4] Although rare as compared to gestational thrombocytopenia, ITP is the most common cause of isolated thrombocytopenia in the first and early second trimesters of pregnancy.^[5]

The aim of treating ITP in pregnancy is to prevent bleeding. Thus, treatment is, generally, not required in patients who are not bleeding and with platelet counts >20,000–30,000/ μ L. Epidural anesthesia in a thrombocytopenic patient increases the risk of epidural hematoma formation. Therefore, those patients who wish to receive epidural anesthesia, require higher platelet counts.^[6] A platelet count of at least 75×10^9 /L is, generally, recommended to allow administration of epidural anesthesia. Some believe that a

platelet count of at least 50×10^9 /L is adequate to allow for cesarean section.^[7]

Corticosteroids are the first-line of therapy for ITP even in pregnancy. However, corticosteroids can lead to diabetes and hypertension in pregnancy. Some reports link use of corticosteroids in the first trimester with congenital anomalies, such as orofacial clefts. For these reasons, the use of corticosteroids should be adjusted to the minimal effective dose in pregnancy. Others have argued that due to the toxicity of corticosteroids, IVIG should be considered the first-line of therapy for ITP in pregnancy. Thus, the therapy should be decided keeping the various factors in mind such as the gestational age when the therapy is required, the expected duration of therapy, and specific characteristics of the patient.^[6]

For patients who do not respond to corticosteroids or IVIG as monotherapy, combinations of these therapies should be given.^[7] If this fails, laparoscopic splenectomy may be safely performed during the second trimester of pregnancy. The rationale behind this is that surgery earlier in pregnancy may lead to premature labor, and later in pregnancy splenectomy may be technically difficult due to obstruction of the surgical field by the gravid uterus.^[6]

For refractory ITP in pregnancy, very few therapeutic agents are available. Most cytotoxic agents such as azathioprine and cyclosporine A are teratogenic but have been used safely in pregnant patients with neoplasia and renal transplants. There is very little data available about the safety of use of thrombopoietic agents such as romiplostim and eltrombopag in pregnancy. Rituximab causes a delay in neonatal B-lymphocyte maturation but does not lead to any significant clinical consequences and is thus used in treating ITP in pregnancy.^[8]

Antiplatelet antibodies can cross the placenta and cause destruction of fetal platelets. The development of fetal thrombocytopenia cannot be predicted and has no consistent correlation with the degree of maternal thrombocytopenia or any other parameters. 15% of babies of mothers with ITP develop thrombocytopenia with platelet count <100,000/ μ L. 10.1% of babies have platelet count below 50,000/ μ L, and only 4.2% babies develop platelet count <20,000/ μ L.^[9] Neonates with thrombocytopenia may have intracranial hemorrhage during vaginal delivery which can prove to be fatal. Previously, all patients of ITP used to undergo cesarean section due to this concern.^[7] However, the results of several studies have demonstrated that the risk of fetal intracranial hemorrhage in the offspring of mothers with ITP is only between 0% and 1.5%^[9] and that there is no evidence this risk is increased by vaginal delivery.^[10] These studies have led to the establishment of

current guidelines, which suggest that the mode of delivery in pregnant patients with ITP should be dictated only by maternal indication. However, the neonatal platelet count should still be determined for the next 5 days, because the nadir of neonatal platelet count may not develop until several days after delivery. All neonates with platelet counts $<50,000/\mu\text{L}$ should undergo transcranial ultrasound to rule out intracranial hemorrhage.^[7]

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Cystic Lymphangioma of the Colon: Case Report and Literature Review

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Abstract

An 18-year-old female presented with a history of pain in the abdomen with abdominal distension, vomiting, and fever for 2 weeks. Diagnostic imaging showed a multiseptate thin-walled cystic lesion in right lumbar region extending from subhepatic region superiorly to the urinary bladder inferiorly. On exploration, a huge transilluminant multiseptate cystic lesion was present arising from the serosal surface of ascending and transverse colon extending into the lesser sac with attachment to the greater curvature of stomach antrum and encroaching on the head of the pancreas. Histopathology showed multiple dilated lymphatic spaces suggestive of lymphangioma of colon. Lymphangiomas are rare asymptomatic lesion with low threshold for malignancy discovered accidentally with increasing use of colonoscopy. Clinical manifestations are highly variable. Diagnosis is difficult. Hence, it requires careful colonoscopy/endoscopic ultrasonography for proper evaluation. Complete surgical excision is the gold standard treatment to prevent recurrence as they have the potential to grow and can lead to serious complications.

Key words: Abdomen, Abdominal cystic lymphangioma, Case report, Colon, Histopathology, Surgical outcome

INTRODUCTION

Lymphangiomas are rare benign congenital malformations of the lymphatic vasculature with a rate of hospitalization of 1/250,000–1/20,000.^[1] Lymphangiomas occur mostly in the head, neck, and axilla region in children with 90% of these becoming evident in few years after birth. However, occurrence in the abdominal or mediastinal cavity is extremely rare, particularly in adults, constituting approximately 5% of all lymphangiomas [Figure 1].^[1,2]

The etiology is unclear, but probable causes for intestinal lymphangiomas could be intramural lymphatic obstruction, disturbed endothelial permeability, inflammation, congenital absence of lymphatics, and aging of the bowel wall.^[3] Patients may present with a variety of non-specific

symptoms such as abdominal distension, abdominal pain, constipation, loss of appetite, nausea, and vomiting.^[4] Its pre-operative diagnosis is important so as to occurrence of associated complications.

CASE REPORT

An 18-year-old female came to tertiary care hospital with the history of pain in the abdomen on the right side with abdominal distension, vomiting, and fever for 2 weeks. On per abdomen examination, right hypochondriac region was distended and tender. Reported weight loss was 15 pounds along with loss of appetite for the past 2 months. She had no history of fever, chills, hemoptysis, hematochezia, and change in bowel habit. There was no history of trauma and previous surgeries. No derangements were noted in general blood test, blood chemistry, or urinalysis. Ultrasonography (USG) was suggestive of gross free fluid in the abdomen seen with multiple thick septa within and abdominal lymphadenopathy. Computed tomography (CT) abdomen showed a $9.5 \times 15.9 \times 23.7$ cm sized multiseptated thin-walled cystic lesion with enhancing septa noted in the right lumbar region extending from subhepatic region superiorly to the urinary bladder inferiorly. The lesion was

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seen displacing the bowel loops, compressing the head of the pancreas, inferior vena cava, and right ureter leading to mild hydroureter and hydronephrosis. Anteriorly, it was seen scalloping posterior and inferior surface of liver and gallbladder. No solid component was noted. Decision was taken to carry out an exploratory laparotomy. On exploration, a huge transilluminant multiseptate cystic lesion was present arising from the serosal surface of ascending and transverse colon extending into the lesser sac with attachment to the greater curvature of stomach antrum and encroaching on the head of the pancreas [Figure 2].

Incomplete excision of the cyst leaving behind the posterior wall, which was encroaching over the head of pancreas along with the resection of the bowel, which was densely adhered to the cystic wall, was done for the patient [Figure 3].

Histopathology confirmed multiple multilocular cysts ranging from 1 to 10 cm on serosal aspects of ascending and transverse colon. Cysts contained seromucinous exudate. Intestinal mucosa was flattened at places. On microscopic examination, cysts on serosal wall showed multiple dilated spaces lined by flattened epithelium, underlying tissue showed lymphocytic infiltrate, and at places, lymphoid aggregates were seen suggestive of lymphangioma [Figure 4]. Post-operative course was uneventful. The patient is currently disease free.

1-year follow-up with USG showed no recurrence.

DISCUSSION

Lymphangiomas of the gastrointestinal (GI) tract are very rare, most of them arise in the mesentery, omentum, mesocolon, and retroperitoneum, and those arising in the wall of the intestine are considered to be even rarer and tend to be located in the right half of the colon.^[5] The above case highlights the rarity as well as the importance of cystic lymphangioma of colon occurring on the right side to be kept as an important differential when a surgeon encounters a cystic lesion per the abdomen or in pelvis. Intra-abdominal cystic lymphangioma can present as diagnostic challenge on imaging and can easily be confused with other cystic intra-abdominal lesions, ranging from pancreatic pseudocysts to abdominal tuberculosis, Hydatid disease, or malignancies such as mucinous carcinomatosis. Histologically, lymphangiomas could be capillary, cavernous lymphangiomas, or cystic hygroma. Rarely, a fourth subtype, the hemangio-lymphangioma also occurs.^[6] The most common lymphangioma type in the colon was found to be the cystic hygroma type as found in our case.

In the article on review of 279 cases of lymphangioma of colon by Matsuda *et al.*, the mean age of onset was 55.2 ± 14.1 years and the male-to-female ratio was 150:92 indicating a higher incidence in males. However, Goh *et al.* series demonstrated that abdominal lymphangiomas have a male preponderance and present more acutely in pediatric patients, whereas in adults, female patients predominate and the history is more chronic as present in our case.^[7] It commonly affects the transverse colon followed by the ascending colon, cecum, and descending colon.^[8] Although they less commonly involve the GI tract, the clinical presentations of GI lesions are myriad, ranging from asymptomatic adenoma-like polypoid lesions to large obstructing masses. Abdominal pain was the most frequent symptom, followed by bloody stool, constipation, and diarrhea. Weight loss seen in this patient is not a typical finding, but protein-losing enteropathy associated with a large tumor has been reported,^[9] which may have resulted in weight loss in our case as well. Complications include compression of surrounding structures, rupture, secondary infection, volvulus, intestinal obstruction, GI

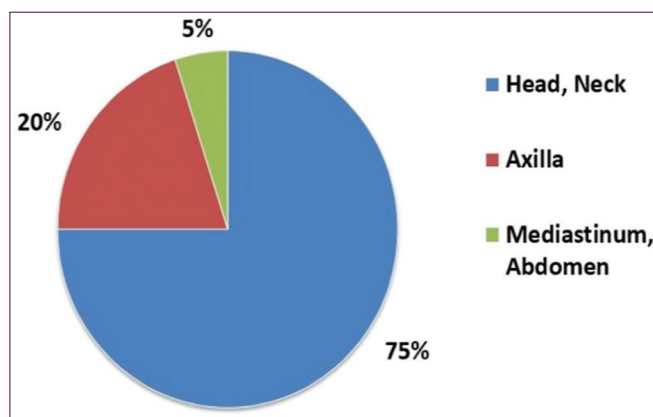


Figure 1: Distribution of lymphangiomas



Figure 2: Exploratory laparotomy showing a huge multiseptate cystic lesion

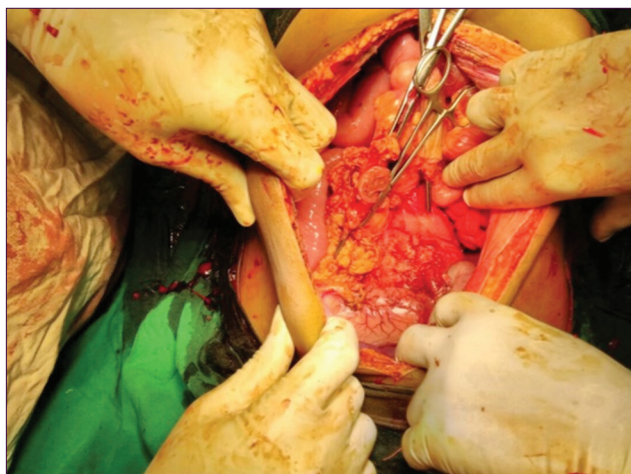


Figure 3: Excision of cystic lesion along with resection of terminal ileum up to right one-third of transverse colon

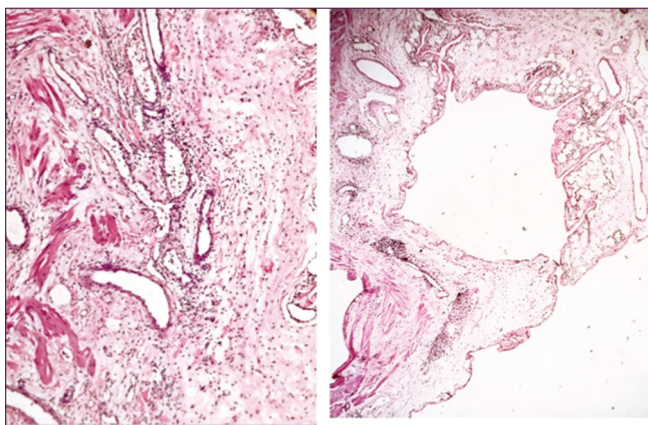


Figure 4: Photomicrograph depicting multiple dilated spaces lined by flattened epithelium with underlying lymphocytic infiltrate

bleeding, and protein losing enteropathy.^[10] The huge multiseptate cystic lesion was seen encroaching on the right ureter causing mild hydronephrosis. The accurate pre-operative diagnosis of intra-abdominal lymphangioma is uncommon, particularly in adult patients. It has been stated that diagnosis is possible on careful colonoscopy.^[8] On CT, these masses show densitometric characteristics of the fluid type, regular margins, and only a peripheral contrast enhancement. The demerit of CT imaging is that lesions <2 cm cannot be identified.^[11] Pre-operative biopsy is helpful to confirm the diagnosis. However, it has been stated that endoscopic biopsy can un-roof the thin wall of these cysts and lead to infection. The diagnosis of lymphangioma is further complicated by histologic overlap with lymphangiectasia of the GI mucosa.^[6] The use of endoscopic USG for definite diagnosis of cystic lymphangioma of colon has shown promising results, overcoming the need for resection for biopsy.^[12] Magnetic resonance imaging is the most useful pre-operative radiological tool for diagnosis and in surgical planning.^[13,14] Complete surgical excision remains the gold

standard treatment to prevent recurrence. Pedunculated or semi-pedunculated colonic lymphangioma of about 2 cm or smaller can be managed by polypectomy as reported by Yildiz *et al.* Other treatment options include de-roofing the lymphangioma lesion with cyst drainage and aspiration injection of sclerosant agents.^[10] However, these are not recommended due to the high recurrence rates.

Accurate anatomic localization and definition of the lesions are important in pre-operative planning because lymphangiomas have an insinuating nature that makes complete surgical excision difficult as in our case. Although these are rare lesions showing no malignancy, with many cases asymptomatic which were discovered accidentally due to increasing use of endoscopy, they may often lead to life-threatening conditions, such as infection, volvulus, obstruction, or bleeding into the lumen of a cyst that is usually very difficult to manage. They should be treated surgically as they have the potential to grow resulting in recurrence.

In our case, large size of the lesion, critical location, extensive spread within the peritoneum, compression of the surrounding structures, and possibility of malignant nature of the lesion guided our choice for surgical resection.

Pre-operative diagnosis of abdominal cystic lymphangioma is usually difficult due to its variable misleading clinical presentations, rarity of the disease, and its resemblance to many other intra-abdominal cysts, and hence, anterior cruciate ligament should be kept in the list of differentials when the patient is encountered with intra-abdomen multiseptate cystic lesion.

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Methemoglobinemia in a Child with Glucose-6-phosphate Dehydrogenase Deficiency - A Case Report

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Abstract

Methemoglobin is the reduced form of hemoglobin which is normally found in blood in levels <1%. Methemoglobinemia (MHb) is a disorder which is characterized by methemoglobin levels >1% in blood. Spontaneous formation of methemoglobin is normally counteracted by protective enzyme systems, for example, nicotinamide adenine dinucleotide phosphate methemoglobin reductase. A 2-year-old male child presented with lethargy, oliguria, hemoglobinuria, and icterus. Child had been treated with ofloxacin for urinary tract infection 2 days before presentation. Child had low saturation even with high flow oxygen. Hence, a clinical diagnosis of methemoglobinemia was made. On evaluation, the child was found to have severe hemolysis with low glucose-6-phosphate dehydrogenase (G6PD) activity. Methylene blue, the treatment of choice for MHb, is contraindicated in the presence of G6PD deficiency. Child improved with packed cell transfusion and supplemental oxygen. This case illustrates the potential for severe hemolysis with the use of methylene blue in a case of MHb presenting with G6PD deficiency. Hence, it is advisable to check G6PD activity before administering methylene blue.

Key words: Cyanosis, Glucose-6-phosphate dehydrogenase deficiency, Methemoglobinemia, Methylene blue

INTRODUCTION

Methemoglobinemia (MHb) may arise from a variety of etiologies including genetic, idiopathic, and toxicological sources.^[1] Symptoms may vary from mild headache to coma/death and may not correlate with measured MHb concentrations. The diagnosis may be complicated by the effect of MHb on arterial blood gas and pulse oximeter oxygen saturation results. Treatment with methylene blue can be complicated by the presence of underlying enzyme deficiencies including glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficiency is the most common red cell enzymopathy in humans and has an X-linked

inheritance. It has been reported from India more than 30 years ago and the prevalence varies from 0 to 27% in different caste, ethnic and linguistic groups.^[2] The major clinical manifestations are drug-induced hemolytic anemia, neonatal jaundice, and chronic non-spherocytic hemolytic anemia.^[3]

Methemoglobin which is normally produced in blood is neutralized by nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase. Methylene blue provides artificial electron acceptor for NADPH methemoglobin reductase. In a suspected or proven case of G6PD deficiency, methylene blue is contraindicated because G6PD is the key enzyme for production of NADPH through pentose phosphate pathway. G6PD-deficient individuals generate insufficient NADPH to efficiently reduce methylene blue to leukomethylene blue, which is necessary for the activation of NADPH-dependent methemoglobin reductase system^[1].

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CASE REPORT

A 2-year-old male child second order born out of non-consanguineous marriage presented to emergency with complaints of letharginess for the past 1 week and oliguria and hematuria for past 2 days. 2 days earlier to presentation, the child was prescribed ofloxacin for urinary tract infection, following which pallor and yellowish discoloration of eyes were noted by parents. No significant past medical history or family history noted.

Clinical examination revealed severe pallor and icterus with no cyanosis. Tachycardia, HR-184/min with SpO₂ of 60%, was observed (without O₂ therapy). The child was initially started on high flow oxygen support. In view of persistent desaturation, the child was intubated and ventilated. Saturation did not pick up even after mechanical ventilatory support. Hence, ABG was done which showed pH of 7.24, pCO₂ = 36.0 mm Hg, pO₂ = 216 mm Hg, and O₂ saturation = 99.6%. The presence of chocolate brown discoloration of blood along with the saturation gap (SpO₂ -60% and ABG SaO₂ -99% and pO₂-216 mm of Hg) was suggestive of MHb. Methemoglobin (metHb) levels by spectrophotometry were 32.6% (normal- 0–2%).

Hematologic examination showed severe anemia with hemolytic picture. Bedside analysis of whole blood in a test tube showed chocolate brown color. Most notable finding on peripheral smear was the presence of blister cell, which leads to suspicion of G6PD enzyme deficiency. Supravital staining showed Heinz bodies. Sickle test and indirect and direct coombs test were negative, hemoglobin electrophoresis showed normal pattern and normal osmotic fragility test. Qualitative analysis showed low G6PD activity (HEMOPAK-visual dye decolorization method).

In a male child with a background history of ofloxacin intake, hemoglobinuria, indirect hyperbilirubinemia, high lactate dehydrogenase, high reticulocyte count, and blister cells on peripheral smear with low G6PD enzyme activity, the diagnosis of G6PD hemolytic anemia was made.

Although IV methylene blue is treatment of choice, it is contraindicated in the presence of G6PD deficiency, the other modalities of therapy were blood transfusion or exchange transfusion.^[4] Hence, packed red blood cell transfusion was done and the child's saturation improved along with improving general condition. The child was discharged with a list of drugs to be avoided, which may induce hemolysis.

On follow-up 3 months later, his Hb was 11.7 g% and metHb level was 8.6%, and he was clinically well.

DISCUSSION

G6PD deficiency anemia is an X-linked recessive hereditary disease. It is the most common human enzyme defect, being present in more than 400 million people worldwide.^[5] G6PD is a metabolic enzyme involved in the pentose phosphate pathway, especially important in red blood cell metabolism. Individuals with the disease may exhibit non-immune hemolytic anemia in response to a number of causes, most commonly infection or exposure to certain medications or chemicals (oxidants). G6PD is the rate-limiting enzyme of this metabolic pathway that supplies reducing energy to cells by maintaining the level of the coenzyme NADPH. The NADPH in turn maintains the supply of reduced glutathione in the cells that is used to mop up free radicals that cause oxidative damage. The G6PD/NADPH pathway is the only source of reduced glutathione in red blood cells [Figure 1]. The role of red cells as oxygen carriers puts them at a substantial risk of damage from oxidizing free radicals except for the protective effect of G6PD/NADPH/glutathione. People with G6PD deficiency are therefore at risk for hemolytic anemia in states of oxidative stress.

MHb is a disorder characterized by the presence of >1% metHb in the blood.^[6] metHb, an oxidized form of hemoglobin (contains Fe³⁺ in place of Fe²⁺ in Hb),^[4] has slightly greater affinity for oxygen due to its chemical structure, thus shifting the oxygen dissociation curve to the left, resulting in decreased release of oxygen in tissues. Spontaneous formation of metHb is normally counteracted by protective enzyme systems, for example, NADH metHb reductase (cytochrome-b5 reductase) (major pathway), NADPH metHb reductase (minor pathway),^[7] and to a lesser extent the ascorbic acid and glutathione enzyme systems [Figure 2]. MHb can be treated with supplemental oxygen and methylene blue, which acts by providing an artificial electron acceptor for NADPH metHb reductase.

However, known or suspected G6PD deficiency is a relative contraindication to the use of methylene. G6PD-deficient individuals generate insufficient NADPH to efficiently

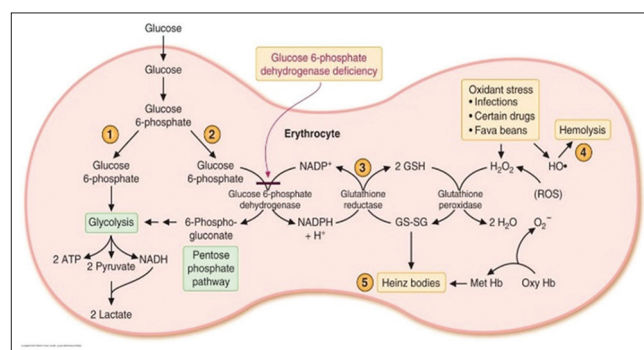


Figure 1: NADPH/ G6PD pathway

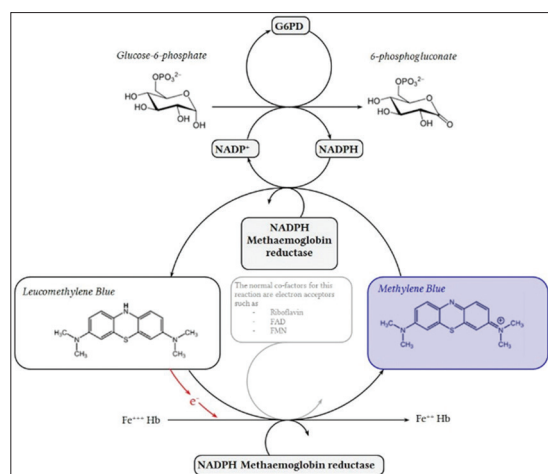


Figure 2: Methemoglobin reduction pathway

reduce methylene blue to leucomethylene blue, which is necessary for the activation of the NADPH-dependent methHb reductase system. G6PD-deficient individuals are also prone to methylene blue-induced hemolysis. Methylene blue may also add to oxidative hemolysis. Moreover, in the presence of hemolysis, high-dose methylene blue can itself initiate methHb formation.^[8,9]

TREATMENT OF METHEMOGLOBINEMIA

Hereditary methemoglobinemia is treated with ascorbic acid, 300 to 600 mg orally daily divided into 3 or 4 doses.^[10]

The first-line therapy for drug-induced methemoglobinemia is IV methylene blue (1–2 mg/kg). Treatment should be considered when the metHb is 30% in an asymptomatic patient and 20% in a symptomatic patient after exposure to oxidizing drugs.^[11] Exchange transfusion is reserved for patients in whom methylene blue therapy is ineffective.

CONCLUSION

Methylene blue (BLUE) cures cyanosis (BLUE) of MHB, but we should be cautious about the presence of accompanying G6PD deficiency or else, it can be potentially hazardous to the condition of patient causing excessive hemolysis, and sometimes, even leading to fatality. Therefore, in any patient presenting with MHB associated with severe hemolytic anemia, it is desirable to check G6PD activity before administering methylene blue.

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Primary Leiomyosarcoma of Liver: A Rare Clinical Presentation

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Abstract

Primary hepatic leiomyosarcoma are rare tumors with <30 cases reported in the English literature. Non-specific presentations and often diagnosis delayed until they reach a large size is the norm with therapy leading to an often dismal prognosis. A 67-year-old man presented complaining of abdominal pain and a palpable abdominal mass. Abdominal ultrasonography and abdominal computed tomography revealed a large tumor in the left lobe of the liver. Surgical exploration was undertaken, and an extended left hepatectomy with extension onto the dorsal part of segment 8 preserving the middle hepatic vein with partial resection of segment 6 was undertaken. The weight of the resected specimen was 1300 g of the left lobectomy specimen and 8 g of the segment 6 partial resection specimen. The pathology report confirmed the diagnosis of leiomyosarcoma. On immunohistochemistry, the tumor cells were positive for smooth muscle actin stain. The patient is on regular follow-up. We report the case of a resected primary hepatic leiomyosarcoma and emphasize the need for a global database for these rare tumors to promote a better and broader understanding of this less understood subject.

Key words: Hepatectomy, Primary hepatic leiomyosarcoma, Smooth muscle actin, Smooth muscle

INTRODUCTION

Primary hepatic leiomyosarcoma are rare tumors with <30 cases reported in the English literature. Primary hepatic mesenchymal tumors are rare tumors. Sarcomas constitute only 1–2% of all primary malignant tumors of the liver with the majority being either hepatocellular carcinoma or cholangiocarcinoma.^[1] Nearly, all primary sarcomas of the liver are angiosarcomas, epithelioid hemangioendotheliomas, or undifferentiated embryonal sarcoma constituting nearly 70% with leiomyosarcoma being a modest 8–10% of all sarcomas.^[2] Most hepatic leiomyosarcoma are metastatic from other sites of leiomyosarcoma including the gastrointestinal tract, uterus, retroperitoneum, and lung.^[3] Hence, exclusion of metastatic leiomyosarcoma in the liver is an essential event in diagnosing a primary lesion. Leiomyosarcoma

are malignant neoplasms that arise from smooth muscle. Hepatic leiomyosarcoma may arise from intrahepatic vascular structures, bile ducts, or ligamentum teres. Tumors arising from the hepatic veins may develop Budd–Chiari syndrome and have a worse prognosis with tumors arising from the ligamentum teres having a better prognosis due to its increased respectability.^[4] No underlying etiologic factors are known, although thorotrast, acquired immunodeficiency syndrome, Epstein–Barr virus,^[5] prior history of immunosuppression in the form of post renal transplant^[6] and previously treated Hodgkin's lymphoma,^[7] and the rare association with hepatitis C virus liver cirrhosis which was not directly implicated,^[8] have all been described in the literature. The median age of diagnosis is 58 years with sporadic occurrence of the tumor in the younger age group.^[9]

Primary hepatic leiomyosarcoma present a clinical dilemma: Not only are they unusual and rare with <50 cases described in the literature but also they are often asymptomatic until they become large, and even then they produce nonspecific symptoms. Patients may be afflicted with a wide spectrum of symptoms such as abdominal pain, weight loss, anorexia, vomiting, jaundice, and rarely acute intra-abdominal bleeding secondary to

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tumor rupture.^[10] Tenderness of the upper abdomen, hepatomegaly, and mass may be the main signs. Some patients may have abnormal liver function tests, but essentially the α -fetoprotein and other serological markers are normal. The non-specific nature of symptoms and the lack of serological markers make the diagnosis of hepatic leiomyosarcoma challenging.

Non-specific presentations and diagnosis often delayed until they reach a large size is the norm with therapy leading to an often dismal prognosis. The rarity of these tumors has precluded our understanding of them, and therefore, the standard of care has not been well defined. We herein report a case of primary hepatic leiomyosarcoma, which was treated surgically and reviews the English literature with an emphasis on management outcomes.

CASE REPORT

A 67-year-old man was presented with chief complaining of pain in the abdomen and a palpable abdominal mass since 6 years. He had no history of liver disease or alcohol abuse. His past medical history and family history were unremarkable. Physical examination revealed marked hepatomegaly extending 6 cm below the right costal margin. Laboratory analysis revealed normal liver function tests including serum albumin level and prothrombin time. White blood cell count, platelet, α -fetoprotein, CA 19-9, and carcinoembryonic antigen were normal. Antibody to hepatitis C virus and hepatitis B surface antigen were negative. Impedance cardiogram clearance at 15 min was 10%. Abdominal ultrasonography revealed a hypoechoic mass, measuring 14 cm in diameter, in the left lobe of the liver. Abdominal computed tomography (CT) showed a hypodense lesion on plain scans, heterogeneous enhancing lesion on arterial phase and delayed washout on portal venous phase occupying segments 2, 3, 4, and 8 [Figure 1]. CT arterio-portalography revealed a hypodense lesion. Selective angiography of the celiac trunk and superior mesenteric artery showed a faint tumor stain in the left lobe of the liver and stenosis of the left portal vein. Chest CT, upper gastrointestinal and lower gastrointestinal endoscopy were within normal limits.

Pre-operative diagnosis was unconfirmed, written informed consent was obtained, and surgical exploration was undertaken. A huge tumor, measured 17 cm \times 7 cm \times 14 cm, occupying almost the whole left lobe of the liver was found [Figure 2]. Intraoperative ultrasound revealed that the tumor also extended into the dorsal aspect of segment 8 and another small hypoechoic lesion in segment 6. An extended left hepatectomy with

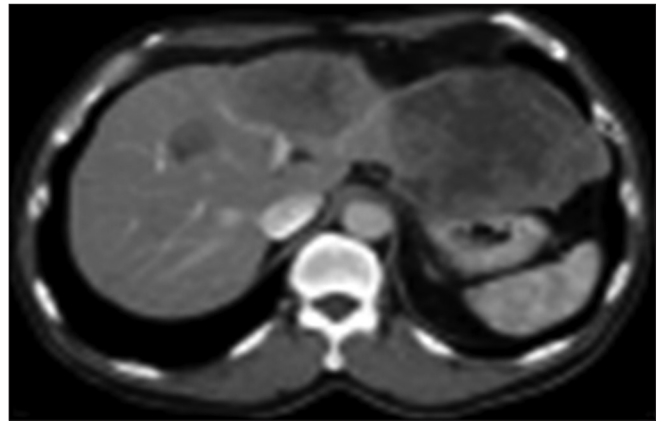


Figure 1: Computed tomography scan showing a large heterogeneously enhancing tumor in the left lobe of the liver

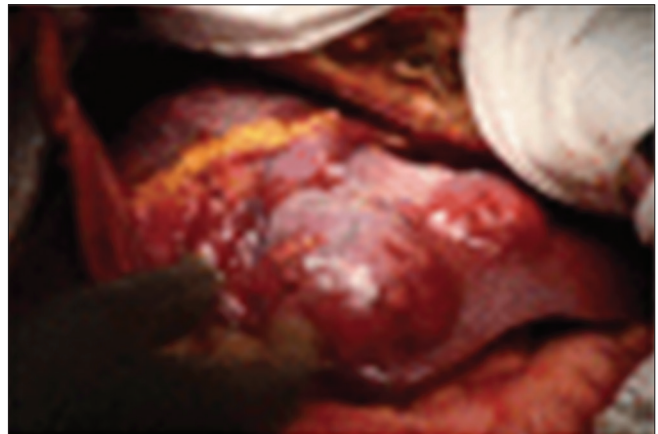


Figure 2: Intraoperative photo showing the large left lobe tumor

extension onto the dorsal part of segment 8 preserving the middle hepatic vein with partial resection of segment 6 was undertaken. The pringle time was 60 min, and the operative blood loss was 520 mL. The weight of the resected specimen was 1300 g of the left lobectomy specimen and 8 g for the segment 6 partial resection specimen. Careful inspection of the abdominal and pelvic contents did not reveal any other mass or lesions. Grossly, the tumor was lobulated, well encapsulated, and prominent in fibrotic bands. The pathology report confirmed the diagnosis of leiomyosarcoma. Light microscopy demonstrated the typical pattern of growth of leiomyosarcoma, predominantly fascicular, with tumor bundles intersecting each other at wide angles and merging of tumor cells with blood vessel walls, an important diagnostic clue [Figure 3]. The individual cells had elongated, blunted nuclei and acidophilic fibrillary cytoplasm. Numerous mitoses were present. On immunohistochemistry, the tumor cells were positive for the smooth muscle actin (SMA) stain [Figure 4]. The patient is on regular follow-up and referred to an oncologist for further care.

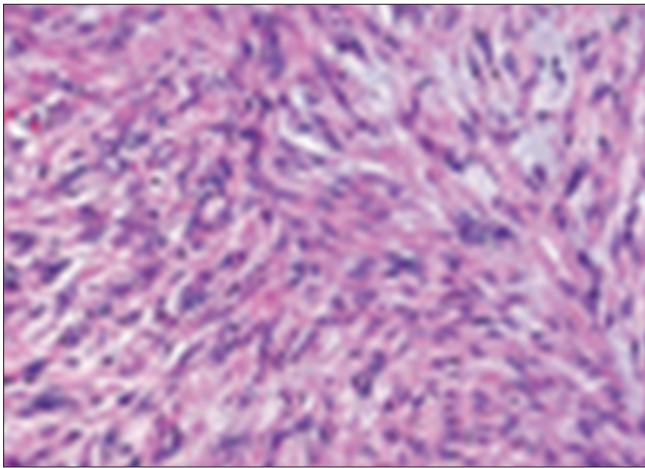


Figure 3: Histomicrograph showing fascicular growth pattern with tumor bundles intersecting each other at wide angles and merging of tumor cells with blood vessel walls

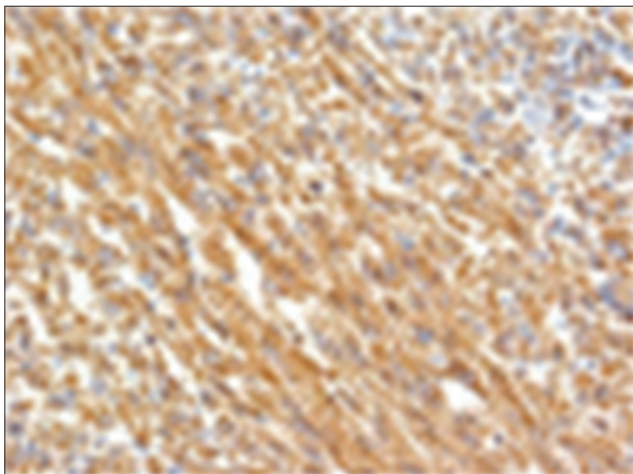


Figure 4: Tumor cells are positive for smooth muscle actin by immunohistochemical stain

DISCUSSION

Primary hepatic mesenchymal tumors are rare tumors. Sarcomas constitute only 1–2% of all primary malignant tumors of the liver with the majority being either hepatocellular carcinoma or cholangiocarcinoma.^[1] Nearly, all primary sarcomas of the liver are angiosarcomas, epithelioid hemangioendotheliomas, or undifferentiated embryonal sarcoma constituting nearly 70% with leiomyosarcoma being a modest 8–10% of all sarcomas.^[2] Most hepatic leiomyosarcoma are metastatic from other sites of leiomyosarcoma including the gastrointestinal tract, uterus, retroperitoneum, and lung.^[3] Hence, exclusion of metastatic leiomyosarcoma in the liver is an essential event in diagnosing a primary lesion.

Histological pre-operative diagnosis of hepatic leiomyosarcoma is controversial as with other liver tumors, as most of the tumors are treated presuming to

be hepatocellular carcinoma with its inherent propensity for needle track seeding. Histological examination reveals tumor composed of intersecting bundles of spindle-shaped cells. Immunohistochemistry is positive for desmin, vimentin, and SMA but negative for keratin, S-100 protein, and neuron-specific enolase and FNA biopsy will allow for specific FNA diagnosis in most cases.^[11]

CT findings of primary hepatic leiomyosarcoma have been described as a large, well-defined, heterogeneous-hypodense mass with internal and peripheral enhancement or cystic mass with an enhancing thick wall. Cystic variant of leiomyosarcoma may be misdiagnosed as hydatid cyst or liver abscess.^[12] On magnetic resonance imaging, the tumor displays homogenous or heterogeneous hypointensity on T1-weighted images and hyperintensity on T2-weighted images with the occasional observation of encapsulation.^[13] Due to the rarity of primary hepatic sarcomas in general, and primary hepatic leiomyosarcoma in particular, the standard of care has not been defined. However, surgical resection followed by adjuvant chemotherapy is being widely followed in an empirical manner.^[2]

Resection surgery forms the cornerstone of successful management of primary hepatic leiomyosarcoma with the intention of R0 resection. All patients with potentially resectable tumors with adequate remnant liver volume should undergo surgical exploration and liver resection. The surgical outcome for R0 resection extrapolated from 2 large series was 67% disease-specific survival at 5 years with 0% 3 years survival for patients who underwent R1+ resection.^[2,14] Age was another major prognostic factor with patients <50 years achieving better survival. The role of adjuvant chemotherapy/chemoradiotherapy is not well defined. Adjuvant chemotherapy in the form of doxorubicin and ifosfamide seems to slow the course of the disease and may prolong survival in R1 resections, but the evidence is lacking as the data are extrapolated from the unresectable or metastatic leiomyosarcoma setting.^[15]

CONCLUSION

Primary hepatic leiomyosarcoma are a rare tumor with often delayed diagnosis and poor prognosis. This case highlights the need for swift early diagnosis with aggressive management. This also raises the question of the possibility of an unidentified factor, making apparently healthy patients susceptible to this malady.

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Surgical Pleth Index: Do we need to know more

Sir,

The primary responsibility of anesthesiologist is to protect the patients from the surgical stress of surgery with balanced anesthesia, i.e. triad of hypnosis, analgesia, and muscle relaxation. In modern medicine, with short-acting anesthetic drugs and increase in high-risk patients for surgery, it becomes necessary to maintain anesthesia with judicious administration of anesthetic drugs using advanced monitors to avoid overdose or inadequate effect.

Electroencephalogram variable based monitors such as bispectral index and entropy enables anesthesiologists to maintain adequate depth by adjusting dose of hypnotic agents, and reducing probability of intraoperative awareness as well as hypnotic overdose. Neuromuscular monitors are an integral part of monitoring to precisely adapt muscle relaxation as well as to test for the residual neuromuscular blockade.

Similarly, optimal analgesic titration is desirable as intraoperative stress resulting from inadequate analgesia can influence the post-operative outcome. However, no gold standard exists for assessment of nociception/antinociception, and the administration of analgesics in a clinical setting is still based on anesthesiologist's experience and judged on clinical signs such as patient movement, changes in vital parameters, lacrimation, and pupillary reaction.

The newly developed surgical pleth index (SPI) monitors propose to quantify the intraoperative stress level or nociception during general anesthesia. It is based on two variables pulse photoplethysmographic amplitude (PPGA) and heart rate data from pulse oximetry. The SPI ranges from 0 to 100, high value being associated with high-stress level. The optimal range is not yet determined, but SPI of 50 is supposed to reflect mean stress level with balanced nociceptive and anti-nociceptive factors [Figure 1].

Several studies support the correlation of SPI in detecting noxious stimuli and its clinical effectiveness on titration of analgesic requirement intraoperatively.

Struys^[1] and Gruenewald *et al.*^[2] proved that SPI appeared better measure of nociception-anti-nociception balance during propofol-remifentanyl anesthesia to standardized noxious stimulus than SE, RE, or PPGA. Huiku *et al.*^[3] estimated the surgical stress on patients undergoing gynecological or breast surgery determining SPI high when noxious stimulation was high and remifentanyl concentration inadequate; while SPI low with high remifentanyl concentration and stimulation low.

Chen *et al.*^[4] studied correlation of SPI with stress hormones during propofol-remifentanyl anesthesia and found moderate correlation of SPI to the stress hormones (ACTH, cortisol, epinephrine, and norepinephrine) during general anesthesia, but no correlation during consciousness. Ledowski *et al.*^[5] found that SPI did not accurately reflect the time course of stress hormone changes, it significantly changed with increasing depth of analgesia after bolus doses of fentanyl.

Many studies compared the intraoperative administration of analgesics guided by SPI versus by conventional methods, its impact on hemodynamic stability, recovery, and side effects. Chen *et al.*^[6] reported SPI-guided analgesia resulted in lower remifentanyl consumption, more stable hemodynamics, lower adverse events, and comparable recovery times compared with standard analgesia practice. Bergmann *et al.*^[7] used remifentanyl for outpatient orthopedic operations similarly with faster recovery and no difference in post-operative pain intensity. Study by Won *et al.*^[8] using SPI guided IV oxycodone bolus resulted in reduced oxycodone consumption during surgery and shortened extubation time without negative impact on pain scores and post-operative recovery during sevoflurane anesthesia in patients undergoing thyroidectomy, suggesting usefulness of SPI for analgesic titration during sevoflurane anesthesia, while earlier studies were performed using TIVA.

SPI reflects a change of the autonomic nervous system balance in the body. The increase of the sympathetic activity increases SPI. Potentially, any medication or therapy that affects the sympathetic nervous system balance is reflected in the value of the SPI. However, it does not necessarily change the reactivity of SPI to analgesic

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Figure 1: Surgical pleth index(SPI) trends

medication or surgical stimulation. In fact, the reactivity is usually maintained, but the interpretation of the absolute SPI level is confounded.

Apart from medications, there are other factors demonstrated to confound SPI such as intravascular volume status, pacemaker action, arrhythmias, and posture changes.^[9] SPI varied significantly in healthy volunteers with unimpaired autonomic regulation during trendelenburg and anti-trendelenburg tilt-table. However, in post-operative setting, it demonstrates only moderate sensitivity and specificity in identifying moderate to severe pain.

In pediatric age group, clinical usefulness of the SPI is doubtful as autonomic nervous system is not fully developed in children, and the variables used for SPI are based on adult data which cannot be applicable to children.^[10]

To conclude, with the large armamentarium available today in anesthetists' kit and overlooking marketing strategies of equipment companies, SPI seems to be promising one-stop monitor for balanced anesthesia but needs more data in a variety of surgeries under different conditions to support its supremacy.

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