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Evaluation of Effectiveness and Safety of Oral Bepotastine in the Management of Chronic Urticaria

Dhoot Dhiraj, Mahajan Harshal, Deshmukh Gaurav, Barkate Hanmant

Medical Services, Glenmark Pharmaceuticals Ltd., Mumbai, Maharashtra, India

Abstract

Introduction: Nearly 20% of the total population suffer from urticaria for a minimum of one episode during the entire lifetime. Second-generation antihistamines are preferred in majority cases of urticaria.

Objective: The present survey was undertaken in pursuit of analyzing the effectiveness and safety of bepotastine in the treatment of chronic urticaria (CU).

Materials and Methods: This was a retrospective questionnaire-based survey. Doctors were identified from four directional zones of the country, and each was given prevalidated questionnaire booklets. Clinical response was evaluated by urticaria activity score (UAS) at baseline (D0), day 14 (D14), and day 28 (D28). All the adverse effects were monitored for severity. Specifically, sedation was closely monitored for its occurrence and severity.

Results: A total of 50 doctors completed the survey involving 226 patients. The mean UAS score at D0/baseline was 3.47 which reduced to 1.71 at D14 and 0.73 at D28. 78 patients were having UAS score in the range of 1–2, 89 patients in 3–4, and 59 patients in the range of 5–6 at D0. 59 patients were encountered in Grade 5–6 at D0, which reduced to 45 patients at D14 and 29 patients at D28, while 89 patients in score range 3–4 at D0 reduced to 68 at D14 and 38 at D28. Sedation was reported in only 15 patients (6.6%) that too majority had mild sedation, rated in sedation scale range of 0–5.

Conclusion: The present survey indicates that bepotastine is efficacious and safe in the management of CU.

Key words: Bepotastine, Chronic Urticaria, Retrospective survey, Urticaria activity score

INTRODUCTION

Nearly one-fifth of the total population suffer from urticaria for a minimum of one episode during the entire lifetime. The highest number of sufferers of urticaria are encountered in young adult age group.^[1] Clinically, urticaria manifests in the form of wheals/hives and angioedema. There are three emblematic features of wheals in the form of reflex redness surrounding the area of swelling, connotation with itching, and evanescent in nature.^[2] Depending on the periodicity of lesions, urticaria can be

acute or chronic. If urticaria is <6 weeks, it is labelled as acute urticaria, while >6 weeks it is known as chronic urticaria (CU). Prevalence of CU shows sex variations with predilection toward female sex and male: female ratio of prevalence of 1:2.

Despite exhaustive laboratory investigations, half of the cases of CU remain idiopathic; although a host of factors have been identified to trigger the development of CU, like certain foods and food additives, drugs, etc. The pathogenesis of CU is mainly driven by mast cells. The activated mast cells release histamine and other inflammatory cytokines which lead to chemotaxis, vasodilation, and exudation of plasma into surrounding tissues.^[3]

CU is known to impair the quality of life (QOL) significantly. This impairment is akin to that found in other chronic skin diseases such as psoriasis and atopic

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Corresponding Author: Dr Dhiraj Dhoot, Senior manager, Medical Services, Glenmark Pharmaceuticals Ltd, India.

dermatitis.^[4] QOL is endorsed by the European Academy of Allergy and Clinical Immunology guidelines on the management of CU, as a target for management.^[5-7]

Conventionally, management of CU is done by non-pharmacological and pharmacological options. Non-pharmacological options include removal of aberrant factors such as stress, heat, alcohol, and drugs including angiotensin-converting enzyme inhibitors. Pharmacological treatment is mainly comprised of antihistamines. Since antihistamines inhibit the release of critical inflammatory cytokines and histamine, it is usually advocated that antihistamines be prescribed on daily basis instead of need-based approach. This will also help to curb the misapprehension of therapeutic effectiveness failure. Second-generation antihistamines are preferred in majority cases of CU, while first-generation antihistamines are preferred in cases of nocturnal CU. Preference for second-generation antihistamines is due to their multipronged action on the suppression of inflammatory cytokines, chemotaxis, leucocyte adhesion to vascular endothelium, release of histamine, etc.^[8]

Bepotastine is a methoxypiperidine derivative, non-sedating second-generation antihistamine, which was first approved in Japan in 2002, as an oral drug for the treatment of allergic rhinitis.^[9-11] Later, it was approved for the treatment of urticaria and pruritus associated with allergic skin diseases.^[12,13] Bepotastine has twin mode of action in the form of inhibition of eosinophil chemotaxis to inflamed tissue and stabilization of mast cells.^[9,14] Apart from these, peculiar feature of bepotastine lies in the fact that it has negligible sedation action, which is major hurdle for the use of conventional antihistamines. Impairment of psychomotor functions is another drawback of conventional antihistamines, which is negligible in the case of bepotastine.^[8]

Since second-generation antihistamines are the mainstay of treatment in majority of CU cases, it was dire need of the hour for newer drug in this class, which would overcome major adverse effects of conventional agents but with analogous effectiveness. The present survey was undertaken in pursuit of analyzing the effectiveness and safety of bepotastine in the treatment of CU.

MATERIALS AND METHODS

A pre-validated questionnaire to analyze the safety and effectiveness and safety of bepotastine 10 mg in the treatment idiopathic CU was used to conduct the survey. The total duration of survey was from July to December 2017. Using the SCRIIP database, we initially identified physicians and dermatologists who were treating patients

of CU. In pursuit of taking representation of each zone in the country, we refined our search from the east, west, north, and south zones. Only those doctors were selected who maintained complete patient records. Thus, 50 of 80 doctors were finally selected based on these two criteria. Only those records were included for analysis, whose data were available for complete 28 days.

The prevalidated questionnaire booklet was provided to each of these doctors, and all relevant patient data were extracted and analyzed after collecting these questionnaire booklets at the end of this survey. The methodology adopted for the present survey is depicted in Figure 1.

Effectiveness Analysis

Clinical effectiveness was analyzed using urticaria activity score (UAS). UAS consists of two components - wheals/hives and itching. UAS was recorded at baseline (D0), day 14 (D14), and day 28 (D28). The score ranges from 0 to 6, 0 indicating the absence of disease and 6 indicating severe form of CU [Table 1].^[15] We divided UAS into four categories – 0 indicating no disease, 1–2 indicating mild urticaria, 3–4 indicating moderate urticaria, and 5–6 indicating severe urticaria. Adherence to treatment was also analyzed.

Safety Evaluation

All the adverse effects were monitored for severity. Specifically, sedation was closely monitored for its occurrence and severity.

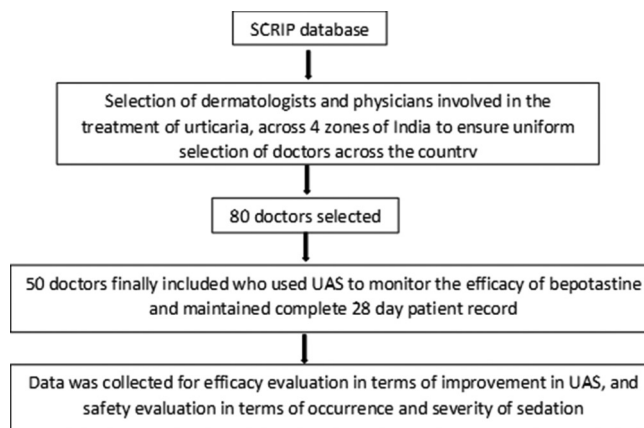


Figure 1: Methodology adopted for the survey

Table 1: Components of UAS (adapted from Jauregui *et al.*)^[15]

Score	Wheals/hives	Itching
0	None	None
1	Mild (<20 wheals/24 h)	Mild
2	Moderate (21–50 wheals/24 h)	Moderate
3	Severe (>50 wheals/24 h or large confluent areas of wheals)	Severe/intense

UAS: Urticaria activity score

RESULTS

A total of 50 dermatologists and physicians participated in the survey, and a total of 250 survey questionnaire booklets were collected at the end of the survey. 226 duly filled survey questionnaire booklets were included for further analysis. The demographic characteristics of the patients are depicted in Table 2. Mean age of the patients was 35.1 years. Of 226 patients evaluated, 90 were male (40%) and 136 (60%) were females with male: female ratio of 1:1.5.

Effectiveness Evaluation

The mean UAS score at D0/baseline was 3.47 which reduced to 1.71 at D14 and 0.73 at D28 [Figure 2].

On analyzing a number of patients achieving specific UAS scores, it was found that 78 patients have UAS score in the range of 1–2, 89 patients in 3–4, and 59 patients in the range of 5–6 at D0. A number of patients in Grade 3–4 and 5–6, i.e., moderate and severe urticaria, respectively, decreased consistently at D14 and D28. 59 patients were encountered in Grade 5–6 at D0, which reduced to 45 patients at D14 and 29 patients at D28, while 89 patients in score range 3–4 at D0 reduced to 68 at D14 and 38 at D28. A number of patients in 0 (no urticaria/complete relief) and 1–2 (mild urticaria) increased consistently from baseline through D14 and D28 [Figure 3 and Table 3].

Adherence to bepotastine treatment was found to be excellent in 25%, very good in 33%, and good in 37% patients, i.e., 95% adhered to bepotastine therapy very well [Figure 4].

Safety Evaluation

Sedation was reported in only 15 patients (6.6%) that too majority had mild sedation, rated in sedation scale range of 0–5. Bepotastine therapy was discontinued in only five patients (2%), due to complete relief or due to sedation (in two patients) [Table 4 and Figure 5].

DISCUSSION

About 20% of the global population suffer from at least one episode of urticaria during their lifetime.^[1] Second-generation antihistamines are the mainstay of symptomatic management of urticaria in majority of the cases. Bepotastine is one of the effective therapeutic options for the treatment of urticaria with crucial advantage of causing minimal sedation. It has shown consistent effectiveness against urticaria, achieving 65–77% significant clinical improvement.^[11,12]

However, conventional second-generation antihistamines, although effective in ameliorating symptoms of urticaria,

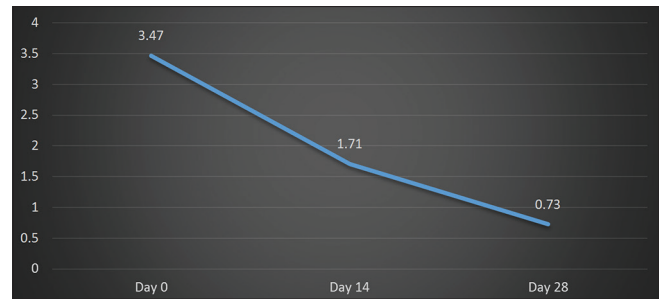


Figure 2: Mean urticaria activity score at D0, D14, and D28

Table 2: Demographic details of patients

Demographic details		
Sr. No.	Particulars	Number of patients (%)
1	Mean age	35.1 years
2	Total patients	226
3	Male	90 (40)
4	Female	136 (60)

Table 3: Number of patients achieving specific UAS scores at D0, D14, and D28

Day	Number of patients achieving UAS score			
	Complete relief	Mild urticaria	Moderate urticaria	Severe urticaria
D0	0	78	89	59
D14	34	79	68	45
D28	46	113	38	29

UAS: Urticaria activity score

Table 4: Number of patient experiencing sedation and discontinuation of bepotastine therapy

Items	Numer of patients	
	Yes	No
Sedation	15	211
Bepotastine was stopped	5	221

sedation, and impairment of psychomotor activities, limit their use in the treatment of urticaria.^[8] Effectiveness of bepotastine in the present survey was analyzed by UAS score which consistently reduced from 3.47 at D0 to 0.73 at D28. The UAS score takes into account the symptoms of histamine-induced inflammation.^[15] Thus, a significant reduction in UAS score indicates potent counteraction of histamine action.

The latest guidelines on the treatment of urticaria laid down by numerous medical societies such as the World Allergy Organization, European Academy of Allergy and Clinical Immunology, Global Allergy and Asthma European Network, and American Academy of Allergy, Asthma, and Immunology recommend UAS score as a

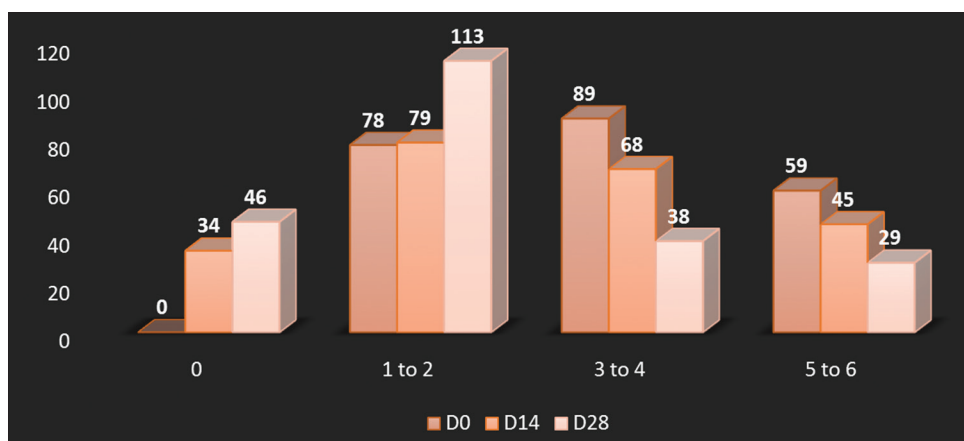


Figure 3: Number of patients achieving specific urticaria activity scores

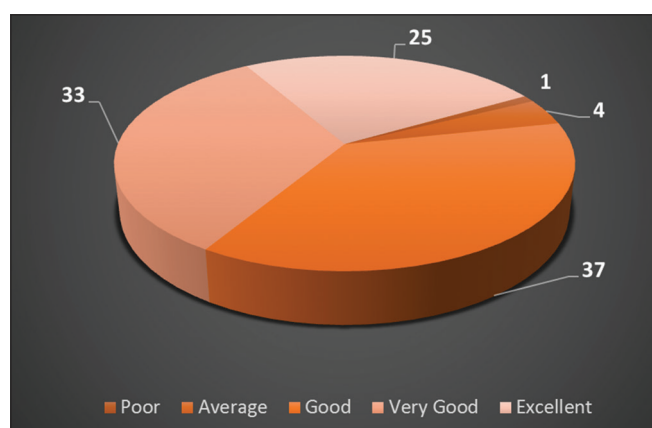


Figure 4: Percentage adherence to bepotastine therapy

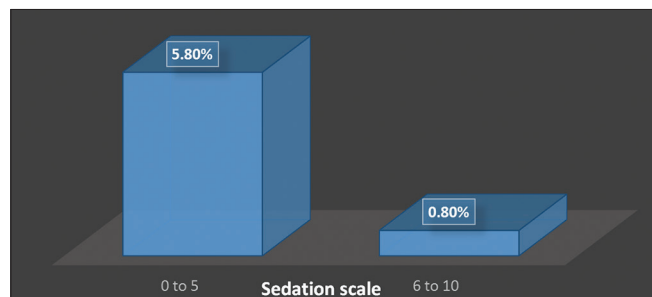


Figure 5: Percentage of patients reporting sedation intensity

target for monitoring effectiveness of antihistamines. This is the reason why UAS scoring is widely used in clinical trials and routine clinical practice in western countries, for monitoring and follow-up of CU.^[16]

Number of patients in moderate and severe grades on D0 reduced at D14 and D28 consistently. Similar results have been obtained in placebo-controlled randomized clinical trial of bepotastine.^[13] The crucial reduction in a number of patients in moderate and severe UAS scores at D14 and D28 indicates effective antihistaminic action of bepotastine. The

increase in a number of mild cases at D14 and D28 was due to improvement in moderate and severe grades, which shifted to mild or completely cured categories. Similar effective improvement rates of around 84% were reported in a post-marketing surveillance done on 549 patients of urticaria associated with skin diseases, who were treated with bepotastine.^[17] This effectiveness of bepotastine might be due to multipronged action of counteracting histamine release and action, mast cell stabilization, inhibition of eosinophil chemotaxis, inhibition of allergic inflammatory cytokines like IL-5, platelet activating factor, leukotriene B4 and D4, and substance P which are responsible for antipruritic effect also.^[18] In a recently published Indian consensus regarding diagnosis and treatment of urticaria, it was strongly recommended to use modern second-line antihistaminic as a first-line therapy for the management of urticaria.^[19]

It has also been studied in head-to-head comparison with conventional terfenadine, and it was found to be as effective as later, in ameliorating the urticaria symptoms as well as global improvement scores.^[20] In a clinical study done to evaluate the efficacy of bepotastine and fexofenadine in histamine-induced wheal and flares, it was found that wheal development at the end of 3 h and 6 h was suppressed more significantly in case of bepotastine as compared to fexofenadine.^[21] In another clinical study on effects of bepotastine, fexofenadine, olopatadine, and cetirizine on histamine-induced wheal and flare response, sedation, and psychomotor performance, it was found that bepotastine showed significant inhibitory effect on wheals and flare, with maximum response among all the drugs on wheal suppression.^[21]

Bepotastine had very negligible sedation in <1% of the patients in the present survey. This was corroborated by the findings of a clinical study, wherein all the conventional second-generation antihistamines such as cetirizine,

fexofenadine, and olopatadine induced significant sedative effect and affected psychomotor performance. In comparison, bepotastine had minimal effect on psychomotor activities and least sedation.^[21] This can be attributed to:

1. Very negligible action at receptors associated with sedation such as dopamine, serotonin, and muscarinic receptors.
2. Limited ability to cross the blood–brain barrier.
3. Efflux from brain cells through P-glycoprotein efflux pump.
4. Internalization of H1 receptors.^[9]

Most common reason for poor adherence to conventional antihistamines is the induction of sedation and impairment of psychomotor activities.^[8] The high adherence rate of 95% in the present survey toward bepotastine can be attributed to negligible sedation and no impairment of psychomotor activities. Thus, complete relief and improvement were seen in >70% of the patients, which is in accordance with other studies establishing the effectiveness of bepotastine.^[21]

CONCLUSION

Bepotastine is a newly introduced non-sedating effective therapeutic option for the treatment of urticaria associated with skin diseases with proven effectiveness and very less adverse effects, especially negligible sedation and absence of impairment of psychomotor activities. The findings of the present real-world survey fortify the favorable effectiveness and safety data of clinical trials.

Limitations of the Survey

Due to the retrospective design of the survey, chances of bias cannot be ruled out. Furthermore, the effect of bepotastine on QOL was not studied.

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Knowledge, Attitude, and Practice about Dental Waste Management among Dentists in Pune - A Questionnaire Study

Amol Jamkhande¹, Mahima Bulani², Darshan Hiremutt³, Amruta Godbole⁴, Deven Rawlani⁴, Harshit Bhadani⁴

¹Associate Professor, Department of Public Health Dentistry, Bharati Vidyapeeth Deemed University Dental College and Hospital, Pune, Maharashtra, India, ²Department of Public Health Dentistry, Dr. D. Y. Patil Dental College and Hospital, Pimpri, Pune, Maharashtra, India,

³Assistant Professor, Department of Oral Medicine and Radiology, Bharati Vidyapeeth Deemed University Dental College and Hospital Pune, Maharashtra, India, ⁴Bharati Vidyapeeth Deemed University Dental College and Hospital, Pune, Maharashtra, India

Abstract

Introduction: Dental profession has expanded considerably, leading to a significant contribution to the production of biomedical waste (BMW). Hence, dentists ought to possess adequate knowledge about BMW management.

Aim: This study aims to assess the knowledge, attitude, and practices about BMW management among private dental practitioners of Pune city.

Materials and Methods: A cross-sectional questionnaire-based survey was conducted among 200 dentists of Pune. A closed-ended, validated, pretested questionnaire comprising four sections with questions on demographics, knowledge, attitude, and practice of BMW management was distributed among 200 private practitioners. The results were expressed as numbers and percentage for each question.

Results: Of 200 dentists, 112 completely filled questionnaires were obtained. It was found that 94.6% of dentists were aware of the BMW management legislation; however, only 81.2% had registered with local BMW management service agency. 100% of dentists considered improper management of dental waste to be hazardous to health. However, segregation and color coding of waste before disposal was followed by only 73.3% and 79.5% of dentists, respectively.

Conclusion: It can be concluded from the present study that in spite of sufficient awareness about BMW management legislation; furthermore, training, awareness, educational, and motivational programs are required to attain better implementation of the laws by the dentists.

Key words: Attitude, Dental waste management, Dentists in Pune, Knowledge, Practice

INTRODUCTION

Biomedical waste (BMW) is defined as the waste generated during the diagnosis, treatment, or immunization of human beings or in research activities pertaining thereto or in the production or testing of biological, and including categories mentioned in Schedule I of the BMW (management and

handling) (second amendment) Rules 2000, by Ministry of Environment and Forests notification.^[1-3]

BMW management is the scientific disposal of BMW through segregation, collection, and treatment which enables decreased spread of infection.^[4] BMW has been given extreme importance by Member States of the World Health Organization (WHO) Regional Office for Europe. It has been in the agenda of Sixth Ministerial Conference on Environment and Health.^[5,6] Waste production in India hiked from 415,429 kg in 2011 to 484,271 kg per day in 2013. Maharashtra is the second maximum biowaste producer after Karnataka followed by Kerala being the third highest biowaste producer of India. BMW management

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Corresponding Author: Dr. Amol Jamkhande, Department of Public Health Dentistry, Bharati Vidyapeeth Deemed University Dental College and Hospital, Pune, Maharashtra, India. Phone: +91-9823185830. E-mail: dr.amolj@gmail.com

rules were put forth by the Ministry of Environment and Forest of Government of India on July 20, 1998, under the Environment Protection Act, 1986.^[1,3,7] Since then, the rules have undergone amendment in 2011 and 2016. The BMW rules, 1998 draft signified 10 categories of BMW which were subsequently reduced to 8 and 4 categories in 2011 and 2016 drafts, respectively. The revised 2016 draft provides better explanation over the classification of BMW as per color-coded containers enabling a clear vision for better segregation and disposal of BMW.^[3,4,7-9] The BMW rules, 1998 (The Gazette of India, 1998) mandatorize clinical and hospital settings to strictly abide by the rules for BMW disposal.^[3,10] With an increased oral health burden and expansion in dental practice, dentistry has contributed widely to the production of hazardous BMW in the form of lead foil in X-ray films, chemicals, scrap dental amalgam, etc.^[11] Hence, it becomes imperative for dentists to have adequate knowledge about the rules of BMW disposal to conserve the environment and prevent health hazards. Hence, this study was undertaken to assess the level of knowledge, awareness, attitude, and practices of dental waste management among dentists in Pune city, thereby enabling formulation of strategies for adequate BMW management and disposal by dentists in the near future.

MATERIALS AND METHODS

A cross-sectional questionnaire-based survey was conducted in December 2017. The target population comprised 500 private dental practitioners selected by simple random sampling from the list of Indian Dental Association, Pune, who were initially contacted over the telephone. About 212 dentists consented to participate in the study. Only private dental practitioners practicing in Pune city who consented to participate were included in the study. Ethical clearance was obtained from the Institutional Ethics Committee.

An initial self-structured, close-ended 27-point questionnaire was designed in English by assembling data through literature search. It comprised four domains - demographics, knowledge, attitude, and practice, respectively. It was then subjected to validity and reliability assessment. Face and content validation was done by 15 subject matter experts (S.M.E) who were experts in the fields of dentistry, dental and general waste management policies, and regulations. Face validation was conducted by discussing the questionnaire with the team of S.M.E's. Thereafter, content validation was done for all 27 questions. The content validity ratio (C.V.R.) was calculated for each question. The C.V.R was found to be less than the required value (i.e., 0.49 for 15 S.M.E's) for four questions indicating their non-essentialness.^[12] Thus,

the questionnaire after validation was structured with 23 close-ended questions.

Reliability

Reliability of the questionnaire was assessed by test-retest method to assess the stability of the questionnaire and Cronbach's alpha value enabled to measure the internal consistency of the questionnaire. Test-retest was done by distributing the pre-validated questionnaire twice among 25 dental practitioners at an interval of 12 days. Intraclass correlation coefficient with 95% confidence interval was used to assess the reliability enabling the measurement of the level of agreement between repeated measurements. The values were found to be 0.89, 0.92, and 0.83 for knowledge, attitude, and practice sections, respectively. Cronbach's alpha values were 0.79, 0.84, and 0.87 for the three sections, respectively.

Pretesting

The 23-point pre-validated questionnaire was pretested to assess the clarity, unambiguity, and explicability of the questionnaire. It enabled to know about adequate and easy interpretation of the questionnaire by the dentists. A convenience sample of 25 dentists was selected to distribute the questionnaire. They were explained the filling procedure. Their doubts and difficulties were resolved. The responses were assessed, thereby modifying the questionnaire. Thus, the final pre-validated, self-structured, close-ended 23-point questionnaire was prepared.

The data were compiled and tabulated in Microsoft Excel spreadsheet and were subjected to frequency distribution analysis using the Statistical Package for the Social Sciences software version 18.

RESULTS

The questionnaire was distributed among 212 private dental practitioners among which 189 dentists responded to it and completed the entire questionnaire. The response rate was 89.1%.

Of the participating dentists, 57.1% were male and 42.9% were female with 45.5% of dentists being aged <30 years and 54.5% >30 years of age. Postgraduation was completed by 38.4% of dentists while 61.6% were graduates.

The knowledge section of the questionnaire comprised six questions. 94.6% and 85.7% of dentists were aware of BMW legislation and about the local dental waste management agency, respectively. Safe disposal of waste was considered to be a team effort by 92.8% of dentists. Correct knowledge about the cytotoxic category for expired medicines and soiled waste category for impression

materials and infected cotton was known by 23.2% and 20.5%, respectively. 72.3% of dentists correctly answered about the disposal of sharps in white translucent puncture-proof containers [Table 1].

The attitude-based section of questionnaire comprised five questions. Segregation of dental waste from general waste was considered to be essential by 86.6% of dentists. 93.8% of dentists were interested in attending voluntary programs on waste management and 30.4% of dentists answered safe management of dental waste to be an extra burden on work. All the dentists considered improper waste management to be hazardous to health while 52.7% of dentists considered autoclaving of infectious waste before disposal as essential [Table 2].

The practice-based section comprised eight questions. 73.3% and 79.5% of respondent's segregated waste before disposal and color coded the waste, respectively. >81% of dentists had registered with the BMW disposal service provider. 71.4% of dentists burnt and disposed the needle

while only 42% and 43.8% reported the correct disposal of fixer and X-ray film lead foils, respectively. Excess and leftover silver amalgam was reported to be stored in fixer by 22.3% of dentists. Extracted teeth were correctly disposed in yellow bags by 70.5% of dentists [Table 3].

DISCUSSION

Adequate management and disposal of waste are essential to prevent health hazards. According to the WHO, the health-care sector of eleven Southeast Asian countries generates 0.3 million tons of waste per year which is approximately 1000 tons/day.^[13,14]

The dental sector endows considerably toward the production of hazardous BMW. Hence, it is the responsibility of dentists to abide by the government rules of waste disposal to prevent environmental pollution. Contribution of human element toward waste management over technology was emphasized to be more important by the WHO.^[11,13,15]

Table 1: Knowledge-based questions

Questions	Options	Response (%)
Are you aware of BMW management legislation in India?	Yes	94.6
	No	5.4
Do you know the agency responsible for dental waste management in your city?	Yes	96
	No	16
Safe management of dental waste is the duty of	Only government	7.2
	Teamwork of government, dental surgeons and auxiliaries	92.8
Sharps (such as broken needles, surgical blades, and burs) should be disposed in	Yellow bag	13.4
	Red bag	14.3
	White translucent puncture-proof containers	72.3
	Do not know	0.0
Expired medicines belong to which category?	Chemical waste	70.5
	Cytotoxic waste	23.3
	Biotechnological waste	0
	Do not know	6.3
Impression materials and infected cotton are included in which category?	Solid waste	0
	Soiled waste	20.5
	Infected waste	65.2
	Do not know	14.3

Table 2: Attitude-based questions

Questions	Options	Response (%)
Do you think it is important to segregate dental waste from general waste?	Yes	94.6
	No	5.4
Will you be interested to attend voluntary programs that enhance and upgrade your knowledge about waste management?	Yes	96
	No	16
Do you think safe management of dental waste is an extra burden on work?	Yes	30.4
	No	59.8
	No comments	9.8
Do you think infectious waste should be sterilized from infections by autoclaving before shredding and disposal?	Yes	52.7
	No	27.7
	Do not know	19.6
Do you think improper waste management can be hazardous to health?	Yes	100
	No	0

Table 3: Practice-based questions

Questions	Options	Response (%)
Do you segregate waste before disposal?	Yes	73.3
	No	16.9
	Sometimes	9.8
Do you follow color coding of waste?	Yes	79.5
	No	10.7
	Sometimes	9.8
Are you registered with a certified waste carrier service to dispose BMW of your clinic?	Yes	81.2
	No	18.8
How do you dispose an infected needle?	Common bin	28.6
	Burn and dispose	71.4
How do you dispose used fixer solution?	Directly in basin and sewer	33.9
	Handover for offsite disposal to a certified agency	42
	Do not use solution	24.1
How do you dispose X-ray film lead foils?	Common bin	34.8
	Handover for offsite disposal to a certified agency	43.8
	Do not use	21.4
How do you dispose excess leftover silver amalgam?	Common bin	0
	Store in fixer solution	22.3
	Store in container with water	17.9
	Do not use	59.8
How do you dispose extracted teeth?	Common bin	22.3
	Red bag	70.5
	Yellow bag	2.7
	None of the above	4.5

Adequate segregation, storage, collection, and disposal of BMW are imperative. Collection of BMW should be done as per BMW management rules, 2016. The containers/boxes should be labeled with a biohazard and cytotoxic symbol.^[9] Non-chlorinated plastic bags which can be incinerated should be used to prevent release of pollutants such as dioxins and furans released by normal plastic bags.^[16] Maximum time limit of 48 h has been specified by the guidelines for storage of BMW before transporting to the waste treatment facility.^[3,16]

In our study, 94.6% of dentists were aware of the BMW legislation in India similar to findings obtained in studies conducted earlier by Khatri *et al.* (98.67%)^[17] and Lakshmikantha *et al.* (88.4%).^[13] However, lesser awareness was found among dentists in the study conducted by Khandelwal *et al.* (41%)^[18] and Shah *et al.* (65%)^[19] 85.7% of dentists were aware of the local dental waste management agency in our study similar to the awareness noticed among dentists by Lakshmikantha *et al.* (79.5%).^[13] These results thus obtained signify sufficient awareness about BMW management among dentists of Pune. 92.8% of dentists considered safe dental waste management to be a team effort of government, dentists, and auxiliaries similar to findings obtained among dentists in a study conducted by Khandelwal *et al.* (92%)^[18] in 2013. Thus, a unanimous initiative by all three classes is required to safely handle dental waste disposal. Sharps should be disposed in white translucent puncture-proof containers to prevent injuries by puncture and cuts as per

BMW management rules, 2016.^[9] 72.3% of dentists were aware of this in our study similar to the findings obtained among other studies conducted at Pune by Khatri *et al.* (61%)^[17] and Amritsar by Narang *et al.* (60%)^[20] respectively. Expired medicines belong to cytotoxic category were known by only 23.2% of dentists similar to findings obtained in studies conducted in Southern region of India by Charania and Ingle (30%)^[21] and Northern part of India by Bansal *et al.* (24%)^[22] Only 20.5% of dentists had correct knowledge about impression materials and infected cotton belonging to the category of soiled waste similar to findings of studies conducted by Bansal *et al.* (16%)^[22] and Singh *et al.* (39.4%).^[23] This signifies that the knowledge among dentists about categorization of wastes was considerably less and measures need to be initiated toward it.

Segregation of BMW in color-coded containers or bags at the point of generation before disposal is essential as per Schedule I of BMW rules, 2016 (Gazette).^[9] However, this was considered to be important by only 86.6% of dentists in our study similar to findings obtained by Rudraswamy *et al.* (82.6%)^[24] and Goyal *et al.* (89.8%).^[10] A large number of dentists (93.8%) perceived the willingness of attending programs to get updated about BMW rules similar to findings obtained by Lakshmikantha *et al.* (84%)^[13] and Khandelwal *et al.* (92%)^[18]

Only 30.4% of dentists considered safe management of dental waste to be a burden on work similar to findings

of the study conducted by Lakshmikantha *et al.* (27%),^[13] in 2016. An overwhelming 100% response of dentists was obtained in our study regarding consideration of improper dental waste management to be hazardous for health similar to response obtained by Narang *et al.* (100%),^[20] in 2012. Additional importance has been given to pretreatment of BMW before disposal by revised rules of BMW, 2016 as per the WHO or National AIDS Control Organization guidelines to prevent microbial contamination.^[4,9] However, only 52.7% of dentists considered it to be important in our study similar to findings obtained by Lakshmikantha *et al.* (59.1%)^[13] in Southern region of India in 2016.

Thus, this section of questionnaire signified a positive attitude of dentists toward following and upgrading themselves about BMW legislations.

Regarding the practices of BMW rules by the dentists of Pune, it was found that segregation of waste before disposal was carried out by 73.3% of dentists similar to results obtained by Abhishek *et al.* (70.5%).^[25] However, only 35.7% of dentists practiced segregation in a study conducted by Sudhakar *et al.*,^[26] in 2008. Color coding of waste was carried out by 79.5% of dentists in our study similar to findings reported by Navya *et al.* (90%)^[16] and Narang *et al.* (85%).^[20] However, contrasting results were obtained by Khandelwal *et al.* (36%).^[18] Segregation of BMW at source is a mandatory requirement by the authorities. In a city like Pune, implementation guidelines are strictly adhered and there have been reported incidents of practicing dentists being penalized for not following the same. With almost over 25% of the study sample in our study still not following the guidelines, it is a matter of concern and more awareness campaigns should be undertaken by the government.

Registration with local BMW carrier agency is essential;^[9] however, only 81.2% of dentists reported of being registered similar to findings of the study conducted earlier at Pune itself in 2014 by Khatri *et al.* (74.66%)^[17] but definitely higher than findings of studies conducted by Bangennavar *et al.* (59%)^[27] and Abhishek *et al.* (68%).^[25] Complacency on part of the authorities along with a lack of door-to-door collection of BMW in Pune city may have been resulted in 19% of study sample to be still out of the ambit of registration for BMW.

Infected needles should be handled carefully as they are blood contaminated and may predispose cross infection on accidental penetration. Hence, it is mandatory to burn them and then dispose. However, only 71.4% of dentists followed this in our study similar to findings of the study conducted by Bansal *et al.* (66%),^[22] in 2013,

and higher than the findings reported by Singh *et al.* (21.9%),^[23] in 2014.

The fixer solution contains silver which increases the metal content in sewer if disposed in the basin directly. Ideally, it should be handed over to certified buyers who extract silver from it. Hence, handing over for offsite disposal or to certified buyer is the prescribed manner of disposal^[9] of fixer solution which was followed by only 29.5% of dentists in our study. This was practiced even lesser in the study conducted by Singh *et al.* (5.6%).^[23] X-ray film foils contain the heavy metal lead which cannot be incinerated or treated as common waste as it may leach from landfills, thereby contaminating soil and groundwater, leading to impaired neurological development and functions. Hence, ideally, it should be handed over to certified buyers or for offsite disposal, whereby the lead extracted from them may be used as a raw material in other industries.^[23,28] However, this ideal practice of the disposal of X-ray film lead foils was conducted by only 43.8% of dentists in our study which was higher than findings of the study conducted by Singh *et al.* (2.5%),^[23] in 2014. Disposal of leftover fixer solution and X-ray film foils has to be meticulously followed by dental auxiliary staff. Thus, proper training programs involving these parodontal persons would help in proper BMW disposal.

Inhalation of mercury vapors may lead to mercury toxicity. Hence, it should be handled with extreme care. Scrap amalgam contains mercury. Mercury-containing wastes should not be incinerated or autoclaved. On incineration, mercury volatilizes while it tends to escape from autoclave doors on opening them, thereby mercury vapors entering atmosphere risking to mercury toxicity.^[29,30] Hence, the American Dental Association recommends storage of amalgam in “photographic fixer” in a closed container before disposing to prevent health hazards.^[7,31] However, this was practiced by only 22.3% of dentists in our study similar to the finding of the study conducted by Bharadwaj *et al.* (31%),^[29] in 2017. However, this practice was found to increase from 10% in 2013 to 31% in 2017 as reported by Bansal *et al.*^[22] and Bharadwaj *et al.*^[29]

Extracted teeth should be disposed in yellow bags (Gazette, 2016)^[9] which was followed by 70.5% of dentists in our study similar to findings obtained by Bansal *et al.* (62%),^[22] in 2013.

Proper disposal of BMW is the collective responsibility of the dentist, auxiliary staff, and the authorities. Even though the onus lies with the clinic owner who generates BMW, conscious involvement of the dental auxiliaries and support staff is of utmost important.

The government authorities should also play their part by awareness of the proper guidelines and strict implementation thereafter.

Thus, it can be inferred that dentists of Pune practice BMW rules but still need to be provided guidance, information, and motivation to follow them more correctly and regularly.

Proper disposal of BMW is a social responsibility. It is also necessary for all the dentists to give adequate importance to this matter. A “team up approach” by government, dentists and auxiliaries can solve the issue. Educational and motivational training programs should be conducted. Furthermore, undergraduate curriculum should include this topic along with practical demonstration classes on waste disposal. The concept of “habits die hard” should be followed by making the dental students habituated from incipient stage by their teachers to abide by these rules in educational institutions by assigning them duties of waste segregation, color coding, etc. In our study, we had used a self-reported questionnaire which may have led to subjective bias. Thus, we recommend further studies with a larger sample size and also repeated timely surveys to be conducted to monitor the change in practices which will help furthermore to formulate strategies to promote inculcation, upgradation, and adoption of BMW management rules.

CONCLUSION

It can be concluded that dentists of Pune practice BMW rules but still need to be provided guidance, information, and motivation to follow them more correctly and regularly. It is also necessary for all the dentists to give adequate importance to this matter. A “team up approach” by government, dentists and auxiliaries can solve the issue. Educational and motivational training programs should be conducted. Furthermore, undergraduate curriculum should include this topic along with practical demonstration classes on waste disposal. The concept of “habits die hard” should be followed by making the dental students habituated from incipient stage by their teachers to abide by these rules in educational institutions by assigning them duties of waste segregation, color coding, etc. In our study, we had used a self-reported questionnaire which may have led to subjective bias. Thus, we recommend further studies with a larger sample size and also repeated timely surveys to be conducted to monitor the change in practices which will help furthermore to formulate strategies to promote inculcation, upgradation, and adoption of BMW management rules.

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Feto-maternal Outcome in Placenta Previa in Scarred versus Non-scarred Uterus

Mansi Shrigiriwar¹, Shweta Kesarwani², Sangita Ramteke¹

¹Associate Professor, Department of Obstetric and Gynecology, Government Medical College and Hospital, Nagpur, Maharashtra, India,

²Junior Resident, Department of Obstetric and Gynecology, Government Medical College and Hospital, Nagpur, Maharashtra, India

Abstract

Introduction: Placenta previa complicates 0.3–0.5% of all pregnancies and is a major cause of third-trimester hemorrhage. It affects both mother and fetus; therefore, it is important to study this condition and its complications.

Aims and Objectives: The aims and objectives of this study were to compare the incidence of placenta previa, associated factors, complications, placental position, mode of delivery, and fetal and maternal outcome in non-scarred uterus and scarred uterus.

Materials and Methods: A total of 100 patients identified with the diagnosis of placenta previa beyond 28 weeks of gestation were taken. The cases were divided into two groups: Scarred and unscarred. Both the groups were compared for parameters such as maternal age, parity, frequency of placenta previa, fetal outcome, operative procedures, and maternal morbidity and mortality.

Results: Of 100 patients, 23% were in the age group between 18 and 25, 49% between 26 and 30, and 28% between 31 and 40 years. 6% of patients in scarred uterus had 2 or more previous dilatation and curettage. In all patients of scarred uterus, 80% of the patients had previous 1 cesarean section, while 15% had two previous sections and 4.5% had previous three cesarean sections. Chances of placenta previa increase both with dilatation and curettage and previous cesarean sections. However, it was found in this study that fetal outcome did not differ much with the presence of scarred uterus.

Conclusion: It can be concluded that, in our study, the cesarean section had a significant relationship with placenta previa and this risk becomes very high with escalation in number of cesarean sections.

Key words: Cesarean section, Curettage, Dilatation, Maternal mortality, Placenta previa, Scarred uterus, Unscarred uterus

INTRODUCTION

The placenta is the life support system of the fetus. Placenta previa is an obstetric condition characterized by abnormal implantation of the placenta into the lower uterine segment, covering whole or part of the cervix.^[1] Placenta previa complicates 0.3–0.5% of all pregnancies and is a major cause of third-trimester hemorrhage.^[2] The reported incidence is 1 case per 300–400 deliveries. Almost 30% maternal deaths in the Asian population are due to major obstetrical hemorrhage in placenta previa, especially due to the rise in the incidence of cesarean sections.^[3]

Placental migration is used to describe the apparent movement of the placenta away from the internal os. Many of those placentas that migrate most likely never were circumferentially implanted with true villous invasion that reached the internal os. Several factors can increase the risk of placenta previa such as:

- Advanced maternal age
- Multiparity
- Multifetal gestation
- Cigarette smoking
- Previous cesarean sections.

There is an evident literature support which suggests that the chances of placenta previa are not only more in patients who had a previous history of a cesarean section but the chances also increase with the number of the caesarean section in the past.

Abnormal placentation is currently the most common indication for peripartum hysterectomy. Placenta previa

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Corresponding Author: Dr. Shweta Kesarwani, Room No 26, MARD Hostel, Government Medical College, Nagpur, Maharashtra, India.
Phone: +91-9960806789, 7311110797. E-mail: shweta.kesar@gmail.com

accounts for one-third of all cases of antepartum hemorrhage.^[4] Placenta previa is a major risk factor for obstetric hemorrhage, especially in women with a previous uterine scar.^[5]

Thus, given the increased incidence of placenta previa *per se*, following prior cesarean delivery must be acknowledged as a real concern by obstetricians, given the rising cesarean section delivery rates that we have been experiencing over the past few decades, especially, as the incidence of hysterectomy in such cases is very high and that there is a notable increase in maternal morbidity and mortality. Thus, we conducted this study to know about the association of placenta previa with previous cesarean section pregnancy so that early recognition of placental location abnormalities and timely intervention can have a significant impact on the maternal and perinatal outcome.

Aims and Objectives

The aims and objectives of this study were as follows:

1. To compare the incidence of placenta previa, associated factors, complications, placental position, mode of delivery, and fetal and maternal outcome in non-scarred uterus and scarred uterus.
2. To reduce maternal and fetal morbidity and mortality by early diagnosis and prompt management in cases of placenta previa.

MATERIALS AND METHODS

It was an institutional-based prospective study conducted in the Department of Obstetrics and Gynecology at Government Medical College and Hospital, Nagpur, India, between January 2017 and July 2018.

A total of 100 patients identified with the diagnosis of placenta previa beyond 28 weeks of gestation were taken. Diagnosis was confirmed by transabdominal and transvaginal ultrasound as and when required. The cases were divided into two groups:

- Unscarred uterus - including cases with placenta previa who have no previous history of cesarean section or any uterine surgery like curettage.
- Scarred uterus - including cases with placenta previa who have a history of 1 or more previous cesarean section or uterine surgery like myomectomy or uterine rupture repair.

Both the groups were compared for parameters such as maternal age, parity, frequency of placenta previa, fetal outcome, operative procedures, and maternal morbidity and mortality.

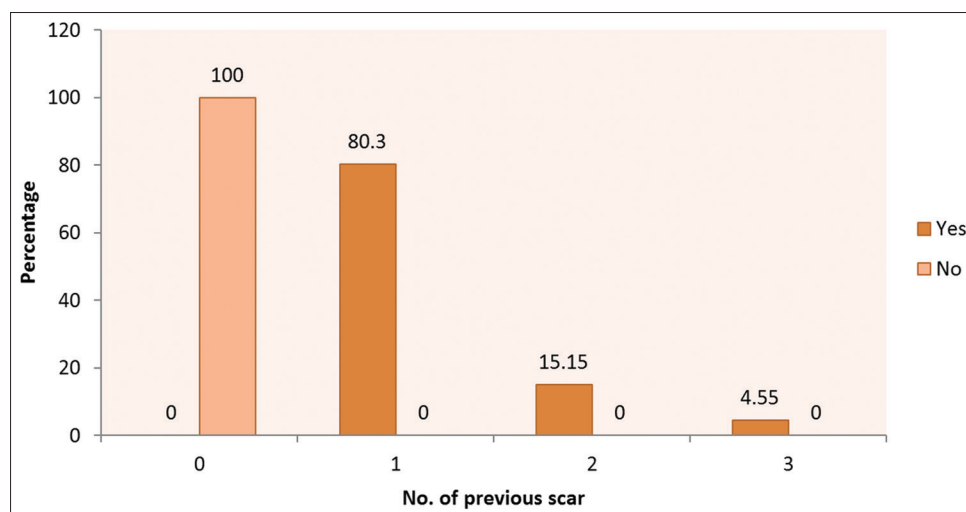
Inclusion Criteria

All pregnant women diagnosed with placenta previa beyond 28 weeks of gestation were included in the study. A detailed history was taken and a thorough clinical examination was done, followed by relevant investigation as required by the study.

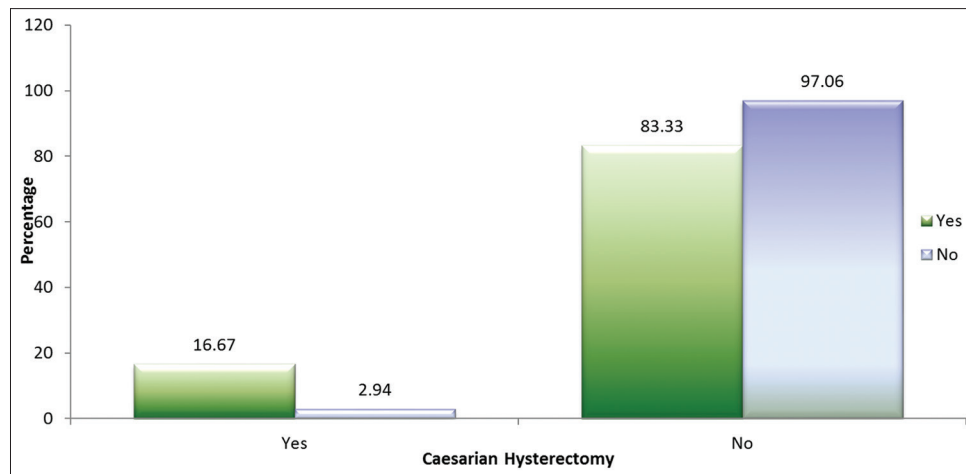
All the data were duly recorded in the standard prepared pro forma.

Exclusion Criteria

1. All pregnant women having placenta previa before 28 weeks of gestation were excluded from the study.
2. Cases of placenta previa with any other maternal morbidity such as severe pregnancy-induced hypertension, severe IUGR, and gestational diabetes mellitus were excluded.



Graph 1: Incidence of placenta previa according to a number of previous scar



Graph 2: Comparison according to cesarean hysterectomy

RESULTS

A total of 100 cases were included in this study. In scarred uterus, the most common age group was 26–30 years. 51% of patients were in this age group, while in unscarred uterus, 44% of patients were in this group. As the age group increased to 31–40 years, scarred uterus had 33% of patients while unscarred had only 17% of patients [Table 1]. $P = 0.024$ was considered to be statistically significant, and hence, as the age increases, the chances of having placenta previa in scarred uterus also increase.

As the parity is increased to ≥ 2 , 25% of the patients were found in scarred uterus while 26% in unscarred uterus. $P = 0.001$ was considered to be statistically significant and showed that, as the parity increases, chances of having placenta previa in scarred uterus also increase.

About 33% of the patients in scarred uterus had a history of previous one dilatation and curettage, while only 11% of the patients in unscarred uterus had one dilatation and curettage. 6% of patients in scarred uterus had 2 or more previous d n c, while only 2% of patients in unscarred uterus had 2 or more d n c. $P = 0.04$ was considered to be statistically significant which showed that chances of placenta previa increase with increase in a number of previous d n c in scarred uterus [Table 2].

In all patients of scarred uterus, 80% of the patients had previous one cesarean section, while 15% had two previous sections and 4.5% had previous three cesarean sections. $P = 0.001$ and Fischer's exact was 0.00 which was statistically significant [Graph 1]. Therefore, as the number of previous cesarean sections increases, chances of having placenta previa also increase. Maximum patients were in 34–37 weeks' group in scarred uterus, that is, 51%. $P = 0.023$ was considered to be statistically significant

Table 1: Relation of previous scar with age

Age (years)	Previous scar n (%)	
	Scarred	Unscarred
18–25	10 (15.15)	13 (38.24)
26–30	34 (51.52)	15 (44.12)
31–40	22 (33.33)	6 (17.65)
Total	66 (100)	34 (100)

$\chi^2 (2) = 7.4215, P: 0.024$

Table 2: Relation of previous scar and history of dilatation and curettage

Number of dilatation and curettage	Previous scar n (%)	
	Scarred	Unscarred
0	40 (60.61)	29 (85.29)
1	22 (33.33)	4 (11.76)
2	4 (6.06)	1 (2.94)
Total	66 (100)	34 (100)

$\chi^2 (2) = 6.4340, P: 0.040$

which shows that, as the gestational age increases, chances of having placenta previa in scarred uterus also increase.

About 72% of the patients in scarred uterus and 52% of the patients in unscarred uterus had anterior placenta. Grade 3 placenta was found in 71% of the scarred uterus and 44% of unscarred uterus. Only 6 cases of 100 had invasive placenta. 3% of cases in scarred uterus had placenta accreta while 2.9% in unscarred uterus had placenta accreta. 4.5% of the cases in scarred uterus had placenta percreta, while no cases were there in unscarred uterus.

About 500–1000 ml of blood loss was found in 45% of scarred uterus and 73% of unscarred uterus. >1000 ml blood loss was found in 53% of scarred uterus and 23% of unscarred uterus. $P = 0.018$ was considered to be statistically significant. Bilateral uterine artery dilatation was done in 33% of cases of scarred uterus and 11% of

cases of unscarred uterus. $P = 0.02$ was considered to be statistically significant. Uterine compression sutures were used in 18% of the cases of scarred uterus and 2.9% of the cases of unscarred uterus. $P = 0.032$ was considered to be statistically significant, and hence, it was found that uterine compression sutures were more commonly used in patients with scarred uterus.

Cesarean hysterectomy was done in 16% of the cases of scarred uterus and 2.9% of the cases of unscarred uterus. $P = 0.045$ was considered to be statistically significant [Graph 2]. Hence, it was found that, as the number of previous cesarean sections increases, the amount of blood loss and other complications and eventually the chances of cesarean hysterectomy increase. Bladder injury was found in only 4 cases of the total of 100 and all of them were in scarred uterus group. Maternal mortality occurred in three cases in scarred uterus and one case in unscarred uterus.

Cephalic presentation was found in 84% in scarred uterus and 76% in unscarred uterus. Premature babies were found in 63% of the cases in scarred uterus and 41% of the cases in unscarred uterus. $P = 0.032$ was considered to be statistically significant [Table 3]. Hence, it was found that prematurity was more common in scarred uterus as compared to unscarred uterus.

Live birth occurred in 90% of the cases of scarred uterus and in 91% in case of unscarred uterus. Thus, it was found in this study that fetal outcome such as live birth, stillbirth, and neonatal death did not differ much with the presence of scarred uterus.

DISCUSSION

Hemorrhage in pregnancy is the most important cause of maternal deaths worldwide. Its contribution to maternal mortality rate is even more striking in countries with low resources.^[6] Placenta previa is one of the most dreaded complications in obstetrics due to its associated adverse maternal and perinatal outcome. The frequency of cesarean section is increasing worldwide with a parallel rise in maternal mortality and morbidity. The higher incidence of cesarean delivery today is strongly associated with greater frequency of placenta previa. Similar results were found in this study.

Table 3: Comparison according to prematurity

Prematurity	Previous scar n (%)	
	Scarred	Unscarred
Yes	42 (63.64)	14 (41.18)
No	24 (36.36)	20 (58.82)
Total	66 (100)	34 (100)

$\chi^2 (2) = 4.5941, P: 0.032$

The most common age group in this study was 26–30 years both in the scarred and unscarred groups. This result was similar to the results obtained in the studies of Kaur *et al.*,^[7] Pravin *et al.*,^[8] Katke *et al.*,^[9] Parikh *et al.*,^[10] and Fauzia *et al.*^[11] A maximum number of patients in this study were multigravidas. Around 65% of patients had parity between 1 and 2. Various literatures have concluded that increasing parity increases the risk of placenta previa.^[12,13]

Most of the patients in this study were from urban areas around 76%. Residence did not have much effect on placenta previa ($P = 0.199$). Most of the patients were unbooked. Results were similar to the studies of Katke *et al.*,^[9] Parikh *et al.*,^[10] and Fauzia *et al.*^[11] As the number of previous dilatation and curettage increases, the chances of having placenta previa in scarred uterus also increase ($P = 0.04$). The results were similar to the results of Kaur *et al.*^[7] and Fauzia *et al.*^[11]

An increase in the number of previous cesarean section increases the chances of placenta previa in subsequent pregnancies. The results were significant in our study with $P = 0.001$. Many studies conducted around the world confirm a 2–5-fold increased risk of placenta praevia with a previous history of c-section.^[14] These findings were similar to the results of Kaur *et al.*,^[7] Pravin *et al.*,^[8] Katke *et al.*,^[9] Parikh *et al.*,^[10] and Fauzia *et al.*^[11]

The anterior placenta was more common in our study scarred uterus ($P = 0.048$) similar to the results of Kaur *et al.*,^[7] Pravin *et al.*,^[8] Katke *et al.*,^[9] Parikh *et al.*,^[10] and Fauzia *et al.*^[11]

There were only two cases of placenta accreta in the scarred uterus and one case in unscarred uterus and 3 cases of placenta percreta in scarred uterus. More chances of adherent placenta are there in scarred uterus.

More than 1000 ml blood loss was found in 53% of the patients in scarred uterus. $P = 0.018$ was considered to be statistically significant, and hence, it was found that the amount of blood loss increases as the number of previous cesarean section increases. This was also found in the studies of Kaur *et al.*,^[7] Parikh *et al.*,^[10] and Fauzia *et al.*^[11]

Bilateral uterine artery ligation was used as a method to reduce intraoperative blood loss and postpartum hemorrhage. It was used in 33% of the cases in scarred uterus. This result was significant ($P = 0.02$) and comparable to the results of Kaur *et al.*^[7] and Parikh *et al.*^[10]

Uterine compression sutures were used in 18% of the cases in scarred uterus with placenta previa. $P = 0.032$ was considered to be statistically significant and similar to the results of Kaur *et al.*^[7] and Parikh *et al.*^[10]

Cesarean hysterectomy was required in 11 cases in scarred uterus and 1 case in unscarred uterus group. Results were statistically significant ($P = 0.045$), and similar results were found in the studies of Kaur *et al.*,^[7] Katke *et al.*,^[9] and Parikh *et al.*,^[10] Bladder injury was found in only four cases in scarred uterus. Bladder injury occurred accidentally or in cases of placenta percreta. Maternal mortality occurred in 3 cases in scarred uterus and 1 in unscarred uterus.

Malpresentations are common in placenta previa; however, cephalic is still the most common. However, in all these patients, the head was high floating or deflexed even at term.

Prematurity was found in 63% of the cases of scarred uterus. $P = 0.032$ was considered to be statistically significant. Therefore, it was found in this study that scarred uterus with placenta previa had more chances of having a premature baby as compared to unscarred uterus.

Live birth occurred in 90% of the cases of scarred uterus and 91% in case of unscarred uterus. Stillbirth occurred only in two cases of scarred uterus. Neonatal death was found in four cases of scarred uterus and three cases of unscarred uterus. Thus, fetal outcome did not differ much with the presence of scarred uterus. This was similar to the results of Kaur *et al.*,^[7] Pravin *et al.*,^[8] Katke *et al.*,^[9] Parikh *et al.*,^[10] and Fauzia *et al.*^[11]

CONCLUSION

Placenta previa, whether found fortuitously by ultrasound or with the clinical emergency of maternal hemorrhage, carries significant maternal and fetal risk. Accurate diagnosis, judicious expectant management with blood transfusion as required, and timely delivery can lead to the most favorable outcome.

It can be concluded that in our study the cesarean section had a significant relationship with placenta previa and this risk becomes very high with escalation in a number of cesarean sections.

An increasing use of primary cesarean section results in increasing incidence of placenta previa as well as accreta. As the maternal and perinatal morbidity and mortality due to placenta previa is preventable, efforts should be made to bring down these rates which can be achieved by spacing pregnancies, limitation of family size, antenatal registration of all pregnant patients, use of routine USG in pregnancy, and early referral of high risk pregnant women to tertiary care centers.

In conclusion, primary prevention in the form of reduction in the rate of primi cesarean section must be done to prevent likelihood of placenta previa in scarred uteri. The emphasis should be on institutional delivery in a tertiary care center with multidisciplinary care, i.e., involvement of senior obstetrician, anesthetist, neonatologist, sonologist, and hematologist. Sonographic detection of the anterior placenta is very important to predict maternal outcome in placenta previa, and in such cases, obstetricians should be aware of maternal massive hemorrhage. The family planning services should be further improved to attain a decline in the number of women of high parity. The morbidity associated with placenta previa can be reduced by detecting the condition in the antenatal period by ultrasound before it becomes symptomatic. Early diagnosis by ultrasound and planned delivery should be the goal.

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Comparison of Effects of Laryngeal Mask Airway Supreme Cuff Inflation with Air, Air: Oxygen Mixture, and Oxygen: Nitrous Oxide Mixture in Adults: A Randomized Double-blind Study

Ranjana Khetarpal¹, Veena Chatrath², Anu Sharma³, Kirti Jangwal⁴

¹Professor, Department of Anaesthesiology and Critical Care, Government Medical College, Amritsar, Punjab, India, ²Professor and Head, Department of Anaesthesiology and Critical Care, Government Medical College, Amritsar, Punjab, India, ³Assistant Professor, Department of Anaesthesiology and Critical Care, Government Medical College Amritsar, Amritsar, Punjab, India, ⁴Resident, Department of Anaesthesiology and Critical Care, Government Medical College, Amritsar, Punjab, India

Abstract

Introduction: Laryngeal mask airway (LMA) cuff pressure has been implicated as a prime reason for post-operative sore throat. LMA cuff pressure increases when the air is used for the cuff inflation during oxygen: Nitrous oxide (O_2 : N_2O) anesthesia, which results in post-operative pharyngolaryngeal adverse events. We conducted this study to compare the effect of LMA supreme cuff inflation with air, air: Oxygen, and oxygen: Nitrous oxide mixture in adults.

Aim: The aim of the study was to compare the changes in cuff pressure intraoperatively with different gas composition (air, air: Oxygen mixture, and oxygen: Nitrous oxide mixture) used to inflate the LMA supreme by a manometer and post-operative pharyngolaryngeal morbidity.

Design: It was a potential randomized double-blind study which was conducted on 120 patients admitted for elective surgery under general anesthesia.

Materials and Methods: A total of 120 patients were randomly allocated into three groups of 40 each according to the composition of gases used to inflate the supreme LMA cuff to achieve 40 cm H_2O cuff pressure, air was used as cuff inflation medium in Group A, air: Oxygen mixture in Group AO, and oxygen: Nitrous oxide mixture in Group ON.

Statistical Analysis: The cuff pressure, ventilatory parameters, and post-operative pharyngolaryngeal complications were noted. The analysis was done by Student's *t*-test and Chi-square test. $P < 0.05$ was considered statistically significant.

Results: In Group A and Group OA cuff pressure significantly increased from initial cuff pressure of 40 cm H_2O until the end of the surgery to 74.35 ± 7.41 cm H_2O and 56.35 ± 3.63 cm H_2O , respectively. An initial decrease in cuff pressure was observed at 15 min to a mean of 32.85 ± 1.42 cm H_2O in Group ON which again gradually increased to near initial pressures to a mean of 40.10 ± 2.31 cm H_2O toward the end of surgery. Cuff volume increased in Group A and Group AO; however, it decreased in Group ON (23.18 ± 4.45 ml, 18.73 ± 2.61 ml, and 11.50 ± 1.93 ml, respectively) from initial values. Ventilatory and hemodynamic parameters were comparable in all the three groups. A significant difference in pharyngolaryngeal morbidity was observed between Group A and Group ON.

Conclusion: Cuff inflation with 50% O_2 : N_2O mixture provided more stable cuff pressure in comparison to air and O_2 : Air mixture during O_2 : N_2O anesthesia. Ventilatory parameters and hemodynamic parameters did not change with variation in SLMA cuff pressure. Post-operative pharyngolaryngeal morbidity had a strong correlation with cuff pressure and was more in Group A and least in Group ON.

Key words: Cuff inflation, Cuff pressure, Laryngeal mask airway supreme, Pharyngolaryngeal morbidity

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INTRODUCTION

Airway devices including laryngeal mask airway (LMA) have cuffs which are permeable to various gases depending on their solubility and partial pressures. Nitrous oxide (N_2O)

Corresponding Author: Dr. Anu Sharma, 25-second floor HIG Flats, B Block New Amritsar, Punjab, India. Phone: +91-9814185884.
E-mail: Anu.anaesthesia.97@gmail.com

is an inhalational anesthetic that is frequently used for general anesthesia. However, N₂O increases the intracuff pressure due to diffusion of N₂O into the cuff during general anesthesia.^[1] Intracuff pressure during anesthesia is also affected by various factors such as composition and thickness of cuff material and gases used to inflate the cuff. Intracuff pressure increases steadily and reaches a level high enough to impede the microcirculation in the tracheal mucosa within 1 h^[2,3] which may cause damage to the tracheal tissue. Thus, LMA cuff pressure has been implicated as a prime reason for a post-operative sore throat. A number of studies suggested that manometer should be used to monitor cuff pressure intraoperatively.^[4]

Several methods have been described to prevent an increase in cuff pressure including filling the cuff with anesthetic gas mixture^[5,6] or saline^[7] partial cuff deflation technique, intracuff pressure monitoring, or limiting to the pressure at which the seal occurs.

We have planned this study keeping in mind that use of air only, O₂: N₂O mixture, and air: O₂ mixture as LMA cuff inflating medium leads to cuff pressure changes and affects the post-operative pharyngolaryngeal morbidity, and by proper monitoring of cuff pressure, we can get to know which gas mixture used in anesthesia could provide stable and better intracuff pressures resulting in decreased incidence of post-operative sore throat.

Statistical Analysis

The sample size was calculated keeping in view at most 5% risk, with minimum 85% power, and 5% significance level (significant at 95% confidence interval). Raw data were

recorded in a Microsoft Excel spreadsheet and analyzed using Statistical Package for the Social Sciences (SPSS version 23.00). The continuous data were presented as mean with standard deviation (mean \pm SD). Number of patients and/or percentage of cases expressed discrete categorical data. Categorical variables were analyzed using Chi-square test. Normally distributed continuous variables were analyzed using independent sample *t*-test. Power analysis was done to compare cuff pressure by taking α error of 5% and beta error of 20%. The power achieved was well above 90%. The blinding was opened at the end of the study.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Committee, along with written and informed consent, a total of 120 adults of either sex belonging to American Society of Anesthesiologists (ASA) Grades I and II aged 18–60 years and scheduled to undergo general anesthesia were enrolled in a prospective randomized, double-blind, comparative study. Patients with inadequate mouth opening, body mass index >35 kg/m², anticipated difficult airway, patient having increased risk of aspiration such as gastroesophageal reflux disease, hiatus hernia, oropharyngeal pathology, ASA Grades III and IV, cervical spine pathology, and pregnancy were excluded from the study.

The study included a total of 120 patients which were selected randomly through computerized software [Figure 1]. The patients were further divided into three

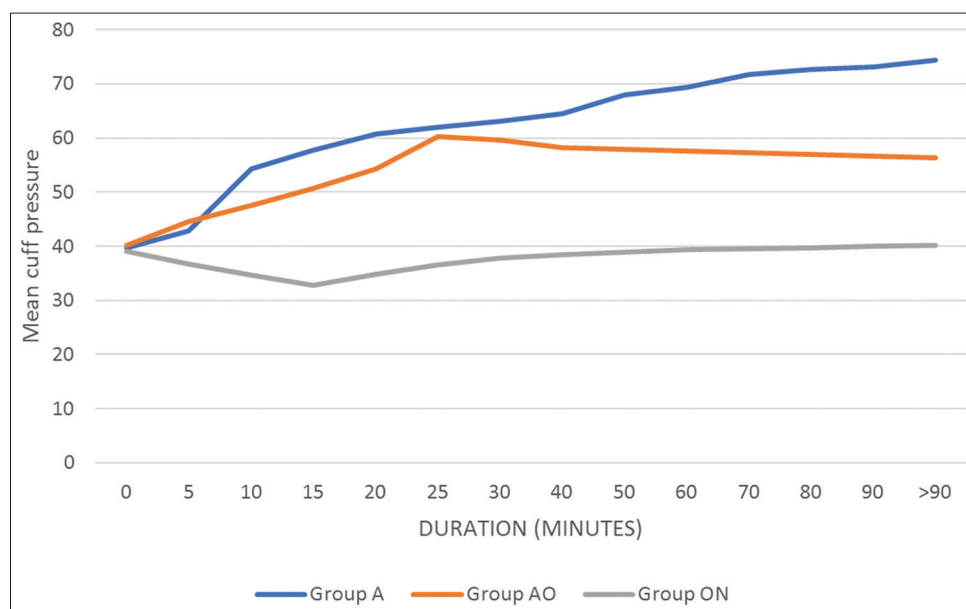


Figure 1: Cuff pressuring monitoring

groups, with each group containing 40 patients which were posted for surgery under general anesthesia using LMA Supreme cuff inflation with:

- Group A: Air only
- Group AO: Oxygen: Air mixture
- Group ON: Oxygen: Nitrous oxide mixture.

To maintain the blinding, the investigator was not involved in opening the envelope. The other anesthesiologist not involved in the study was asked to open the envelope just before the administration of general anesthesia and an appropriate gas-filled syringe was prepared according to the code to inflate the cuff. The same anesthesiologist was not allowed to take part in the management and observations. Gases of different composition were prepared just before the induction in the pre-operative room for each patient by an anesthesiologist not involved in the study.

Preanesthetic checkup including a detailed history and thorough general physical examination of the patient was carried out a day before surgery and was recorded. Venturi mask tubing was attached to the fresh gas outlet of anesthesia work station for the desired composition of gas for different groups that are Group A, Group AO, and Group ON. The other end of the tubing was attached to 50 ml syringe through three-way assembly. The fresh gas flow was set at a desired concentration and gas mixture at 5 L flow. Once desired gas was filled in the syringe, three-way was put in off position toward syringe and was disconnected from the tubing. The size of the LMA supreme was decided according to the manufacturer guidelines. The LMA cuff was checked for any leak. General anesthesia was induced with injection (inj.) propofol 1.5–2.5 mg/kg and inj. fentanyl 2 µg/kg given intravenously. After confirming adequate bag-mask ventilation, inj. vecuronium 0.1 mg/kg was administered and ventilation was performed with 100% O₂ at 5 L fresh gas flow for 3 min. A fully deflated LMA Supreme was inserted by a single anesthesiologist with more than 1 year of experience in insertion. The LMA cuff was inflated by the specified syringe to obtain a cuff pressure of 40 cm H₂O with the help of aneroid cuff pressure manometer attached to the pilot balloon. The volume of gas inflated was noted. Successful insertion was assessed by chest expansion and capnography.

At cuff pressure of 40 cm H₂O, oropharyngeal leak pressure was checked by closing adjustable pressure limiting valve at a fixed gas flow of 3 L/min. The airway pressure at which leak was heard (by stethoscope) was noted. Volume controlled ventilation was initiated, and initial ventilatory settings were adjusted to maintain end-tidal carbon dioxide (EtCO₂) between 35 and 45 mmHg. Fresh gas flow composition was changed to O₂:N₂O (50:50) with

desflurane (0.8–1.4 minimum alveolar concentration) at 3 L for initial 5 min, then subsequently, flow was reduced to 1 L/min (500 ml O₂: 500 ml N₂O).

The cuff pressure and ventilator parameters were noted every 5 min for the first 30 min and then every 10 min until N₂O is switched off and 100% O₂ is given to the patient.

At the end of surgery, inj. myoppyrolate (neostigmine + glycopyrrolate) 0.04–0.06 mg/kg was given as reversal. When the patient was awake and following commands, LMA supreme was removed, inflated. Parameters such as the presence of blood stain on the cuff, attempts for LMA supreme insertion, ease of insertion, use of Guedel's airway (due to difficult mask ventilation or to relieve post-operative upper airway obstruction), aspirated volume of gas from the LMA supreme cuff, and laryngospasm were noted. Oral suction was avoided as far as possible and if done was noted.

The patient was then shifted to the post-anesthesia care unit. After surgery, pharyngolaryngeal complications, consisting of a sore throat, dysphonia, and dysphagia were assessed at 1st, 2nd, 12, and 24 h postoperatively. The predetermined definitions of pharyngolaryngeal complications were used for the assessment. The post-operative sore throat pain was treated by intravenous fentanyl 1–1.5 µg/kg in titrated doses according to the patient's comfort. Patient satisfaction scores using visual analog scales (VAS) score was assessed at 1st, 2nd, 12, and 24 h postoperatively.

RESULTS

With respect to the demographic parameters, the patients in the three groups were analogous as is evident from Table 1. The mean duration of surgery was 58.97 ± 12.88 min in Group A, 60.35 ± 11.05 min in Group AO, and 53.77 ± 9.07 min in Group on. The difference was statistically nonsignificant ($P > 0.05$). Hemodynamic and ventilatory parameters were also found statistically and clinically insignificant ($P > 0.05$).

In our study in Group A, we observed a significant and progressive increase in mean cuff pressures from 40 cm H₂O to 74.35 ± 7.41 cm H₂O until the end of the surgery. In Group OA, cuff pressure increased significantly until 25 min to mean of 60.23 ± 3.70 cm H₂O and then gradually decreased to mean 56.35 ± 3.63 cm H₂O until the end of surgery. Intracuff pressures were almost stable in subjects belonging to Group ON during the course of anesthesia. An initial decrease in cuff pressure was observed at 15 min to a mean of 32.85 ± 1.42 cm H₂O which again gradually increased to near initial pressures to a mean of 40.10 ± 2.31 cm H₂O toward the end of surgery. Intracuff pressure was found to be statistically significant between the three groups ($P < 0.05$) [Table 2].

Table 1: Demographic characteristics of patients

Demographic data	Group A (air)	Group AO (air:Oxygen)	Group ON (Oxygen:Nitrou oxide)	P value
Age (years) mean±SD	30.05±15.4	32.65±9.49	31.73±8.94	>0.05
Sex (males:females)	8:32	18:22	16:24	>0.05
Duration OF surgery (minutes) mean±SD	58.97±12.88	60.35±11.05	53.77±9.07	>0.05
Duration of low flow anesthesia (minutes) mean±SD	52.65±8.40	55.32±14.46	56.35±15.39	>0.05

Duration (minutes)	Group A Mean±SD	Group AO Mean±SD	Group ON Mean±SD
0	39.75±1.10	40.13±0.79	39.13±1.92
5	42.88±5.72	44.58±1.20	36.65±1.08
10	54.30±6.58	47.48±1.47	34.73±1.18
15	57.70±5.96	50.73±2.05	32.85±1.42
20	60.75±4.78	54.33±2.80	34.80±1.42
25	61.95±5.11	60.23±3.70	36.53±1.28
30	63.15±4.48	59.55±3.79	37.78±1.42
40	64.45±4.86	58.15±3.87	38.48±2.14
50	68.00±6.63	57.88±4.69	38.98±2.45
60	69.28±7.08	57.63±5.72	39.30±4.93
70	71.73±7.59	57.23±4.90	39.55±4.51
80	72.68±8.62	56.93±3.03	39.73±3.95
90	73.08±8.38	56.63±3.31	40.03±3.25
>90	74.35±7.41	56.35±3.63	40.10±2.31

A minimal effective cuff inflating volume was used to achieve the LMA cuff pressure of 40 cm H₂O in our study. The initial volume of gas used to inflate LMA Supreme in Group A, Group AO, and Group ON was 13.98 ± 1.83 ml, 13.08 ± 2.28 ml, and 15.63 ± 2.18 ml which was enough to reach the desired pressure of up to 40 cm H₂O. In Group A and Group AO, mean difference between initial and final intracuff volume was observed to be 9.38 ± 4.27 ml and 5.08 ± 1.87 ml. In Group ON, mean difference between initial and final intracuff volume observed was 4.13 ± 1.24 ml. A significant difference between initial and final intracuff volume was observed in three groups ($P < 0.05$) [Table 3].

The incidence of a sore throat, dysphagia, and dysphonia was higher in Group A at 1st, 2nd, 12, and 24 h postoperatively in comparison to Group AO and Group ON. A significant difference in a sore throat, dysphagia was observed between Group A and Group ON in our study. Reduced post-operative morbidity (sore throat, dysphagia, and dysphonia) was observed in Group ON (<0.05). A more stable intracuff pressure trend observed in Group ON was directly related to decrease in the incidence of post-operative pharyngolaryngeal morbidity in this group. In our study, a significant difference in dysphonia was observed between Group A and Group ON at 1st h postoperatively. However, dysphonia at 2nd, 12, and 24 h was found to be statistically insignificant ($P > 0.05$) [Table 4].

VAS was measured postoperatively for a sore throat at 1st, 2nd, 12, and 24 h. Mean VAS scores for Group ON were

observed to be 3 at a 1st h, 3 at 2nd h, 1 at 12 h, and 1 at 24 h postoperatively. The mean VAS scores for Group A and Group OA were observed to be 4.4 at 1st h, 3.3 at 2nd h, 3.2 at 12 h, and 3.2 at 24 h postoperatively. There was a significant difference in sore throat pain score between three groups ($P < 0.05$) and sore throat pain score was comparatively lower in Group ON at the end of 1st, 2nd, 12, and 24 h postoperatively [Table 5].

Rescue analgesia in the form of injection fentanyl 1–1.5 mcg/kg was given in patients with VAS >3 at 1st, 2nd, 12, and 24 h. The result was highly significant in terms of the need for rescue analgesia in Group ON/Group A (<0.05) at a 1st h. Due to the limited duration of action and reoccurrence of throat pain injection fentanyl were repeated at 2nd, 12, and 24 h according to the patient's complaint. In Group ON at 1st h postoperatively, 6 patients were given rescue analgesia. 5 patients were given rescue analgesia at 2nd h. 3 patients and 1 patient were given rescue analgesia at 12 h and 24 h, respectively.

DISCUSSION

Air is most commonly used to inflate the cuff. Nitrous oxide (N₂O) is the least potent and the oldest inhaled anesthetic which has the property to diffuse into air-filled cavities and also through the semipermeable membrane of LMAs cuff, thereby gradually increasing the cuff pressures. High intracuff pressure can cause severe pharyngolaryngeal complications including a sore throat or hoarseness after LMA removal postoperatively. Although the application of minimum effective cuff inflating volume is suggested to maintain airway sealing and adequacy of ventilation for patients receiving general anesthesia with LMA at a lower level of the intracuff pressure, it is currently not standard care in most of the anesthetic departments.

Thus, the study was carried out keeping in mind that use of O₂; N₂O, Air: O₂, and air only as LMA cuff inflating medium leads to cuff pressure changes and effects the post-operative pharyngolaryngeal morbidity. LMA cuff pressure is an inherent risk factor for the development of this common complication, yet a number of techniques can reduce the incidence. Airway devices have cuffs which are permeable to a variety of gases depending on their partial pressure and solubility. The composition and thickness of the cuff material

(latex, silicone or polyvinyl chloride) play a significant role in the intracuff pressure changes during anesthesia.

All the three groups were compared with respect to changes in cuff pressure intraoperatively with a manometer and effect of LMA Supreme cuff pressure change on intraoperative ventilatory and hemodynamic parameters. Post-operative pharyngolaryngeal morbidity in the form of a sore throat, dysphagia, dysphonia, and rare complications of LMA insertion such as recurrent

laryngeal nerve palsy, hypoglossal nerve palsy, and lingual nerve palsy was noted.

In our study, there was a significant difference in cuff pressure in Group A, AO, and ON. The cuff pressure was noted every 5 min for the first 30 min and then every 10 min until N₂O was switched off. In Group A, we observed a significant and progressive increase in mean cuff pressures from 40 cm H₂O to 74.35 ± 7.41 cm H₂O until the end of the surgery. Similar increase in intracuff pressure was observed under N₂O: O₂ anesthesia in a study by Pallavi *et al.* in 2018 where cuff pressure and volume achieved at the end of surgery were much higher in air group as compared to lignocaine group ($P < 0.05$). Despite filling the ET cuff with air at below critical initial cuff pressure of 30 cm H₂O, there was an increase in mean cuff pressure to 49.86 ± 0.72 cm H₂O toward the end of surgery.^[8]

In Group AO, cuff pressure increased significantly until 25 min to mean of 60.23 ± 3.70 cm H₂O and then gradually decreased to mean 56.35 ± 3.63 cm H₂O until the end of surgery. There has been not much literature to evaluate the effect of O₂ and air mixture on cuff pressure. However, a study by Mona *et al.* in 2016 found similar results where LMA Proseal cuff inflation with O₂: Air mixture increased the cuff pressure at 5 min which became statistically

Table 2: Cuff pressure monitoring in intraoperative period

P value		
A/AO	AO/ON	A/ON
0.04	0.00	0.04
0.03	0.00	0.00
0.00	0.00	0.00
0.00	0.00	0.00
0.00	0.00	0.00
0.04	0.00	0.00
0.00	0.00	0.00
0.00	0.00	0.00
0.00	0.00	0.00
0.00	0.00	0.00
0.00	0.00	0.00
0.00	0.00	0.00
0.00	0.00	0.00
0.00	0.00	0.00
0.00	0.00	0.00

Table 3: Intracuff volume variation

Variables	Group A	Group AO	Group ON	t-value			P value		
	Mean±SD	Mean±SD	Mean±SD	A/AO	AO/ON	A/ON	A/AO	AO/ON	A/ON
Initial	13.98±1.83	13.08±2.28	15.63±2.18	1.36	-5.10	-3.07	0.03	0.00	0.00
Final	23.18±4.45	18.73±2.61	11.50±1.93	5.20	11.81	12.22	0.00	0.00	0.00
Difference	9.38±4.27	5.08±1.87	4.13±1.24	5.11	2.53	6.56	0.00	0.00	0.00
Percentage change	64.11±17.97	39.67±13.19	26.52±6.38	6.33	5.50	10.19	0.00	0.00	0.00

Table 4: ST AT 1st, 2nd, 12 and 24-hour post operatively

Sore throat (hour)	Group A	Group AO	Group ON	Total	P value		
	n (%)	n (%)	n (%)	n (%)	A/AO	AO/ON	A/ON
1 st h	16 (40.00)	12 (30.00)	6 (15.00)	34 (28.40)	>0.05	>0.05	<0.05
2 nd h	14 (35.00)	10 (25.00)	5 (12.50)	29 (24.16)	>0.05	>0.05	<0.05
12 h	10 (25)	7 (17.50)	3 (7.50)	20 (16.60)	>0.05	>0.05	<0.05
24 h	7 (17.50)	5 (12.50)	1 (2.50)	13 (10.83)	>0.05	>0.05	<0.05

St: Sore throat

Table 5: VAS score for sore throat in post operative

Time in hours	Group A	Group AO	Group ON	t value			P value		
	Mean±SD	Mean±SD	Mean±SD	A/AO	AO/ON	A/ON	A/AO	AO/ON	A/ON
1	4.38±0.59	4.15±0.58	3.20±0.41	1.02	6.92	9.68	0.04	0.00	0.00
2	3.38±0.54	3.18±0.45	3.00±0.39	1.77	1.87	3.55	0.04	0.03	0.00
12	3.18±0.38	2.20±0.41	1.10±0.30	10.03	-9.53	1.94	0.00	0.00	0.02
24	2.25±0.49	1.18±0.38	1.05±0.22	11.58	1.82	17.48	0.00	0.04	0.00

VAS: Visual analog scales

significant at 10 min until 30 min then again decreased gradually until 90 min.^[9]

Intracuff pressures were almost stable in subjects belonging to group ON during the course of anesthesia. An initial decrease in cuff pressure was observed at 15 min to a mean of 32.85 ± 1.42 cm H₂O which again gradually increased to near initial pressures to a mean of 40.10 ± 2.31 cm H₂O toward the end of surgery [Figure 2]. It is hypothesized that when LMA Supreme cuff is inflated with 50% N₂O, it creates a pressure above the atmospheric pressure at 40 cm H₂O which leads to a pressure gradient between the inside and outside of the cuff resulting in the diffusion of N₂O out of the cuff resulting in an initial decrease in pressure and volume. The results are consistent with that of an earlier study done in 2017 by Puneeth *et al.* where cuff inflation with N₂O: O₂ resulted in a significant decrease in intratracheal cuff pressure from 30 cm H₂O to mean pressure of 24.10 ± 0.90 cm H₂O at the end of 90 min in comparison to increased mean cuff pressures with air ($P < 0.001$).^[10] Shenoy *et al.* stated that the practice of using 50% N₂O: O₂ for filling endotracheal tube cuff facilitates an inexpensive method for providing safe and stable cuff pressures during anesthesia.^[11]

A minimal effective cuff inflating volume was used to achieve the LMA cuff pressure of 40 cm H₂O in our study. The volume of gas used to inflate LMA Supreme in Group A, Group AO, and Group ON was 13.98 ± 1.83 ml, 13.08 ± 2.28 ml, and 15.63 ± 2.18 ml which was enough to reach the desired pressure of up to 40 cm H₂O. Furthermore, a significant difference in the initial and final aspirated volume was observed in our study in all three

groups [Figure 3]. Intracuff volume variation was more in Group A in comparison to Group AO whereas the least change in cuff volume was observed in Group ON. Mitchell *et al.* observed a progressive decrease in cuff pressure and final cuff volume when a gas mix (O₂: N₂O) was used to inflate the cuff.^[11]

A significant difference in a sore throat, dysphagia was observed between Group A and Group ON in our study. Reduced post-operative morbidity (sore throat, dysphagia, and dysphonia) was observed in Group ON (<0.05). A more stable intracuff pressure trend observed in Group ON was directly related to decrease in the incidence of post-operative pharyngolaryngeal morbidity in this group. We also assessed the intensity of sore throat pain in three groups using VAS. Our study showed mean VAS scores for Group ON being 3 at 1st h, 3 at 2nd h, 1 at 12 h, and 1 at 24 h postoperatively. The mean VAS scores for Group A and Group AO were observed to be 4.4 at 1st h, 3.3 at 2nd h, 3.2 at 12 h, and 3.2 at 24 h postoperatively. There was a significant difference in sore throat pain score between three groups ($P < 0.05$) and sore throat pain score were comparatively lower in Group ON at the end of 1st, 2nd, 12, and 24 h postoperatively.

Rescue analgesia in the form of injection fentanyl 1–1.5 mcg/kg was given in patients with VAS >3 at 1st, 2nd, 12, and 24 h. In Group A, 16 patients required rescue analgesia at 1st h, 14 patients at a 2nd h, and 12.7 patients at 12 and 24 h postoperatively. A significant difference in the patients requiring rescue analgesia was observed at 1st, 2nd, 12, and 24 h ($P < 0.05$) postoperatively and need was least in Group ON at 1st h due to the comparatively low

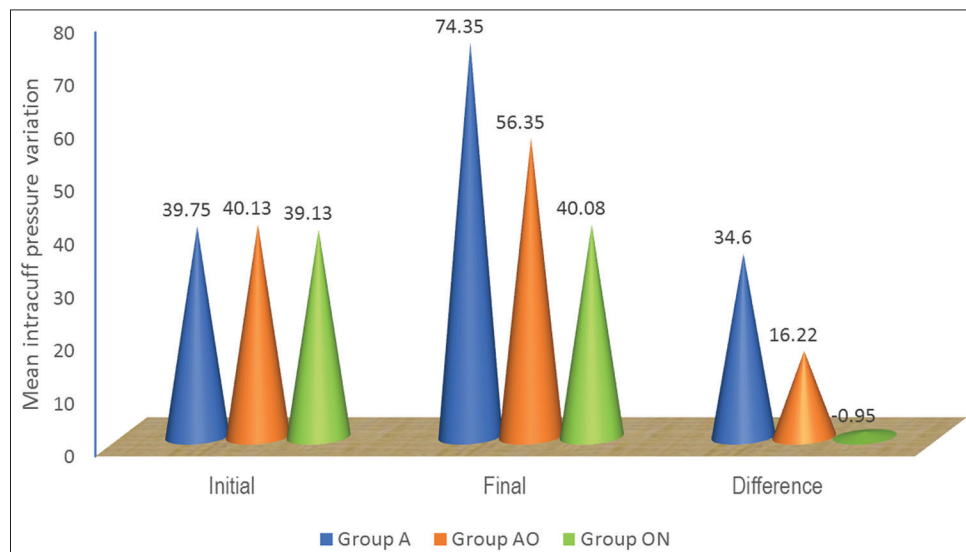


Figure 2: Intracuff volume variation

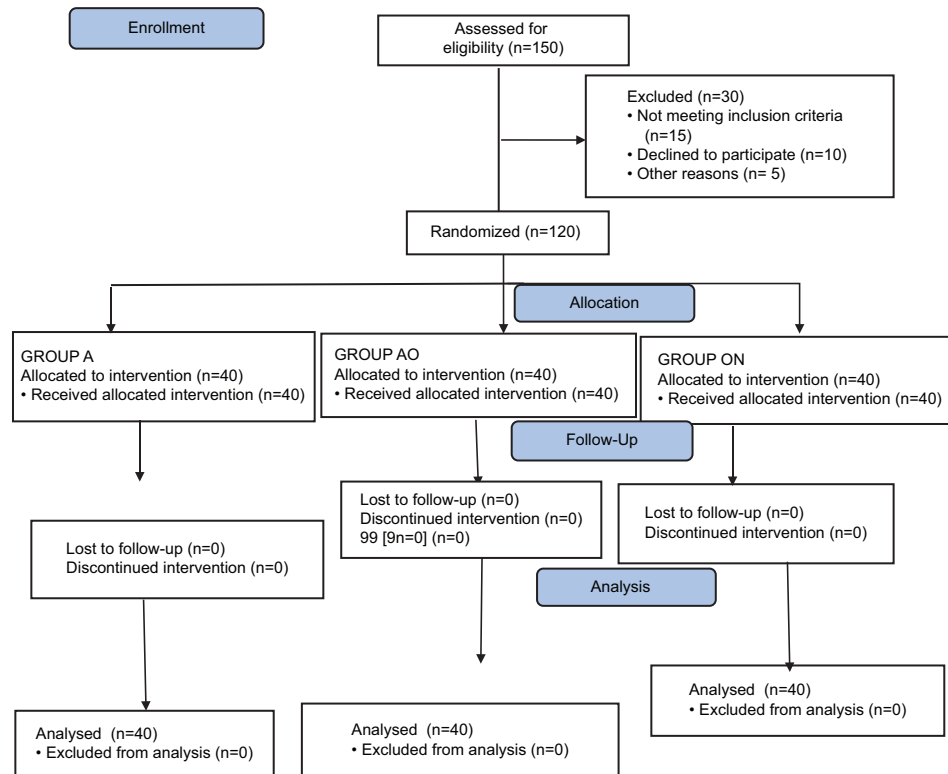


Figure 3: Consort flow diagram

incidence of a sore throat resulting in better pain score in this group.

The unique distinction of our study is that we have also taken into account the potential known confounders for pharyngolaryngeal complications that are the ease of LMA insertion, number of attempts of LMA insertion, use of Guedel's type airway, incidence of laryngospasm, presence of blood on LMA Supreme after removal, and use of pharyngeal suctioning. These univariate predictors of a sore throat were found to be non-significant ($P > 0.05$) and were comparable in all the groups.

LIMITATIONS

Limitations of the study were the inability to assess the concentration of N_2O inside the cuff at the start and end of general anesthesia as it would have given an idea of the concentration of N_2O diffusion into and out of cuff and its effect on emergence phenomenon. Another limitation of our study was the lack of enough number of patients to estimate the impact of intracuff pressure on the incidence of rare and more serious complications of LMA insertion such as recurrent laryngeal nerve palsy, hypoglossal nerve palsy, and lingual nerve palsy. In our study, the duration of

surgery taken was from 90 to 100 min. Hence, due to the uniformity in the duration of surgery in three groups, no conclusion can be drawn regarding the incidence of a sore throat related to the duration of anesthesia. A more detailed study with varying duration of the procedure is required to further substantiate our findings. Furthermore, the correct position of LMA was not confirmed by fiberoptic bronchoscopy.

CONCLUSION

Thus, from our study, we are clearly able to conclude that the rise of cuff pressure with the progression of surgery during general anesthesia ($N_2O:O_2$) is better overcome when LMA Supreme is inflated with $N_2O:O_2$ mixture as compared to air and air: O_2 mixture. The practice of using 50% $N_2O:O_2$ mixture for filling LMA Supreme facilitates an inexpensive method for providing safe and stable cuff pressure during anesthesia and an improved protective effect in preventing post-operative pharyngolaryngeal morbidity in the form of sore throat, dysphagia, and dysphonia. Furthermore, we are able to show a clear benefit from the use of manometer after insertion of LMA Supreme to reduce pharyngolaryngeal complications.

FUTURE REFERENCE

From our study, we can say that N₂O:O₂ mixture provides a safe and stable cuff pressure during N₂O: O₂ anesthesia in comparison to other cuff inflating mediums. Thus,

N₂O: O₂ mixture can be used as an inexpensive medium for cuff inflation and prevention of post-operative laryngopharyngeal morbidities. However, limited data are available, and more future studies need to be done so as to prove the same.

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Spot Urine Uric Acid Level as Early Marker of Kidney Injury in Birth-asphyxiated Newborns

Darshan Kataria¹, Karan Joshi², Jyoti Singh³

¹Post Graduate, Department of Pediatrics, Shyam Shah Medical college and Gandhi Memorial Hospital, Rewa - 486001, Madhya Pradesh, India, ²Associate Professor, Department of Pediatrics, Shyam Shah Medical college and Gandhi Memorial Hospital, Rewa - 486001, Madhya Pradesh, India, ³Professor and Head, Department of Pediatrics, Shyam Shah Medical college and Gandhi Memorial Hospital, Rewa - 486001, Madhya Pradesh, India

Abstract

Introduction: Perinatal asphyxia is a condition defined as hypoxemia, hypercapnia, and acidosis in neonate. Cellular hypoxia leads to increased excretion of uric acid. This study was conducted to assess the feasibility of urine uric acid level for the identification of kidney injury in asphyxiated newborns in first 48 h of life.

Aims and objectives: The aims and objectives of this study were to evaluate the utility of urinary uric acid levels within 48 h of birth as non-invasive and early biochemical means of identifying kidney injury in birth asphyxiated neonates.

Material and methods: Study design - this was a prospective observational cohort study. Settings - this study was conducted at neonatal intensive care unit in tertiary level hospital in Central India. Duration - the study duration was from July 2017 to June 2018. Due to financial constraints, 100 neonates were enrolled and urine sample collected within 48 h of life was evaluated for urine uric acid level. On day 3rd of life, serum creatinine was done. Statistical analysis was performed by Mann-Whitney U-test.

Results: The mean rank of urine uric acid (32.76 vs. 20.29) was significantly higher in term newborns as per asphyxia ($P = 0.005$). The mean rank of urine uric acid (24.13 vs. 15.46) was significantly higher in term asphyxiated as per urine output ($P = 0.031$). However, the mean rank of urine uric acid (23.29 vs. 16.00) was not significant in term asphyxiated newborns as per serum creatinine ($P = 0.08$).

Conclusions: Urine uric acid = 16.10 $\mu\text{mole}/24\text{ h}$ has a sensitivity (61.4%) and specificity (72.2%) for detecting asphyxia in newborns. Similarly, urine uric acid = 22.3 $\mu\text{mole}/24\text{ h}$ has a sensitivity (66.7%) and specificity (91.4%) for detecting kidney injury in asphyxiated newborns.

Key words: Birth asphyxia, Neonatal kidney injury, Urine uric acid

INTRODUCTION

Perinatal asphyxia is a condition where impaired gas exchange leads to hypoxemia, hypercapnia, and acidosis in fetus or neonate. The incidence of perinatal asphyxia is 2–10/1000 term newborns (1–5.6% of all live births). In India, 0.5–1 million cases of birth asphyxia are seen per year and it comes out to be the main cause of mortality (28.8%) and morbidity and chief cause of

stillbirth (45.1%).^[1] Birth asphyxia can involve any organ, i.e., the kidney (50%), heart (25%), or brain (28%) and hence can lead to multisystem failure. As the severity of birth asphyxia increases, the chances of having kidney injury also increase. Brief hypoxia damages cerebral oxidative metabolism leading to an anaerobic glycolysis, yielding only two molecules of adenosine triphosphate (ATP) as compared to 32 molecules of ATP during aerobic conditions.^[2] Lack of ATP and increased cellular destruction will cause an accumulation of adenosine monophosphate and adenosine diphosphate, which will then get catabolized to its constituents of adenosine, inosine, and hypoxanthine.^[3,4] Continuous tissue hypoxia and consequent reperfusion injury will result in hypoxanthine being oxidized to xanthine and uric acid in the presence of xanthine oxidase. Increased excretion of uric acid caused by metabolic changes, reflecting

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Corresponding Author: Dr. Karan Joshi, Associate Professor HIG-75C, Jaiprakash Narayan Nagar, Behind P.K. School, Rewa - 486001, Madhya Pradesh, India. Phone: +91-9425184975. E-mail: darshank300@gmail.com

the cellular hypoxia, has been reported by a number of studies.^[5,6] Urine uric acid: creatinine ratio has been found to be raised in asphyxia in many studies, but no study was relating to urine uric acid with kidney injury. Hence, in this study, we tried to assess the value of urine uric acid in the identification of kidney injury in asphyxiated patients in first 2 days of life.

MATERIALS AND METHODS

Study Design

This was a prospective observational cohort study.

Settings

This study was conducted at neonatal intensive care unit in tertiary level hospital in Central India.

Duration

The study duration was from July 2017 to June 2018.

Inclusion Criteria

Newborns of both sexes irrespective of gestational age or birth weight having:

1. Persistence of Apgar score <3 at 5 min and/or
2. Newborns requiring resuscitation with positive pressure ventilation (PPV) for >1 min before achieving stable spontaneous respiration were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. Newborns with any congenital urological anomaly.
2. Family history of genetic disorder (disease running in families).
3. Newborn who could not be included due to researcher financial constraints.

Initially, 250 newborns came as sample size, but, due to financial constraints, only 100 patients were enrolled in the study (Flow chart).

The urine sample was collected within first 48 h of life with all aseptic precautions and was assessed for uric acid by autoanalyzer using spectrophotometry uricase method. Serum creatinine was analyzed on the 3rd day of life by Jaffe's alkaline picrate method, respectively.

Kidney injury

An abrupt decrease in glomerular filtration with or without underlying structural abnormalities often presents with:

- Reduction in urine output (<1 ml/kg/h for 6 h) and/or
- Serum creatinine value of >1.5 mg/dl irrespective of gestational age and days of life.

Analysis was performed using the commercially available statistical software-IBM SPSS version 22 and Microsoft Excel. The statistical analysis between variables was done using Mann-Whitney U-test. $P < 0.05$ was considered to be statistically significant.

RESULTS

Of 100 neonates enrolled in study, 20 neonates could not complete the study, and hence, 36 normal and 44 asphyxiated neonates completed the study. Of 80 neonates, 55 (68.75%) neonates were male. As per gestational age, 23 (28.7%) neonates were pre-term, 2 (2.5%) were post-term, and 55 (68.8%) were term neonates [Table 1 and Chart 1].

The mean rank of urine uric acid (32.76 vs. 20.29) was significantly higher in term asphyxiated newborns than in term non-asphyxiated newborns ($P = 0.005$). The mean rank of urine uric acid (13.13 vs. 11.40) was not statistically significant in preterms as per asphyxia indicator ($P = 0.561$) [Table 2].

The mean rank of urine uric acid (24.13 vs. 15.46) was significantly higher in term asphyxiated as per urine output ($P = 0.031$) [Table 3]. However, the mean rank of urine uric acid (23.29 vs. 16.00) was not significant in term asphyxiated newborns as per serum creatinine ($P = 0.08$) [Table 4].

Urine uric acid has a sensitivity (61.4%), specificity (72.2%), and PPV (73%) in asphyxiated term newborns. Similarly, urine uric acid has a sensitivity (66.7 %), specificity (91.4%), and PPV (67%) in term asphyxiated newborns as per urine output [Table 5].

DISCUSSION

Perinatal asphyxia is a condition that can lead to alteration in normal functioning of various body organs, but the

Table 1: Distribution of sample as per gestational age and birth asphyxia

Asphyxia indicator	Total number of patients	Pre-term	Term	Post-term
Yes	44	8	34	2
No	36	15	21	0

Table 2: Comparison of urine uric acid in term and preterm neonates as per asphyxia indicator

Asphyxia Indicator	Number of newborns		Urine uric acid ($\mu\text{mole}/24\text{ h}$) mean rank	
	Preterm	Term	Preterm	Term
Yes	8	34	13.13	32.76
No	15	21	11.40	20.29

P value in term=0.005, significant, P value in preterm=0.561, non-significant

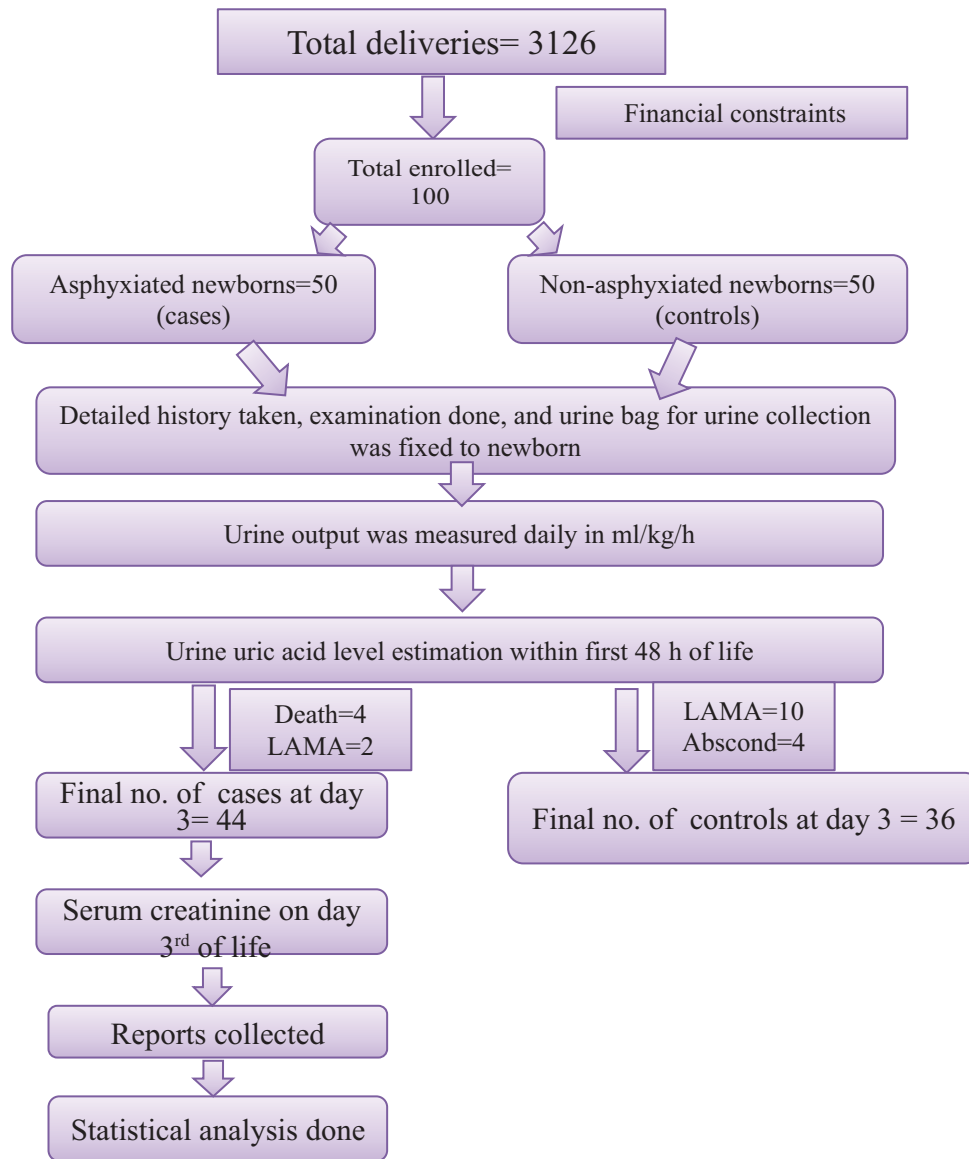


Chart 1: Flow chart sample of newborn

Table 3: Comparison between urine uric acid and term asphyxiated neonates as per urine output

Urine Output (ml/kg/h)	Number of neonates (asphyxiated)	Urine uric acid (μmole/24 h) mean rank
Urine output ≥1 ml/kg/h	26	15.46
Urine output <1 ml/kg/h	8	24.13

Observed $P=0.031$, non-significant

Table 4: Comparison of urine uric acid in term asphyxiated neonates as per serum creatinine

Serum creatinine level (mg%)	Number of neonates	Urine uric acid (μmole/24 h) mean rank
Serum creatinine ≤1.5	27	16.00
Serum creatinine >1.5	7	23.29

P value=0.08, non-significant

most commonly affected organ is the kidney. There are a number of studies available that focused on urine UA/Cr

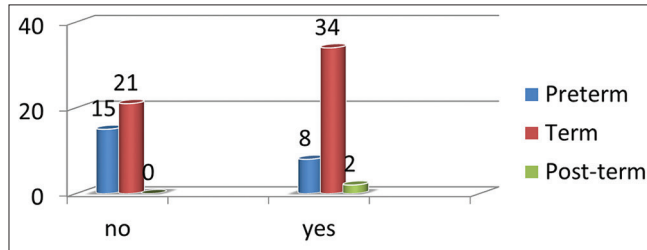
ratio while considering asphyxiated and non-asphyxiated neonates.

In 2008, Basu *et al.*^[7] conducted a case-control hospital-based study over 12 months' time on 31 asphyxiated and 31 normal newborns to see whether urinary uric acid and creatinine ratio can be used as a marker of perinatal asphyxia. It was found that the ratios were significantly higher in cases than controls (3.1 ± 1.3 vs. 0.96 ± 0.54 ; $P < 0.001$) and among asphyxia patients.

Table 5: Comparison of sensitivity and specificity of urine uric acid test

Comparison group (term newborns)	Urine uric acid ($\mu\text{mole}/24\text{ h}$)	Sensitivity (%)	Specificity (%)	PPV (%)
Asphyxiated versus non-asphyxiated newborns	16.10	61.4	72.2	73
Among asphyxiated newborns as per urine output	22.3	66.7	91.4	67

PPV: Positive pressure ventilation

**Figure 1: Asphyxia indicator**

In 2017, Patel *et al.*^[8] conducted a case-control study at a teaching hospital in Central Gujarat. 40 healthy newborns and 40 asphyxiated newborns were collected, and the mean (UA/Cr ratio) (2.75 ± 0.18 vs. 1.78 ± 0.23) was significantly higher in asphyxiated group than in the control group ($P < 0.0001$).

In our study, we observed that $P = 0.005$ for comparing urine uric acid level between term asphyxiated and term non-asphyxiated neonates was less than the calculated P value at 95% confidence interval. Thus, we concluded that urine uric acid was higher in term asphyxiated as compared to term non-asphyxiated newborns.

We observed $P = 0.561$ (95% confidence interval) when comparison was made between urine uric acid in preterm asphyxiated and non-asphyxiated newborns.

There was a significant correlation between high urine uric acid values and term asphyxiated neonates as per urine output (observed $P = 0.031$), but non-significant correlation was seen between high urine uric acid values and term asphyxiated neonates as per serum creatinine values (observed $P = 0.08$).

Urine uric acid value = $16.10 \mu\text{mole}/24\text{ h}$ has a sensitivity (61.4 %) and specificity (72.2%) for detecting asphyxia in newborns. Similarly, urine uric acid value = $22.3 \mu\text{mole}/24\text{ h}$ has a sensitivity (66.7%) and specificity (91.4%) for detecting kidney injury in asphyxiated newborns.

CONCLUSIONS

In our study, urine uric acid was high in asphyxiated term neonates as compared to non-asphyxiated term

neonates. Urine uric acid was not statistically significant in preterm asphyxiated and preterm non-asphyxiated newborns. Urine uric acid was high in term asphyxiated neonates as per urine output but non-significant as per serum creatinine.

Limitations

We could not find a significant correlation between urine uric acid and serum creatinine in term asphyxiated newborns due to:

1. Sample size was small.
2. Time period boundation or shorter duration of the study.
3. It may be likely that the high serum creatinine in some newborn without kidney injury was due to high maternal levels.
4. Normally, a rise in serum creatinine levels is not seen even when 25% kidneys have been damaged.
5. Baseline serum creatinine was not taken.
6. We did not monitor serial rise in serum creatinine levels instead we did only 1 time evaluation.
7. Due to cost factor, urine uric acid estimation of only 80 neonates was possible.

Recommendations

Urine uric acid was higher in term asphyxiated newborns as per urine output. Thus, it is recommended that a larger study with more cohorts needed to validate urinary uric acid as non-invasive and early biochemical means of identifying kidney injury in asphyxiated newborns.

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Efficacy of Nalbuphine and Magnesium Sulfate with Ropivacaine for Quality of Supraclavicular Brachial Plexus Block and Post-operative Analgesia

Joginder Pal Attri¹, Amar Parkash Kataria¹, Surbhi Grag², Anu Sharma³

¹Professor, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India, ²Junior Resident, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India, ³Assistant Professor, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India

Abstract

Background: Adequate post-operative analgesia is the prime duty of anesthesiologist and several adjuvants have been used along with local anesthetics to prolong the duration of brachial plexus block. The present study aimed to compare the effect of nalbuphine and magnesium sulfate as an adjuvant to ropivacaine and ropivacaine alone in nerve stimulator guided supraclavicular brachial plexus block in patients scheduled for orthopedic upper limb surgeries.

Materials and Methods: A total of 90 patients of in the age group of 20–65 years of either sex of the American Society of Anesthesiologists Grade I and II were divided into three groups of 30 each. Group R received 30 ml of 0.75% ropivacaine alone, Group RM received 30 ml of 0.75% ropivacaine plus 150 mg of magnesium sulfate, and Group RN received 30 ml of 0.75% ropivacaine plus 20 mg of nalbuphine. All the groups were compared with respect to onset and duration of sensory and motor blockade, post-operative analgesia, need for rescue analgesia, hemodynamics, and side effects.

Results: Onset of sensory and motor block was earliest in Group RN and was highly significant ($P < 0.001$) when compared to Group R and Group RM. Mean duration of post-operative analgesia was 8.70 ± 1.18 h in Group R, 11.73 ± 1.23 h in Group RM, and 14.40 ± 1.25 in Group RN. Duration of sensory and motor block and post-operative analgesia were significantly prolonged ($P < 0.001$) both in Group RM and Group RN when compared to Group R.

Conclusion: Both nalbuphine and magnesium sulfate are effective adjuvant as compared to ropivacaine alone as they prolong the duration of block as well as post-operative analgesia when used for supraclavicular brachial plexus block. However, nalbuphine has proven to be a better adjuvant as compared to magnesium sulfate as it also results in earlier onset of sensory and motor block and better patient and surgeon satisfaction scores.

Key words: Magnesium sulfate, Nalbuphine, Ropivacaine, Supraclavicular brachial plexus block

INTRODUCTION

Skillful application of peripheral neural blockade broadens the anesthesiologist's range of option for providing optimal anesthetic care. It is preferred technique both in emergency and day care surgeries.^[1] Supraclavicular block

can be used for surgery from midhumerus level down to hand.^[2] Ropivacaine is one of the safest and longest acting among various local anesthetics.^[3] Extension of analgesia into post-operative period is highly desirable by anesthesiologist, thus various adjuvants have been used along with local anesthetics till date. The current study compared nalbuphine and magnesium sulfate with respect to the duration of block and post-operative analgesia.

MATERIALS AND METHODS

After the approval of the Institutional Ethics Committee, Government Medical College, Amritsar, written informed

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Corresponding Author: Dr. Anu Sharma, Department of Anaesthesia, Government Medical College, Amritsar, Punjab – 143001, India.
Phone: +91-9501025275. E-mail: drjpattri@gmail.com

consent was taken from patients. 90 patients of 20–65 years age were selected for the study. These cases were posted for elective surgeries of humerus, fracture both bone forearm, procedures of wrist and hands. They were randomly divided into three groups of 30 each. All the patients belonged to the American Society of Anesthesiologists (ASA) physical Status I and II. Patients in Group R received 30 ml of ropivacaine, in Group RM received 30 ml of 0.75% ropivacaine plus 150 mg of magnesium sulfate, and in Group RN received 30 ml of 0.75% ropivacaine plus 20 mg of nalbuphine for supraclavicular brachial plexus block under guidance of nerve stimulator (NS).

Using a computer-generated number list, patients were allocated one of the three groups. Sealed envelopes of study drugs were prepared. Staff nurse of the operation theater was handed the envelope and was asked to prepare and fill the drugs in syringes. Those were then handed over to the anesthesiologist performing the block. In this manner, both the anesthesiologist and patient were blinded to the study group. The anesthesiologist, usually the resident recording the parameters and observations, was also blinded to the study group.

Patient refusal, pregnant women, morbidly obese, patients with coagulation disorders and/or on anticoagulation therapy, allergy to any of the three study drug, and any anticipated difficulty in regional anesthesia were considered as exclusion criteria.

A day before surgery, a thorough preanesthetic checkup comprising general physical examination and systemic examination of all patients was conducted. On arrival to operation theater, intravenous line was secured with 18 G angiocatheter and the patients were preloaded with 10 ml/kg body weight of Ringer's lactate solution over 15–20 min. Multipara monitors were applied and baseline respiratory rate, pulse rate, noninvasive blood pressure, SPO₂, and electrocardiogram (ECG) were recorded. Injection midazolam 0.04 mg/Kg body weight was given through intravenous route immediately before the procedure.

With the patient in supine position, head end of the bed was elevated at 30°. With the upper arm kept by patient's side, elbow flexed and wrist supinated on patients abdomen, clavicular head of sternocleidomastoid was palpated at its clavicular insertion. The positive electrode of the NS was attached to an ECG electrode and stuck on the ipsilateral arm. The subclavian artery was then palpated and immediately lateral to it, an intradermal wheal was raised with 2% lignocaine (2 mL) using a 24 G needle. A 20 G insulated needle attached to the negative electrode of the NS was then inserted through the skin wheal in a

backward, inward, and downward direction. NS was set to deliver a current of 1.5 mA in the internal mode. Twitching of shoulder muscles was seen on advancing the needle. Needle was further advanced caudal, parallel to the midline, and perpendicular to the clavicle, at a 10° angle. Pectoralis, triceps, wrist, and then finger twitch were seen. Once the desired twitch was obtained at 1.5 mA, amplitude was decreased to 0.4–0.5 mA at frequency of 1–2 Hz, and it was assured that the desired twitch was still present. The goal was isolated twitch of the fingers only. If the desired twitch was not obtained, needle was redirected, keeping in mind that it did not advance >2 cm caudally. When contraction was elicited at a current of 0.5 mA and no twitch with a current of 0.2 mA, needle was fixed and local anesthetic solution injected after negative aspiration for air or blood.

Onset of sensory and motor block was monitored every 5 min till the development of complete surgical anesthesia. Sensory blockade was measured with pin-prick test at a 3-point scale, motor blockade was assessed by technique described by Bromage.

Intraoperatively, respiratory rate, pulse rate, noninvasive blood pressure, and SPO₂ were recorded every 5 min interval till 30 min, every 10 min till 60 min, and then every 15 min till 180 min. Postoperatively, vitals were recorded from monitor every hourly till 8 h, then 2 hourly till 12 h, and then 3 hourly till 24 h.

In case, patient experienced mild pain (visual analog scale [VAS] <3) intraoperative supplementation was given with injection ketamine 0.5–1.0 mg/kg. General anesthesia was given to the patient of failed block or VAS >3 and the case excluded from the study.

Postoperatively, duration of sensory and motor block was assessed every hourly till effect weaned off. Duration of analgesia was measured by interviewing the patients and rescue analgesia was given in the form of injection diclofenac 75 mg i/m when VAS score was >3.

Side effects and complications (procedure or drug related) and if any occurred, were recorded and followed postoperatively.

Operating surgeon was enquired of surgeon satisfaction score (quality of intraoperative muscle relaxation) on a scale of 1–3. Patients were enquired of patient satisfaction score on a scale of 1–5 at 24 h postoperatively.

RESULTS

Duration of analgesia was taken as the outcome measure of interest for sample size calculation. Sample size was

calculated keeping in view at most 5% risk, with minimum 80% power and 5% significance level (significant at 95% confidence interval). Raw data were recorded in a Microsoft Excel spreadsheet and analyzed using the Statistical Package for the Social Sciences (SPSS version 23.00). Continuous data were presented as mean with standard deviation. Categorical data were expressed as percentages. Numerical variables were normally distributed and were compared using Chi-square test for non-parametric data and Student's "t" test for parametric data. P value was then determined to evaluate the level of significance.

90 patients belonging to ASA Grade I and II of age group 20–65 years of either sex admitted in the orthopedic department of Guru Nanak Dev Hospital, Amritsar and scheduled to undergo surgery of the upper limb or hand were recruited. Group R received 30 ml of 0.75% ropivacaine, Group RM received 30 ml of 0.75% ropivacaine plus 150 mg magnesium sulfate, and Group RN received 30 ml of 0.75% ropivacaine plus 20 mg nalbuphine.

As shown in Table 1, the demographic profile consisting of age, weight, and sex was statistically insignificant among the three groups. The three groups were also comparable

Table 1: Demographic profile

Variable	Group R	Group RM	Group RN
Mean age (in years)	37.17±12.87*	36.60±11.91*	40.57±11.23*
Mean weight (in kg)	71.90±12.14*	72.07±10.68*	73.57±6.70*
Sex (M/F)	21/9	20/10	19/11
ASA Grade (I/II)	24/6	21/9	25/5

ASA: American Society of Anesthesiology, *: Data are displayed as mean±standard deviation

Table 2: Onset of sensory and motor block

Onset of Block	Group R	Group RM	Group RN	P value R/RM	P value R/RN	P value RM/RN
Onset of sensory block (mins)	16.90±1.24*	16.24±1.45*	11.17±1.26*	0.08;NS	0.00;HS	0.00;HS
Onset of motor block (mins)	19.23±1.33*	18.73±1.26*	12.97±1.22*	0.07;NS	0.00;HS	0.00;HS

NS: Non-significant, HS: Highly significant, *: Data are displayed as mean±standard deviation

Table 3: Duration of sensory and motor block

Duration of Block	Group R	Group RM	Group RN	P value R/RM	P value R/RN	P value RM/RN
Duration of sensory block (hrs)	7.93±1.14*	10.83±1.18*	13.43±1.19*	0.00;HS	0.00;HS	0.00;HS
Duration of motor block (hrs)	7.14±1.16*	9.93±1.20*	11.33±1.24*	0.00;HS	0.00;HS	0.00;HS

HS: Highly significant, *: Data are displayed as mean±standard deviation

Table 4: Duration of surgery, post-operative analgesia, and number of rescue analgesia

Variable	Group R	Group RM	Group RN	P value R/RM	P value R/RN	P value RM/RN
Duration of surgery (mins)	92.53±21.85*	91.87±19.79*	93.37±18.55*	0.45;NS	0.38;S	0.44;NS
Duration of post-operative analgesia (hrs)	8.70±1.18*	11.73±1.23*	14.40±1.25*	0.00;HS	0.00;HS	0.00;HS

NS: Non-significant, S: Significant, HS: Highly significant, *: Data are displayed as mean ± standard deviation

with respect to ASA physical status and type of surgery performed.

As shown in Table 2, mean onset of sensory block was 16.90 ± 1.24 min, 16.24 ± 1.45 min, and 11.17 ± 1.26 min in Groups R, RM, and RN, respectively. Mean onset of motor block was 19.23 ± 1.33 min in Group R, 18.73 ± 1.26 min in Group RM, and 12.97 ± 1.22 min in Group RN. Onset of block was comparable in Group R and Group RM, whereas Group RN showed significant early onset as compared to Group R and Group RM.

As shown in Table 3, mean duration of sensory block was 7.93 ± 1.14 h, 10.83 ± 1.18 h, and 13.43 ± 1.19 h in Groups R, RM, and RN, respectively. The mean duration of motor block was 7.14 ± 1.16 h, 9.93 ± 1.20 h, and 11.33 ± 1.24 h in Groups R, RM, and RN, respectively. The difference in the duration of block was found to be statistically highly significant ($P < 0.001$) among Groups RM/R, RN/R, and RN/RM.

As shown in Table 4, mean duration of surgery in Group R was 92.53 ± 21.85 min, in Group RM was 91.87 ± 19.79 min, and in Group RN was 93.37±18.55 min. The difference in the three groups was found to be statistically insignificant ($P > 0.05$). The duration of post-operative analgesia was 8.70 ± 1.18 h, 11.73 ± 1.23 h, and 14.40 ± 1.25 h in Groups R, RM, and RN, respectively. The results showed statistically highly significant ($P < 0.001$) difference within Groups RM/R, RN/R, and RN/RM.

As shown in Figure 1, the mean number of rescue analgesic doses in 24 h was 2.73 ± 0.52 in Group R, 2.47 ± 0.57 in Group RM, and 2.23 ± 0.43 in Group RN.

Statistically significant ($P < 0.05$) difference was found in Groups RM/R and RN/RM. Furthermore, statistically highly significant ($P < 0.001$) difference was found in Group RN versus Group R.

As shown in Figure 2, the VAS score was significantly better in Group RM when compared to Group R as well as in Group RN in comparison with both the other groups being Group R and Group RM.

As shown in Table 5, mean patient satisfaction score in Group R was 3.67 ± 0.55 , in Group RM was 4.07 ± 0.91 , and in Group RN was 4.53 ± 0.68 . The mean surgeon satisfaction score was 2.13 ± 0.35 , 2.33 ± 0.48 , and 2.57 ± 0.50 in Groups R, RM, and RN, respectively. The results were statistically significant between Groups RM/R and RN/RM. Results were statistically highly significant between Groups RN/R.

DISCUSSION

Supraclavicular block, being most commonly used approach for brachial plexus block, has wide variety of implications in upper limb orthopedic surgeries. Minimal requirement of drugs

and equipment along with prolonged post-operative analgesia is among the various attractions. Local anesthetics provide excellent intraoperative conditions, but their short duration of action necessitates the use of adjuvants so as to minimize the use of multiple intravenous analgesics postoperatively.

Magnesium, the fourth most abundant cation in the body, is involved in several physiological processes, majority based on voltage-dependent inhibition of calcium influx into cell along with non-competitive antagonism of N-methyl-D-aspartate receptors.^[4] Magnesium sulfate also inhibits catecholamine release from adrenal and peripheral nerve endings, thus resulting in sympathetic blockade.^[5] Above properties prompted the use of magnesium as an additive to local anesthetics. Magnesium sulfate is routinely used for several therapeutic effects such as antihypertensive, antiarrhythmic, and bronchodilator. It has been used in various anesthetic techniques such as spinal,^[6] epidural,^[7] intravenous regional anesthesia,^[8] and various nerve blocks such as peribulbar and paravertebral.

Demonstration of opioid receptors outside the central nervous system led to studies investigating the efficacy of

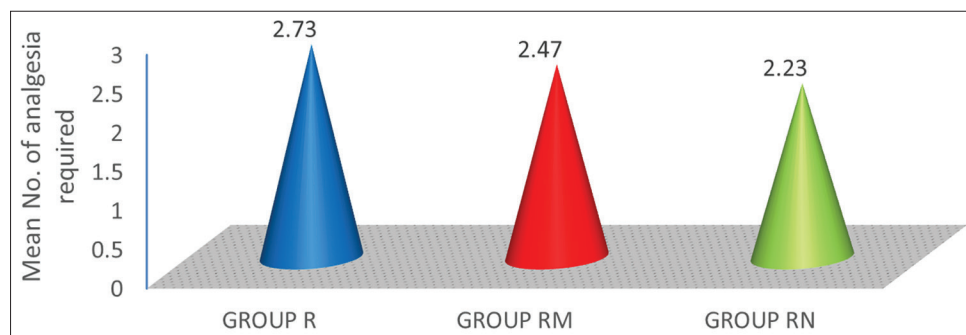


Figure 1: Mean of the total number of doses of rescue analgesia

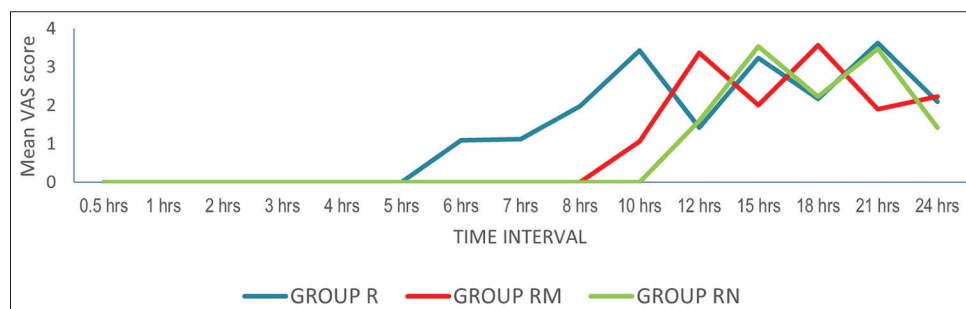


Figure 2: Mean of intra- and post-operative visual analog scale score

Table 5: Patient and surgeon satisfaction score

Variable	Group R	Group RM	Group RN	P value R/RM	P value R/RN	P value RM/RN
Patient satisfaction score	3.67±0.55*	4.07±0.91*	4.53±0.68*	0.02;S	0.01;S	0.00;HS
Surgeon satisfaction score	2.13±0.35*	2.33±0.48*	2.57±0.50*	0.03;S	0.04;S	0.00;HS

S: Significant, HS: Highly significant, *: Data are displayed as mean±standard deviation

combining opioids and local anesthesia for peripheral nerve blocks.^[9] Nalbuphine, a synthetic opioid with agonism on κ (kappa) receptor and antagonism on μ (mu) receptor, is equipotent to morphine as analgesic. It additionally possesses ceiling effect on respiratory depression and cardiac stability. Along with the enhancement of μ opioid-based analgesia, nalbuphine also mitigates μ opioid side effects.^[10] It has been used extensively as sole analgesic as well as along with local anesthetics.

In search of an ideal adjuvant for local anesthetics, the present study was conducted to compare block characteristics and side effects, if any with magnesium sulfate and nalbuphine.

The dose of ropivacaine used in this study was 30 ml of 0.75% which is well within the maximum recommended dose of ropivacaine as stated by Tripathi *et al.*^[11] Dose of magnesium and nalbuphine was also chosen as per recommended and used in of previous studies.^[12,13]

The hemodynamic parameters monitored in the study were respiratory rate, systolic blood pressure, diastolic blood pressure, SpO₂, and pulse rate. All the monitored hemodynamic parameters were stable throughout surgery.

In this study, the onset of sensory block was comparable in magnesium group, whereas significant shortening was observed in nalbuphine group when compared with control group. Similarly, highly significant difference in onset of motor block was seen in nalbuphine group (12.97 ± 1.22 min) as compared to both control group (19.23 ± 1.33 min) and magnesium group (18.73 ± 1.26 min).

Statistically highly significant prolongation in the duration of sensory and motor block was seen both in group magnesium and nalbuphine as compared to control group. Nalbuphine group also showed highly significant prolongation in the duration as compared to magnesium. Similar were the results for the total duration of analgesia.

Our results were concordant with Haghighi *et al.*^[14] and Lee *et al.*^[15] who observed that addition of magnesium sulfate to local anesthetics does not affect the onset of sensory and motor block, whereas it significantly prolongs the duration of sensory and motor block. Lee *et al.* also observed significant prolongation of the total duration of analgesia with magnesium.

Madan *et al.*^[16] observed that addition of nalbuphine results in significantly early onset and prolongation in the duration of sensory and motor block. Das *et al.*^[17] and Abdelhaq and Elramely^[13] also documented that nalbuphine significantly lengthens the duration of sensory and motor block. Das *et al.* also evaluated that addition of nalbuphine to local anesthetic results in significant prolongation of time to

request of the first analgesic.

In the present study, VAS score was significantly lower both with magnesium sulfate and nalbuphine as compared to ropivacaine alone. As the duration of analgesia was significantly higher with nalbuphine when compared to magnesium sulfate, VAS score was significantly lower as well. These results correlated well with the study of Reddy *et al.*,^[18] who concluded that VAS score was significantly lower at several time intervals with magnesium as additive. For Group RN as well, our results were in concordance with Das *et al.*,^[17] who found significantly lower VAS score with nalbuphine.

In the present study, significantly less number of rescue analgesic injection was required in first 24 h in magnesium as well as nalbuphine group as compared to control group. Mukherjee *et al.*^[12] and Das *et al.*^[17] also found that the number of rescue analgesic injections in the form of diclofenac sodium is significantly less with magnesium sulfate and nalbuphine added to local anesthetic, respectively.

Vascular puncture was seen in 1 (3.33%) patient in Group R, 2 (6.67%) patients in Group RM, and 2 (6.67%) patients in Group RN with an overall percentage of 5.56%. In all these cases, the needle was withdrawn and redirected. The drug was then injected after negative aspiration. Signs and symptoms associated with intravascular injection were not encountered in any of the five patients and the block was successful. Three patients in Group R, two in Group RM, and two in Group RN suffered from nausea. No active intervention was required for the same except increasing the transfusion rate of fluid. Two patients in Group R, one in Group RM, and one in Group RN suffered from vomiting. All the patients were managed with slow intravascular injection ondansetron. A total of two patients experienced mild pruritus, one in Group R and Group RM each. It needed no active management and was self-limiting. Two patients in Group R, two in Group RM, and three in Group RN experienced mild sedation. None of the patients exhibited respiratory distress, arrhythmias, or any other serious complication such as pneumothorax, hoarseness, or neuropathy. All the patients were otherwise hemodynamically stable.

Both magnesium sulfate and nalbuphine displayed significantly better patient and surgeon satisfaction scores as compared to ropivacaine alone, whereas nalbuphine also had significantly better scores than magnesium sulfate.

CONCLUSION

Addition of both magnesium sulfate and nalbuphine to ropivacaine prolongs both sensory and motor blockade duration as compared to ropivacaine alone. Nalbuphine

has a number of beneficial effects such as earlier onset of sensory and motor block which may be desirable in a busy operation room schedule and provides longer duration of sensory and motor block and post-operative analgesia, better patient and surgeon satisfaction scores. Therefore, we concluded that nalbuphine is a better adjuvant than magnesium sulfate in relation to supraclavicular brachial plexus block. The prime limitation of the present study was the unavailability of ultrasonography (USG), thus inability to perform USG-guided supraclavicular brachial plexus block.

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Real-World Efficacy and Safety of Novel Second-Generation Antihistamine “Bepotastine” in Management of Pruritus Associated With Skin Disorders

G. A. Deshmukh¹, D. S. Dhoot², H. M. Mahajan¹, H. Barkate³

¹Assistant Manager, Medical Services, Glenmark Pharmaceuticals Ltd., Mumbai, Maharashtra, India, ²Senior Manager, Medical Services, Glenmark Pharmaceuticals Ltd., Mumbai, Maharashtra, India, ³Vice President, Medical Services, Glenmark Pharmaceuticals Ltd., Mumbai, Maharashtra, India

Abstract

Introduction: Pruritus is one of the most common symptoms of skin diseases affecting quality of life. H1 antihistamines are most commonly used drugs for pruritus management. Bepotastine, a novel second-generation antihistamine with antagonistic effect on leukotriene B4 and substance P, was recently approved in India. We conducted this observational survey to assess effectiveness and safety of bepotastine in the management of pruritus in real-world setting.

Materials and Methods: Prevalidated survey booklets were given to select dermatologists to collect information on the efficacy and safety of bepotastine. Data were collected regarding demographic details, pruritus score, medication effectiveness, and sedation potential of bepotastine. Clinical assessment was done by analyzing the change in pruritus score at day 7–14. Patient satisfaction was assessed by analyzing medication effectiveness and sedation on Likert scale.

Results: A total of 50 dermatologists completed the survey involving 500 patients. 440 completed survey questionnaire forms were included for further evaluation. There was a significant reduction in mean pruritus score from 2.93 at baseline to 1.49 ($P < 0.05$) at day 7 and 0.56 at day 14 ($P < 0.05$). On analyzing the severity of pruritus, 75% and 91% of patients with mild pruritus showed complete relief at days 7 and 14, respectively, whereas 65% and 84% of patients with moderate pruritus showed complete relief at days 7 and 14, respectively. Similarly, in patients with severe pruritus, 48% and 83% of patients showed complete relief at days 7 and 14, respectively. No improvement was seen on day 7 in patients with very severe pruritus; however, 73% of patients showed complete relief by day 14. All the patients were highly satisfied with treatment as reflected by medication effectiveness score and sedation score. 4.7% of the patients complained of mild drowsiness.

Conclusion: This real-world data indicate that bepotastine was efficacious and safe in the management of pruritus associated with skin diseases.

Key words: Bepotastine, Pruritus, Real world

INTRODUCTION

Pruritus is an unpleasant sensation associated with desire to scratch. Pruritus is most frequent symptom associated with multiple dermatological disorders.^[1] Even though not life threatening, pruritus has a significant impact on

patient's quality of life (QoL), leading to disturbance in sleep, anxiety, attention, etc. In addition, many systemic diseases are also known to be associated with pruritus and further incapacitating nature of this condition.^[1]

Histamine plays a very significant role in pathogenesis of pruritus associated with skin diseases.^[1,2] Histamine through H1 receptors acts on blood vessels and sensory nerves to produce a flare and wheal response that contributes to pruritus and modulates inflammatory conditions.^[3,4] Due to significant role of histamine, H1 antihistamines are mainstay of therapy in the management of pruritus associated with skin diseases.^[5] The use of non-sedating

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Corresponding Author: Dr. Gaurav Deshmukh, Medical Advisor, Medical Services, Glenmark Pharmaceuticals Ltd.

second-generation H1 antihistamines is preferred to that of older, first-generation H1 antihistamines, due to lack of adverse effects such as sedation and anticholinergic effects that are commonly seen with the older agents.^[5]

Even though antihistamines are mainstay therapy in the management of pruritus, their effectiveness is limited in many patients.^[6] Furthermore, not every patient with pruritus shows characteristic histaminic response of wheal and flare.^[6,7] This points toward the important role of mediators other than histamine in pathogenesis of pruritus. Multiple studies have shown that, in addition to histamine, mediators such as leukotriene B4, platelet-activating factor (PAF), and substance P also play an important role in pathogenesis of pruritus.^[8-14]

Due to these reasons, antihistamine that also suppresses the other mediators may be of benefit in the management of pruritus;^[15] hence, there was a need of novel antihistamine. Bepotastine besilate is one of such novel second-generation, non-sedating antihistamine.^[15,16] Along with selective action on H1-receptor, bepotastine also has multiple additional actions such as mast cell stabilization, inhibition of eosinophilic infiltration, inhibition of leukotriene B4, IL-5, PAF, and substance P, all of which may contribute to its antipruritic effects.^[15-21]

Even though bepotastine was approved in Japan, in 2002, for the management of pruritus and urticaria, it was recently approved in India, in 2017; hence, there is a need of data of the effectiveness and safety of bepotastine in Indian patients in real-world setting. We conducted this retrospective survey to evaluate the effectiveness and safety of bepotastine in the management of pruritus associated with skin disorders in real-world setting.

MATERIALS AND METHODS

This was a multicenter, open-label, observational, retrospective questionnaire-based survey designed primarily to assess the efficacy and safety of bepotastine in the management of pruritus associated with skin diseases. The survey was conducted in compliance with the Declaration of Helsinki and current good clinical practice guidelines.

Dermatologists involved in the management of pruritus were identified through “SCRIP intelligence” database. Among these, 50 doctors who were maintaining the patients’ clinical record were selected across four zones (east, south, west, and north) each by convenient sampling to have uniform representation of population across country.

Each dermatologist was given prevalidated survey questionnaire booklet containing survey forms to evaluate the effectiveness and safety of bepotastine. The questionnaire’s booklets were collected after the end of survey period and data from all the patients were assessed to evaluate the medication effectiveness and sedation potential of bepotastine. Each patient was given bepotastine 10 mg twice daily and evaluated at baseline (day 0), day 7, and day 14. The total survey period was from July 2017 to September 2017.

Patients >18 years of age with presenting with pruritus, redness, or wheals due to any dermatological condition and keeping regular follow-up with dermatologists were included in the survey. Patients with severe dermatological conditions and patients who changed their therapy or who underwent any dermatological procedures during survey period were excluded from final analysis.

Effectiveness Evaluation

Effectiveness assessment was done by analyzing the responses from both patients (patients’ satisfaction) and investigator at baseline, day 7, and day 14. Investigator assessment was done by analyzing pruritus activity score on 5-point pruritus activity scale ranging from complete absence of pruritus to very severe pruritus. Similarly, patients’ satisfaction with the treatment was assessed by analyzing medication effectiveness score and sedation score. Effectiveness of bepotastine in reducing patients’ pruritus was analyzed on 5-point Likert scale ranging from complete improvement in symptoms to no improvement at all. Sedation profile of the drug was evaluated by the assessment of the degree of sleepiness on visual analog scale (VAS) ranging from no sleepiness (0) to extreme sleepiness (10).

Safety Evaluation

Safety assessment was done by analyzing all the reported adverse events during the survey period.

RESULTS

A total of 500 survey forms were collected from 50 dermatologists at the end of 3 months. Of 500, 60 forms were incomplete and, hence, were not considered for further evaluation. Data from 440 patients were considered for final assessment. The average age of the patients was 36.6 years, of total 440 patients evaluated, 62.95% ($n = 277$) were female while 37.05% ($n = 163$) were male patients. In this survey, 27 (6%) patients were having mild pruritus, 114 (26%) patients were having moderate pruritus, 167 (38%) patients were suffering severe pruritus, and remaining 132 (30%) patients were complaining of very severe degree of pruritus.

After treatment with bepotastine 10 mg twice daily, there was a significant reduction in mean pruritus score from 2.93 at baseline to 1.49 ($P < 0.05$) at day 7 and 0.56 at day 14 ($P < 0.05$) [Figure 1].

On further analyzing the data with respect to severity of pruritus, similar results were observed. In patients with mild pruritus, 75% ($n = 20$) and 91% ($n = 25$) of patients showed complete relief at days 7 and 14, respectively. In patients with moderate pruritus, 65% ($n = 74$) achieved complete relief on day 7 while 84% ($n = 96$) of patients achieved complete relief from pruritus on day 14. Similarly, in patients with severe pruritus, 48% ($n = 80$) and 83% ($n = 139$) of patients showed complete relief at days 7 and 14, respectively. In patients complaining of very severe pruritus, no improvement in symptoms was seen on day 7; however, 73% ($n = 96$) of patients showed complete relief by day 14 [Figure 2].

Patients were highly satisfied with the treatment as reflected by their medication effectiveness score and sedation profile. On day 7, 31% ($n = 136$) of patients showed complete or significant improvement in their pruritus symptoms. Duration of treatment was seen to have an effect on symptomatic relief obtained, with 82% ($n = 361$) of patients showing complete or significant improvement in their pruritus on day 14. In this survey, mild sedation on sedation scale was reported by 4.7% ($n = 21$) of patients due to bepotastine. Gastrointestinal upset or nausea was seen in 15 patients while two patients complained of headache. All

adverse events were mild, resolved spontaneously and did not require bepotastine discontinuation or any additional treatment.

DISCUSSION

Pruritus is one of the most common symptoms associated with various dermatological disorders with significant impact on patient's QoL that causes various problems related to sleep, anxiety, attention, etc.^[1] Histamine plays a very significant role in pathogenesis of pruritus associated with skin diseases.^[1,2] Hence, antihistamines, especially the second-generation antihistamines due to their better safety profile, are mainstay of therapy in the management of pruritus.^[5]

Even though antihistamines are mainstay therapy in the management of pruritus, their effectiveness is limited in many patients. Multiple studies have shown that in addition to histamine mediators such as leukotriene B₄, PAF, and substance P also play an important role in pathogenesis of pruritus. This further limits the effectiveness of antihistamines. Hence, there was a need of novel antihistamine which along with histamines also has additional effect on other mediators responsible for pruritus.^[6-14]

Oral bepotastine is a highly selective second-generation histamine H₁ receptor antagonist. In multiple *in vitro* and *in vivo* studies, it has shown long-lasting, dose-dependent antihistaminic and antiallergic activity.^[15] Along with antihistaminic activity, bepotastine has been associated with mast cell stabilization, leukotriene B₄ inhibition, and suppression of nitric oxide production induced by substance P which may contribute to its antipruritic and anti-inflammatory actions.^[15-17] In addition, bepotastine is also associated with decrease in levels of PAF and antigen-induced eosinophilic infiltration as well as suppression of various pro-inflammatory cytokines such as interleukin-5 and interleukin-1 α which may further contribute to its antipruritic activity.^[18-21]

Kawashima *et al.* in their Phase 3 trial with bepotastine 20 mg/day showed significant improvement in itching and cutaneous eruption on day 7 compared to placebo. No significant difference in adverse event rate between bepotastine and placebo was reported by the authors.^[22]

Ishibashi *et al.* in their Phase 3 study reported that bepotastine was as effective as terfenadine in the management of patients with chronic urticaria. Similar number of bepotastine and terfenadine recipients had an improvement from baseline of two or more grades in itching (74.0% vs. 73.7%) or eruption (69.5% vs. 68.6%).^[23]

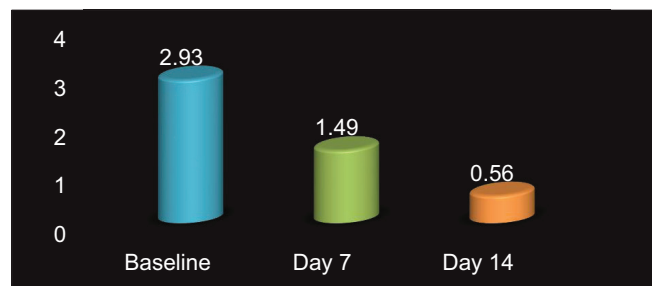


Figure 1: Change in mean pruritus score with bepotastine 10 mg twice daily

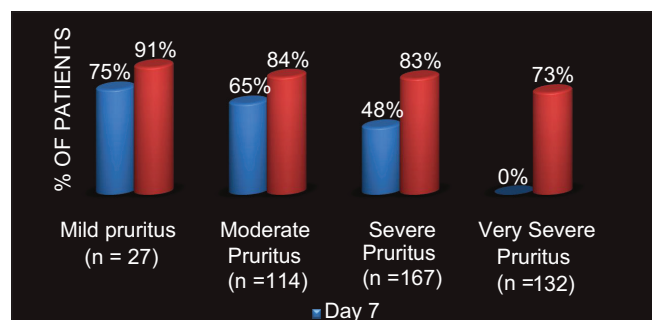


Figure 2: Percentage of patients with complete relief from pruritus according to the intensity of pruritus

Narayan *et al.* in their study on 3415 patients reported significant improvement in symptoms of pruritus, erythema, or wheals in >80% of patients with bepotastine 20 mg/day.^[24]

In post-marketing surveillance study, Kawashima *et al.* reported satisfactory or almost satisfactory rating in 84.3% ($n = 549$) of patients with chronic urticaria and 92.7% ($n = 1101$) of patients with pruritus associated with skin diseases.^[25]

In a 2-week trial in patients with pruritus associated with skin diseases, Ishibashi *et al.* reported global improvement rating of moderate or greater in 64.7% of patients. In the same study, 62.2% of patients reported treatment utility of extremely useful or useful. 70–80% of patients reported significant improvement in intensity of pruritus from moderate or severe at baseline to mild, slight, or no symptoms.^[26]

Horikawa *et al.* and Takahashi and Iizuka in two separate studies reported significant reduction in VAS score for pruritus and scratch mark after 2 weeks in patients of senile pruritus or pruritic skin conditions.^[27,28]

The results of the current survey are in accordance with published studies as described above,^[22-28] establishing real-world efficacy and safety of bepotastine in the management of pruritus associated with skin disorders. In our survey, there was significant improvement in mean pruritus score compared to baseline on day 7 as well as day 14. Similarly, more than 80% of patients showing complete or significant improvement in their symptoms profile. Sedation of mild degree was seen in only 4.7% of patients in our survey which is in accordance with published literature.^[22-28] Overall, adverse event rate has been very low showing good real-world tolerance for bepotastine.

This survey has certain limitations. Due to the observational and retrospective design of the survey, the possibility of selection bias cannot be ruled out. Coprescribed drugs were not taken into consideration which may have impacted the final outcome. Long-term, comparative, control studies to address the shortcomings of the present study are warranted.

CONCLUSION

Bepotastine is a new non-sedative and effective treatment option for patients having cutaneous conditions with pruritis and other symptoms such as erythema, wheal, and angioedema. Adverse event rates are low and if present, are mild, without usually needing treatment discontinuation. This real-world data indicate that bepotastine was

efficacious and safe in the management of pruritus associated with skin diseases.

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Comparison of Intrathecal Nalbuphine with Different Doses of Bupivacaine in Infraumbilical Surgeries

Joginder Pal Attari¹, Manjit Singh², Brij Mohan², Rohit Kumar³

¹Professor, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India, ²Associate Professor, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India, ³Junior Resident, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India

Abstract

Background: Subarachnoid block (SAB) is a widely used regional anesthetic technique for infraumbilical surgeries.

Aims: The study was conducted to compare intrathecal nalbuphine with different doses of bupivacaine in infraumbilical surgeries with respect to hemodynamic changes, side effects, onset and duration of sensory as well as motor blockade, and duration of analgesia.

Materials and Methods: After obtaining Institutional Ethics Committee approval, a prospective study was conducted on 90 patients belonging to American society of Anesthesiology Grades I and II, aged 18–60 years and scheduled for infraumbilical surgeries using SAB. Three Groups A, B, and C each with 30 patients were given 0.8 mg nalbuphine along with 10, 12.5, and 15 mg of hyperbaric bupivacaine, respectively.

Statistical Analysis: Chi-square and unpaired “t” test and following results were observed.

Results: Mean onset of sensory block until T10 dermatome was 2.59 ± 0.43 , 2.49 ± 0.30 , and 2.44 ± 0.33 min while its total duration was 102.23 ± 5.81 , 110.10 ± 8.3 , and 136.33 ± 6.15 min in Groups A, B, and C. Maximum motor blockade was achieved in 7.55 ± 0.57 , 7.41 ± 0.51 , and 7.30 ± 0.62 min and mean duration of motor block was 145.27 ± 11.80 , 155.00 ± 11.58 , and 188.00 ± 10.27 min in Groups A, B, and C. Mean time of total duration of the analgesia in Groups A, B, and C was 240.83 ± 36.34 , 413.77 ± 68.60 , and 719.90 ± 99.93 min. Patients in Group C had hypotension at 8th and 10th min intraoperatively while other parameters and side effects were non-significant.

Conclusion: About 0.8 mg of nalbuphine when combined with 12.5 mg of hyperbaric bupivacaine had optimum duration of analgesia and sensory block with lesser hemodynamic alterations and side effects.

Key words: Bupivacaine, Intrathecal, Nalbuphine

INTRODUCTION

Pain as described by International Association for the study of pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”^[1] Surgical pain may

occur either due to direct tissue injury such as dissection, cutting, incision or inflammation of tissue, or associated nerve injury. The nociceptive pain is caused by stimulation of sensory nerve fibers.^[2] The American Board of Anesthesiology lists “relief and prevention of pain during surgical, obstetric, therapeutic, and diagnostic procedures” as one of the essential components of the specialty. The maximum surgical stress response occurs during the post-operative period and it affects almost every part of the body systems. Previously general anesthesia was the only anesthetic modality available for all types of surgeries irrespective of site and duration of surgery. It has its several disadvantages like multiple drug usage with their adverse effect on the body, loss of consciousness, and longer

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Corresponding Author: Dr. Manjit Singh, Department of Anaesthesia, Government Medical College, Amritsar – 143001, Punjab, India.
Phone: +91-9501025275. E-mail: jpattri12@yahoo.co.in

duration of hospital stay.^[3,4] Regional anesthesia came out as a boon to anesthesia with fewer side effects, less drug usage, better patient compliance, maintenance of consciousness, spontaneous respiration, and better post-operative period with good analgesia. The drawbacks of spinal anesthesia are its shorter duration of action with limited post-operative analgesia when it is performed only with local anesthetics. This problem can be nullified by adding various adjuvants such as opioids, alpha 2-adrenoreceptor agonist, epinephrine, and ketamine to local anesthetics. Intrathecal opioids are most commonly used adjuvants. They improve the quality of neuraxial anesthesia in terms of decreased post-operative pain, prolonged sensory and motor blockade, and maximum post-operative analgesia.^[5] Nalbuphine is a semi-synthetic opioid with κ agonistic and μ antagonistic action. It belongs to phenanthrene series. Its analgesic actions are due to agonistic activity at opioid kappa (“ κ ”) receptors. Its affinity to κ receptors leads to analgesia, sedation, and cardiovascular stability with minimal respiratory depression.^[6,7] The present study was done to compare intrathecal nalbuphine with different doses of hyperbaric bupivacaine in infraumbilical surgeries with respect to hemodynamic changes, side effects, onset and duration of sensory as well as motor blockade, and duration of analgesia.

MATERIALS AND METHODS

This randomized controlled prospective study was done on 90 patients belonging to American Society of Anesthesiology (ASA) Grades I and II, aged 18–60 years of either sex and posted for infraumbilical surgeries, using subarachnoid block (SAB) after obtaining informed and written consent from patients themselves and approval from the Institutional Ethics committee, Government Medical College, Amritsar. The patients were randomly divided into three Groups A, B, and C each having 30 patients and were given 0.8 mg intrathecal nalbuphine along with 10, 12.5, and 15 mg of hyperbaric bupivacaine and 1.2, 0.7, and 0.2 ml of 0.9% normal saline, respectively. A statistician was consulted to calculate the sample size taking account of the duration of analgesia, sensory and motor block, hemodynamic stability, and side effects. Power of study was >85%. All the patients were kept fasting for 6 h before surgery. In the operation theatre, an intravenous line was secured on one arm of the patient with a 20 G intravenous cannula, and pre-loading was started with Ringer's lactate at 10 ml per kg body weight. Monitors such as automated noninvasive blood pressure, pulse oximetry, and electrocardiography (ECG) were attached. Injection midazolam 0.03 mg/kg intravenously was given to all the patients before turning to the left lateral/right lateral decubitus or sitting position for the application of

spinal block. Under all aseptic conditions, the back of the patient was painted with povidone-iodine solution, the area was draped with sterile towels, L₃₋₄ intervertebral space was identified, and a skin wheal was raised by 26 gauge needle with 2% xylocaine. Quincke spinal needle No. 23 was introduced into subarachnoid space using a midline approach. After aspiration of cerebrospinal fluid, the patient was given one of the study drugs intrathecally according to the random number chart. After injecting the drug, spinal needle was taken out and the patients were immediately put in supine position and O₂ was given 5 L/min of through an oxygen inhalational mask. The same anesthesiologists performing the SAB recorded the intraoperative data and follow the patient postoperatively until discharged from post-anesthesia care unit.

Assessment

In our study, sensory and motor blockade was checked every 2 min for first 15 min by pinprick method using 27 G hypodermic needle and modified Bromage scale, respectively. The time of onset of the sensory block was taken as the time interval from injection of local anesthetic intrathecally to loss of pinprick sensation up to T10 dermatome while the duration of sensory block was taken as time to two segment regression from maximum sensory level. Bromage scale three was taken as time to complete motor block. Surgery was allowed to proceed only when full surgical anesthesia had developed. Sensory and motor blockade was not checked once the surgery was started, only pulse rate, heart rate, respiratory rate, non-invasive systolic and diastolic blood pressure, SpO₂, and ECG were monitored, thereafter. In the post-operative period, sensory and motor blockade was checked half hourly for next 3 h, every hourly for next 9 h and then, every 3 hourly until 24 h. Bradycardia (which was defined as heart rate <60 bpm) was treated with intravenously injection atropine sulfate 0.3 mg. Hypotension (defined as fall in systolic blood pressure <20% less than baseline value) was treated with intravenous ephedrine as per required and additional ringer's lactate solution. Continuous monitoring of pulse rate, heart rate, respiratory rate, non-invasive systolic and diastolic blood pressure, SpO₂, and ECG was done for hemodynamic response perioperatively. After SAB, the readings were recorded at 2 min for the first 10 min, then every 5 min up to 30 min, every 15 min up to 120 min, half-hourly up to 180 min and thereafter hourly until the 12 h of surgery in all three groups. Pain assessment was done using visual linear analog scale (VAS)^[8] and sedation was analyzed using Ramsay sedation scale.^[9] The VAS interpretations were explained 1 day before the operation to all patients taken for study to determine the quality of analgesia in the post-operative period. This was carried out with 0–10 cm line. The first end mark “0” means “no pain” and the end marked “10” means “severe pain.” The patients were asked to mark

Table 1: Demographic profile

Parameters	Group A	Group B	Group C	A/B	B/C	A/C
Age	35.70±11.86	36.37±12.28	34.06±11.70	>0.05	>0.05	>0.05
Height (cm)	168.2±7.80	169.10±6.15	167.67±5.94	>0.05	>0.05	>0.05
Weight (kg)	70.7±5.01	69.00±5.55	69.80±5.26	>0.05	>0.05	>0.05
Duration of surgery (minute)	62.74±7.11	63.67±6.91	64.17±7.08	>0.05	>0.05	>0.05

P value non-significant (0.0.05)

Table 2: Variable

Parameters	Group A	Group B	Group C	P value
Onset of sensory block (min)	2.59	2.49	2.44	0.25 (NS)
Onset of motor block (min)	7.55	7.41	7.30	0.16 (NS)
Duration of sensory block (minute)	102.23	119.23	136.33	0.03 (S)
Duration of motor block (min)	145.27	155.00	188.50	0.01 (S)
Total duration of analgesia (min)	240.83	417.77	719.90	0.02 (S)
Mean number of rescue analgesia	3.2	2.63	1.93	0.01 (S)

the severity of the pain experienced. Rescue analgesia was given when VAS score >3. The time from administration of SAB to demand of first rescue analgesia (VAS >3) was defined as total duration of analgesia. Injection diclofenac 75 mg was used as rescue analgesia.

Statistical Analysis

The data of our study were statistically analyzed using IBM SPSS 21 (Armonk, NY: IBM Corp.) software and were expressed as mean, standard deviation, number, and percentages. The non-parametric patient characteristics were analyzed using “Chi-square tests,” and the intergroup comparison of the parametric data was done using the unpaired “t”-test. “P” value was calculated to evaluate the levels of significance. $P > 0.05$ was considered non-significant and $P < 0.05$ was considered as significant at 5% significance level while $P < 0.01$ was considered highly significant at 1% significance level and by taking α error 0.05 > 90% power was achieved.

OBSERVATION AND RESULTS

The groups were comparable with respect to age, weight, height, ASA grade, and duration of surgery as shown in Table 1.

The onset of sensory and motor blockade was non-significant among the groups. Significantly prolonged duration of sensory, motor, and effective analgesia was noted in Group C followed by B and A. Furthermore, the requirement of rescue analgesia was least in Group C as compared to other two groups as shown in Table 2.

VAS Score during Post-operative Period

In Group A, VAS started increasing after 3 h and the first dose of rescue analgesia was given at 4th h postoperatively, the second and third dose of rescue analgesia was given at 10th and 21st h postoperatively. In Group B, VAS started increasing at 5 h and patient demanded first dose of rescue analgesia at 7th h postoperatively, second and third dose of rescue analgesia was given at 15th and 24th h postoperatively. In Group C, VAS started increasing at 10 h and patient was given the first dose of rescue analgesia 12th h, the second dose of rescue analgesia was given at 23rd h postoperatively as shown in the Chart 1.

Heart Rate during Pre-operative, Intra-operative, and Post-operative Period

Preoperatively, the groups were comparable to each other with respect to heart rate. There is a slight fall in heart rate compared to baseline after SAB in all three group patients. The mean heart rates were comparable in all the groups intraoperatively as well as postoperatively. The fall in heart rate was seen in two patients in Group C, one patient in Group B, and in 0 patient in Group A; intraoperatively. The patients in all three groups showed rise in heart rate postoperatively when VAS score was >3 as shown in Chart 2.

Blood Pressure during Pre-operative, Intra-operative, and Post-operative Period

The mean systolic and diastolic blood pressure in the three groups was non-significant during most of the intra-operative and post-operative period. There is a slight fall in blood pressure compared to baseline after SAB in all three group patients. A significant fall in blood pressure was noted at 8th and 10th min after SAB in Group C patients as compared to Groups B and A. Similar to heart rate, there is an increase in blood pressure postoperatively when VAS >3 as shown in Charts 3 and 4.

Side Effects and Complications

A total of 3 (10.00%) patients in Group C and 1 (3.33%) patient in the Group B developed hypotension. 2 (6.67%) patients in Group C, 1 (3.33%) patient in Group B showed bradycardia. None of the patients in Group A had hypotension or bradycardia. Other side effects and complications were comparable among the groups.

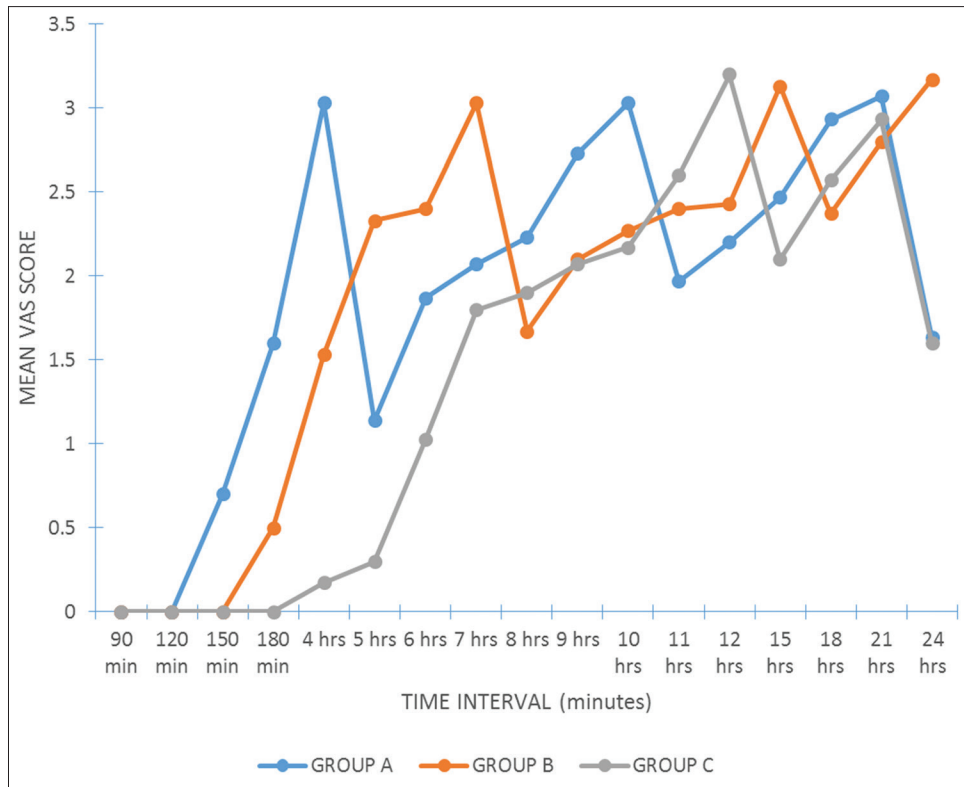


Chart 1: VAS score

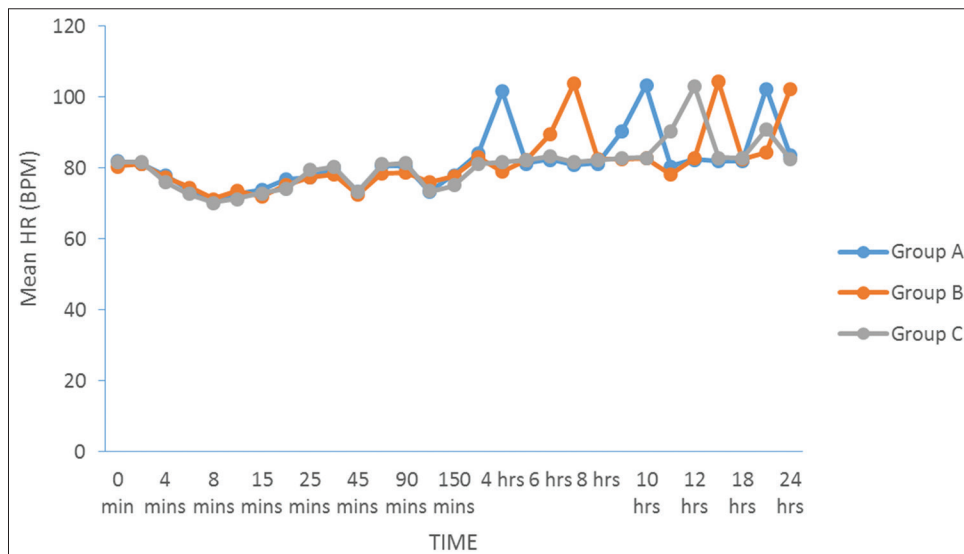


Chart 2: Changes in heart rate

DISCUSSION

Effective pain control is of paramount importance to facilitate rehabilitation and promote early function recovery after various surgeries. For infraumbilical surgeries, spinal anesthesia is the preferred technique over other techniques. It provides reliable surgical anesthesia, good muscle relaxation, and analgesia also. Shorter duration of block and post-operative analgesia is drawbacks of this technique.

To overcome these problems, many intrathecal adjuvants have been used for, for example, opioids, alpha agonists, dexmedetomidine, and other drugs such as dexamethasone and neostigmine ketamine.

In our study, the mean onset time (up to T10 dermatome) of sensory block was 2.59 ± 0.43 min, 2.49 ± 0.30 min, and 2.44 ± 0.33 min and maximum sensory level (up to T6 dermatome) was achieved in 6.63 ± 1.00 min, $6.40 \pm$

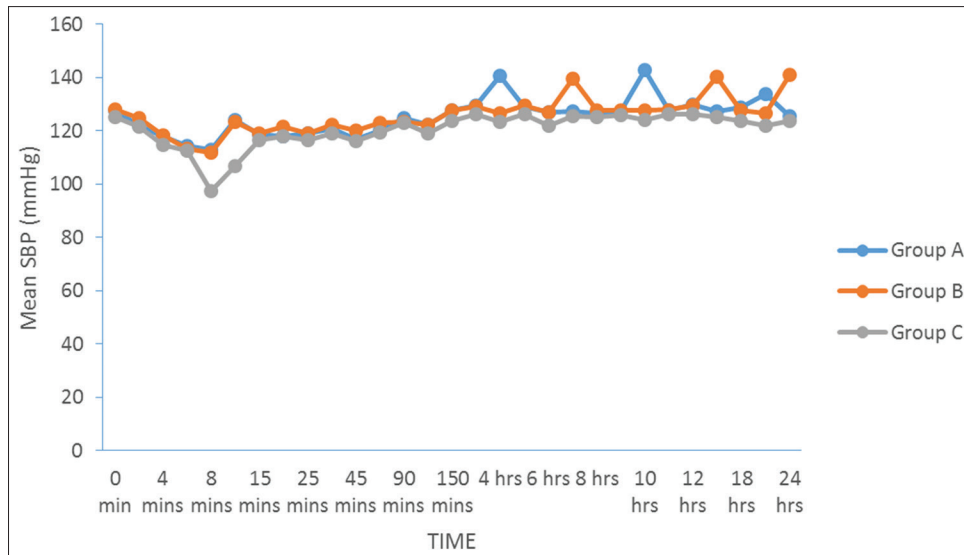


Chart 3: Systolic blood pressure

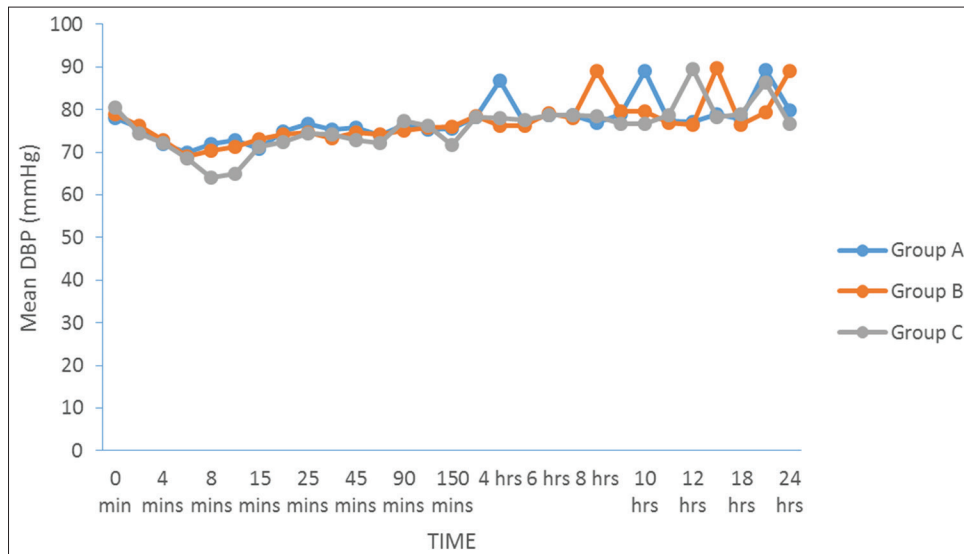


Chart 4: Diastolic blood pressure

0.62 min, and 6.30 ± 0.84 min in Groups A, B, and C, respectively. The mean duration of sensory block (defined by two segment regression) was 102.23 ± 5.81 min, $110.10.83 \pm 83$ min, and 136.33 ± 6.15 min in Groups A, B, and C, respectively. The onset time and maximum sensory level achieved was non-significant while the duration of sensory block was significant among the groups with Group C having maximum sensory block followed by B and A.

The time taken to achieve maximum motor block (Bromage score 3) was 7.55 ± 0.57 min, 7.41 ± 0.51 min, and 7.30 ± 0.62 min while the mean duration of motor block was 145.27 ± 11.80 min, 155.00 ± 11.58 min, and 188.00 ± 10.27 min in Group A, B, and C, respectively. Group C patients had more intense motor blockade at the end of

surgery. Furthermore, the duration of motor block was statistically longer in Group C as compared to Groups B and A.

The mean total duration of analgesia was 240.83 ± 36.34 min, 413.77 ± 68.60 min, and 719.90 ± 99.93 min in Groups A, B, and C, respectively. The result was significant with Group C patients having longest duration of analgesia followed by Group B. Group A have shortest duration of analgesia.

The time of the first request for analgesia in Groups A, B, and C was 4th h, 7th h, and 12th h postoperatively, respectively. This difference was significant with more requirement of rescue analgesia in Group A as compared to Groups B and C.

The mean systolic and diastolic blood pressure was non-significant between the groups during most of intra-operative and post-operative period. Group C patients showed a significant fall in systolic and diastolic blood pressure at 8th–10th min intraoperatively.

The finding of our study is similar to the study done by Sharan *et al.* who compared intrathecal fentanyl with different doses of bupivacaine on lower limb surgeries. They found out that onsets of sensory block were non-significant among the groups. T4 was maximum sensory level achieved in all the three groups. The intensity and duration of motor blockade were prolonged with an increase in the dose of bupivacaine. Furthermore, the time of request of the rescue analgesia and duration of effective analgesia was longest in group given more bupivacaine but at the cost of more hypotension.^[10]

Sendil *et al.* studied the effect of three different doses of bupivacaine along with fentanyl during spinal anesthesia for transurethral resection of prostate surgery. They concluded that addition of fentanyl with higher dose of bupivacaine resulted in prolonged motor blockade as compared to lower doses. The onset and level of sensory and motor block were similar in all the three groups. The time to two segment sensory regression, complete sensory regression, and post-operative analgesia was longest with increased dose of bupivacaine with significant hypotension.^[11]

Gupta *et al.* conducted a study using intrathecal nalbuphine and bupivacaine and intrathecal bupivacaine alone in lower limb surgery. It was seen that addition of nalbuphine improved intraoperatively analgesia without causing any undue side effects and complications, analogous to our study.^[12]

CONCLUSION

Our study concluded that 0.8 mg of nalbuphine when combined with 12.5 mg of hyperbaric bupivacaine (Group B) had optimum duration of analgesia and sensory

block with lesser hemodynamic alterations and side effects. The higher dose of bupivacaine, that is, 15 mg of hyperbaric bupivacaine with 0.8 mg nalbuphine (Group C) was associated with more incidence of hypotension and more intense and prolonged motor blockade after surgery, thus, delaying the recovery from spinal anesthesia and late ambulation. The lower dose of bupivacaine, that is, 10 mg of hyperbaric bupivacaine with 0.8 mg of nalbuphine (Group A) was associated with shorter duration of effective analgesia and sensory block, and thus, there is more requirement of rescue analgesia in this group.

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Interpretation and Clinical Correlation of Tuberculin Skin Test Results among Clinically Diagnosed Childhood Tuberculosis

H Apabi¹, P Arun², J Touthang², K H Paikhomba³, L Braja Mohon⁴

¹Associate Professor, Department of Pediatrics, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Imphal East, Manipur, India,

²Senior Resident, Department of Pediatrics, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Imphal East, Manipur, India, ³Assistant

Professor, Department of Obstetrics and Gynecology, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Imphal East, Manipur, India,

⁴Professor, Department of Pediatrics, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Imphal East, Manipur, India

Abstract

Background: Diagnosing tuberculosis (TB) was still a worldwide big challenge in cases with negative reports of Xpert MTB/RIF, smear, and culture test of acid-fast bacilli (AFB). A single, direct Xpert MTB/RIF test identified 98.2% of the sputum smear-positive TB cases and 72.5% of those with sputum smear-negative TB. Such a diagnosis was often made based on the clinical criteria and other supportive findings like tuberculin skin test (TST).

Objective: Hence, this study was to help in the diagnosis and treatment of clinically diagnosed childhood TB, especially in the limited resource rural areas and developing countries.

Materials and Methods: Based on the WHO revised criteria of TB diagnosis, to include clinically diagnosed TB instead of smear-negative TB disease, an operational definition of clinically diagnosed TB for the selection of participants for TST was established for this study. Based on the recommendation of the CDC team at the Saskatchewan Lung Association, 2007-03-21 at the Wayback Machine, the TST results of the study were interpreted.

Results: Hence, in our study, the sensitivity of TST was 82.35% (≥ 10 mm) in the age group of 1–4 years and 60.16% (≥ 15 mm) in the age group of >4–12 years. However, this study shows that the positivity rate of TST was increased from 60.16% (≥ 15 mm) to 86.15% (≥ 10 mm), if the TST results ≥ 10 mm were interpreted as positive even in this age group of >4 years–12 years.

Conclusion: In such very difficult situations of clinically diagnosed TB, this study observed that empiric anti-TB treatment may be started without microbiological confirmation to clinically diagnosed childhood TB patient with negative reports of Xpert MTB/RIF, smear, and culture test of AFB, presented with one or more of the following symptoms and signs of clinically diagnosed childhood TB: (1) Chronic anorexia, (2) ill health and fatigue, (3) weight loss of >5% during the past 3 months or documented failure to thrive during the preceding 3 months, (4) night sweating and persistent fever >2 weeks, and (5) non-remitting cough >2 weeks but cannot be diagnosed clinically by any possible causes than TB, and positive TST report, in resource-limited rural areas and developing countries.

Key words: Childhood tuberculosis, Diagnosis, Mantoux tuberculin test, Purified protein derivative, Tuberculin skin test

INTRODUCTION

Tuberculosis (TB) remains a leading cause of morbidity and mortality in the world, especially in developing countries.^[1]

The tuberculin skin test (TST) (also called a Mantoux tuberculin test) is one of the methods for detecting *Mycobacterium tuberculosis* infection in an individual and is used in the diagnosis of TB in individual patients, as well as in epidemiological settings, to measure the prevalence of TB infection in population.^[1]

Best results of Ziehl–Neelsen stain are obtained in respiratory samples. Its sensitivity is variable. Sensitivity ranges from 46% to 78% and the specificity is virtually 100%. The sensitivity is grossly compromised when the bacterial load is <10,000 organisms/ml of sputum sample.^[2,3]

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Corresponding Author: Dr. J Touthang, Department of Pediatrics, Jawaharlal Nehru Institute of Medical Sciences, Porompat-795005, Imphal East District, Manipur, India. Phone: +91-7005054145. E-mail: drjtouthang@rediffmail.com

The TST is an imperfect marker of TB infection and previous reports indicate that 10–25% of persons with active TB disease have a negative TST result. However, little is known about the relationship between the TST result and the clinical presentation of TB disease.^[4]

Recently, the WHO revised the criteria of TB diagnosis, to include clinically diagnosed TB instead of smear-negative TB.^[5]

The children with clinically diagnosed TB disease may present one or more of the following symptoms and signs: (1) chronic anorexia, (2) ill health and fatigue, (3) weight loss of >5% during the past 3 months or documented failure to thrive during the preceding 3 months, (4) night sweating and persistent fever >2 weeks, and (5) non-remitting cough >2 weeks.^[5]

Diagnosing TB worldwide still consists of methods that are intended to isolate the pathogen, which is a major limitation when the mycobacterial load (paucibacillary disease) is low, or the site of infection is not easily accessible, or sampling error and technical problems are occurred. For these reasons, diagnosis of smear-negative TB is often delayed, and such a diagnosis is often made based on the clinical response to empiric anti-TB treatment (ATT) without microbiological confirmation.^[6]

Hence, it is rational to take up this study to help in the diagnosis and treatment of childhood TB disease, especially in the limited resource rural areas and developing countries.

MATERIALS AND METHODS

This study was conducted in the Department of Pediatrics, JNIMS, over a period of 2 years from October 2016 to September 2018. The study was approved by the Institutional Ethical Committee of JNIMS. The purposive sampling method was used. Based on the WHO revised criteria of TB diagnosis, to include clinically diagnosed TB instead of smear-negative TB disease, an operational definition (OD) for the selection of participants for TST of the study was established. Hence, the child presented with one or more of the following symptoms and signs: (1) chronic anorexia, (2) ill health and fatigue, (3) weight loss of >5% during the past 3 months or documented failure to thrive during the preceding 3 months, (4) night sweating and persistent fever >2 weeks, and (5) non-remitting cough >2 weeks but cannot be diagnosed clinically by any other possible causes than TB disease was selected for TST of the clinically diagnosed childhood TB in this study.

The following inclusion and exclusion criteria were used.

Inclusion Criteria

1. Those children presented with one or more of the above symptoms and signs of OD but cannot be

diagnosed clinically by any other possible causes than TB disease were selected TST of the study.

2. Both male and female children from 1 year to 12 years of age and children with or without positive contact history of TB and Bacille Calmette–Guérin (BCG) vaccination but fulfilled the OD were included in the study.

Exclusion Criteria

The following patients were excluded from the study:

1. Those children presented with one or more of the symptoms and signs of OD but can be diagnosed clinically by any other possible causes than TB disease, were excluded from the study.
2. Have had a severe reaction to a TST in the past.
3. Those patients having any anaphylactic reaction in the past will be excluded from the study.
4. Have had TB in the past.
5. Have been treated with medicines, such as corticosteroids, that can affect the immune system.
6. Infected with HIV.
7. Have a skin rash that may make it hard to read the skin test.
8. Recent live virus vaccination (e.g., measles and smallpox).
9. Some viral illnesses (e.g., measles and chicken pox).
10. Incorrect method of TST administration.

The gender, caste, ethnicity, and race were not used as inclusion or exclusion criteria.

Those children fulfilled the OD of clinically diagnosed TB disease, but cannot be diagnosed clinically by any other possible causes than TB, were selected by the investigators for TST among the children in the OPD of Pediatrics Department, JNIMS. The selected children were sent to the OPD of Chest Department, JNIMS for TST. The person trained in TST performs the TST in Chest OPD, JNIMS. Five TU of tuberculin PPD RT23 is injected strictly intradermally on the volar aspect of the left forearm, which is the preferred site of the test, using 28 or 26-gauge needle and tuberculin syringe from which 0.1 ml can be delivered accurately. A discrete, pale elevation of the skin (a wheal) 6–10 mm in diameter should be produced when the injection is given correctly. If it is recognized that the first test was improperly administered, another test dose can be given at once, selecting a site several centimeters away from the original injection. A note in the record indicates the site chosen for the second test. The patient is instructed to keep the test site clean, uncovered, and not to scratch or rub the area. The reading of TST was done on 72 h after administration of TST, by the person trained in TST in the Chest OPD, JNIMS. The investigators obtain the informed consent from the parents/guardians. Then, only the

investigator enrolls the selected children for the study. The TST result and report were again checked by the investigator.

The recommendation of the CDC team at the Saskatchewan Lung Association, 2007-03-21 at the Wayback Machine, 5 mm or more of TST induration is positive in HIV-positive persons, persons with recent contacts with TB patients, persons with nodular or fibrotic changes on chest X-ray consistent with old healed TB, patients with organ transplants, and other immunosuppressed patients. 10 mm or more is positive in recent arrivals (<5 years) from high prevalence countries, injection drug users, residents and employees of high-risk congregate settings, mycobacteriology laboratory personals, persons with clinical conditions that place them at high risk, children <4 years of age, or children and adolescents exposed to adults in high-risk categories. 15 mm or more is positive in persons with no known risk factors for TB.^[7]

Based on the above CDC recommendation, the TST indurations of ≥ 10 mm among the age group of 1–4 years and ≥ 15 mm among 4 years–12-year-old patients, with no known risk factors for TB were interpreted as positive TST in this study. Data were collected by the investigators. The TST reports and clinical findings of the children were collected in a pre-designed pro forma.

Evaluations were done at the end of every 6 months and at the end of the study.

Data analysis was done by the statistician.

RESULTS

A total of 507 children of both sexes in the age group of 1 year–12 years were enrolled for TST of the study over the period of 2 years. The patients were divided into two groups. Of the total of 507 children, 153 children of both sexes were in the age group of 1 year–4 years and 354 children of both sexes were in the age group of above 4 years–12 years.

Table 1 shows that 126 (82.35%) of TST results (≥ 10 mm), of the total of 153 TST results, were found to be TST positive, in the age group of 1 year–4 years.

In this age group, 57.51% (88 of 153) of TST (10–<15 mm) results were found to be positive and 24.83% (38 of 153) of TST (≥ 15 mm) results were found to be positive.

Table 2 shows that 60.16% (213 of 354) of TST (≥ 15 mm) results were positive in the age group of >4 years–12 years.

Table 3 shows that 86.15% (305 of 354) of TST results were ≥ 10 mm indurations, in the age group of >4 years–12 years. However, this study also shows that the positivity rate of TST was increased from 60.16% (≥ 15 mm) to 86.15% (≥ 10 mm), if the TST results ≥ 10 mm were interpreted as positive even in this age group of >4 years–12 years.

DISCUSSION

Culture remains the gold standard for laboratory confirmation of TB and is required for isolating bacteria for DST and genotyping.^[8]

Diagnosing TB worldwide still consists of methods that are intended to isolate the pathogen, which is a major limitation when the mycobacterial load is low (paucibacillary disease), or the site of infection is not easily accessible, or sampling error and technical problems are occurred. For these reasons, diagnosis of smear-negative TB is often delayed, and such a diagnosis is often made based on the clinical response to empiric ATT without microbiological confirmation.^[6]

Recently, the International Standards for TB Care recommended that Xpert MTB/RIF and/or sputum cultures should be performed in patients suspected of having pulmonary TB but that has negative sputum smears.^[5]

In a recent study of the performance of Xpert MTB/RIF, among the 561 culture-positive patients (561/1730), a single, direct Xpert MTB/RIF test identified 98.2% (551 of 561) of the sputum smear-positive TB cases and 72.5% (124 of 171) of those with sputum smear-negative TB. The test was specific in 604 of 609 patients (99.2%) not affected by TB. The second Xpert MTB/RIF test among patients with sputum smear-negative and culture-positive

Table 1: Distribution of TST results and positivity rate of TST results, 10mm and above, in the age group of 1-4 years

Age in years	Total TST results	Total TST 0–<10 mm results	Total TST 10–<15 mm results	Total TST ≥ 15 mm results	Total number of positive TST (≥ 10 mm) results
		(%)	(%)	(%)	(%)
1–4 years	n=153	(27 of 153) n=27 (17.64%)	(88 of 153) n=88 (57.51%)	(38 of 153) n=38 (24.83%)	88+38=126 (126 of 153) n=126 (82.35%)

TST: Tuberculin skin test

Table 2: Distribution of TST results and positivity rate of TST results , 15 mm and above, in the age group of above 4 to 12 years

Age in years	Total TST results	Total TST 0–<10 mm results	Total TST 10–<15 mm results	Total TST ≥15 mm results	Total positive TST ≥15 mm results
		(%)	(%)	(%)	(%)
>4–12 years	n=354	(49 of 354) n=49 (13.84%)	(92 of 354) n=92 (25.98%)	(213 of 354) n=213 (60.16%)	(213 of 354) n=213 (60.16%)

TST: Tuberculin skin test

Table 3: Distribution of TST results and positivity rate of TST results ,10 mm and above,in the age group of above 4 to 12 years

Age in years	Total TST results	Total TST 0–<10 mm results	Total TST 10–<15 mm results	Total TST ≥15 mm results	Total positive TST ≥10 mm results
		(%)	(%)	(%)	(%)
>4–12 years	n=354	(49 of 354) n=49 (13.84%)	(92 of 354) n=92 (25.98%)	(213 of 354) n=213 (60.16%)	(305 of 354) n=305 (86.15%)

TST: Tuberculin skin test

TB increased detection sensitivity by 12.6% and the third by 5.1%, to reach 90.2%. When compared to phenotypic DST, the Xpert MTB/RIF assay correctly identified 97.6% (200 of 205) of patients harboring rifampicin-resistant strains and 98.1% (504 of 514) of those with rifampicin-susceptible strains.^[9]

Recently, the WHO revised the TB definition to include clinically diagnosed TB instead of smear-negative TB. A clinically diagnosed TB case is one that does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioners who have decided to give the patient a full course of TB treatment. Clinically diagnosed cases sub-Diagnosis of pulmonary TB <http://dx.doi.org/10.4046/trd.2015.78.2.64> 69 www.e-trd.orgquently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.^[5]

The present study shows that 82.35% (126 of 153) of TST (≥10 mm) results were positive, in the age group of 1–4 years and 60.16% (213 of 354) of TST (≥15 mm) results were also positive in the age group of >4 years–12 years. This study also shows that the positivity rate was increased from 60.16% (≥15 mm) to 86.15% (≥10 mm), if the TST results ≥10 mm were interpreted as positive even in this age group of >4 years–12 years.

According to one study, sensitivity and specificity of Mantoux test in extrapulmonary TB has been reported as 47% and 86%, respectively.^[10]

The findings of the present study were not comparable to this study. In their study, the TST sensitivity 47% was in extrapulmonary TB. In our study, the TST sensitivity was 82.35% (≥10 mm) in the age group of 1–4 years and

60.16% (≥15 mm) in the age group of >4–12 years. In this study, TST sensitivity was done among the clinically diagnosed childhood TB disease.

Ozuah *et al.* sought to determine the sensitivity, specificity, and predictive validity of a New York City Department of Health questionnaire in 2920 children. In all, 14% (413 of 2920) of children had at least one risk factor, and of these, 6% (23 of 413) had a positive TST (≥10 mm). In contrast, 0.16% (4 of 2507) of children without risk factors identified had a positive TST. The sensitivity of the questionnaire was 85% and the specificity was 86%.^[11,12]

The above sensitivity of the questionnaire (85%) is comparable with the TST sensitivity of this study 82.35% (≥10 mm) in the age group of 1–4 years. This study shows that the positivity rate was increased from 60.16% (≥15 mm) to 86.15% (≥10 mm), if the TST results ≥10 mm were interpreted as positive even in this age group of >4 years–12 years.

The past study conducted in Malaysia showed that the sensitivity of Mantoux test in active TB was 86%.^[13]

This 86% sensitivity of TST in Malaysia was comparable with the TST sensitivity of this study. Our study showed that the sensitivity of TST was 82.35% (≥10 mm result) in the age group of 1 year–4 years and 60.16% (≥15 mm result) in the age group of >4 years and 12 years. This study shows that if the TST results ≥10 mm were interpreted as positive TST, even in this age group of >4 years–12 years, the positivity rate was increased from 60.16% (≥15 mm result) to 86.15% (≥10 mm result).

One study reported that the false-negative rate among confirmed pulmonary TB was 20.5% and 11.7% in those with TB lymphadenitis.^[14] The negative TST results of

this study were 15% (≥ 10 mm result) in the age group of 1 year–4 years and 39.84% (≥ 15 mm result) in the age group of >4–12 years which were reduced to 13.85% if the TST results ≥ 10 mm were interpreted as positive TST, even in this age group of >4–12 years.

The presence of BCG vaccination is not a factor influencing tuberculin reactivity. It was earlier believed that previous BCG vaccination can account for PPD positivity depending on the interval between BCG and TST administration. Community-based studies, however, have shown that tuberculin reactivity was similar among those vaccinated in infancy and those who were never vaccinated. The same findings were noted in the study of Gonzales where no association was noted between BCG and tuberculin reactivity.^[15] The same observations were noted in this study.

Nadal concluded that several diagnostic tests have been developed to aid in the detection of TB infection and disease. Nucleic acid amplification techniques (e.g., polymerase chain reaction [PCR]), serodiagnostic methods (e.g., ELISA kits), and T-cell-based assays (e.g., interferon-gamma assay) have been introduced but are not recommended for routine diagnosis of pulmonary TB in children due to its various limitations. These include its high cost, limited local availability (for PCR), and low sensitivity (for ELISA), with only a few studies involving children. Thus, the TST cannot be replaced just yet by these assays.^[16] This present study also recommended that the TST cannot be replaced just yet by these assays, especially in resource-limited rural areas and developing countries.

This present study was in accordance with the studies of Colebunders *et al.* and Siddiqi *et al.* who concluded that a diagnostic approach to an acid-fast bacilli (AFB) smear-negative patient with possible TB includes, where available, a detailed medical history and clinical examination as well as radiological, microbiological, molecular, and histological investigations.^[6,17]

Stuart *et al.* concluded that in contrast, Mantoux testing remains to be a readily available procedure in the detection of TB infection and is widely used in epidemiologic surveys, evaluation of contacts of patient with active TB, selection of persons for chemoprophylaxis, and surveillance of health care workers for TB infection. Unfortunately, the TST is dependent on many variables which may affect its interpretation and result.^[18]

The present study observed that variables which may affect its interpretation and result of TST can be minimized. In this study, the criteria of the selection of patients for TST were the symptoms and signs of clinically diagnosed TB disease.

Fourie PB *et al.* had observed that not one of the clinical manifestations of the study participants was found to be a factor influencing tuberculin reactivity although the previous studies have shown that persistent cough, history of contact with a case of TB, low weight for age, and prolonged fever (in addition to a positive TST) were the most relevant predictors of disease in children.^[19]

Our findings were in contrast to the findings of Fourie *et al.* The present study was supportive to the results of previous studies which have shown that persistent cough, history of contact with a case of TB, low weight for age, and prolonged fever (in addition to a positive TST) were the most relevant predictors of disease in children.

Tanchuan *et al.* had revealed that 52.1% of children in contact with sputum positive cases and 43.1% of those exposed to chest X-ray positive cases were positive PPD reactors.^[20]

The positivity rate of TST in the present study was higher than the previous studies. It is due to the difference in the mode of the selection of patients for TST. In this study, the criteria of selection for TST were the symptoms and signs of clinically diagnosed TB disease.

CONCLUSION

Diagnosing TB was still a worldwide big challenge in cases of Xpert MTB/RIF and culture test reports were negative due to the major limitations when the mycobacterial load (paucibacillary disease) is low, or the site of infection is not easily accessible, or sampling error and technical problems were occurred.

In such very difficult situations, this study observed that empiric ATT may be started without microbiological confirmation to clinically diagnosed childhood TB patient with negative reports of Xpert MTB/RIF, smear, and culture test of AFB, presented with one or more of the following symptoms and signs of clinically diagnosed childhood TB: (1) chronic anorexia, (2) ill health and fatigue, (3) weight loss of >5% during the past 3 months or documented failure to thrive during the preceding 3 months, (4) night sweating and persistent fever >2 weeks, and (5) non-remitting cough >2 weeks but cannot be diagnosed clinically by any possible causes than TB, and positive TST report, in resource-limited rural areas and developing countries.

In this study, TST was done only in the clinically diagnosed childhood TB. Hence, in our study, the TST sensitivity was 82.35% (≥ 10 mm) in the age group of 1–4 years and 60.16% (≥ 15 mm) in the age group of >4–12 years. However, this study shows that the TST positivity rate was

increased from 60.16% (≥ 15 mm) to 86.15% (≥ 10 mm), if the TST results ≥ 10 mm were interpreted as positive even in this age group of >4–12 years.

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Comparison of Dexamethasone and Tramadol as Adjuvant to Levobupivacaine in Supraclavicular Block: A Clinical Study

Amar Prakash Kataria¹, Brij Mohan², Lakhwinder Singh³

¹Professor, Department of Anaesthesiology and Critical Care, Government Medical College, Amritsar, Punjab, India, ²Associate Professor, Department of Anaesthesiology and Critical Care, Government Medical College, Amritsar, Punjab, India, ³PG Resident, Department of Anaesthesiology and Critical Care, Government Medical college, Amritsar, Punjab, India

Abstract

Background: Application of supraclavicular block mostly includes surgery of elbow, forearm, and hand. The present study was conducted to evaluate and compare dexamethasone and tramadol as an adjuvant to levobupivacaine in supraclavicular block.

Materials and Methods: The present study was conducted on 60 patients of the American Society of Anaesthesiologists Grade I and II of age group of 18–60 years of either sex. Patients were divided into two groups: Group A ($n = 30$) in which 30 ml of 0.5% levobupivacaine hydrochloride plus 2 ml tramadol (100 mg) was administered and Group B ($n = 30$) in which 30 ml of 0.5% levobupivacaine hydrochloride plus 2 ml dexamethasone (8 mg) was administered. Both groups were compared statistically.

Results: The mean age \pm standard deviation in Group A males was 40.2 ± 12.45 years and in females was 41.3 ± 12.10 years and, in Group B, males was 42.1 ± 11.61 years and in females was 41.6 ± 11.33 years. The difference was non-significant ($P > 0.05$). We found significant difference in onset of sensory block, motor onset, duration of sensory block, motor block, duration of surgery, and duration of analgesia in both the groups ($P < 0.05$).

Conclusion: Dexamethasone is a better adjuvant than tramadol when added to levobupivacaine in supraclavicular brachial plexus block for upper limb surgeries as it is faster in onset and it prolongs the duration of analgesia, sensory, and motor blockade and results in better satisfaction score.

Key words: Dexamethasone, Levobupivacaine, Supraclavicular blocks, Tramadol

INTRODUCTION

Anesthesia (defined as a reversible loss of sensation with or without loss of consciousness) can be effectively achieved with a wide range of drugs with very diverse chemical structures. The list of such compounds includes not only the classic anesthetic agents, such as the general and local anesthetics, but also many central nervous system depressants, such as analgesics, sedative, hypnotics (barbiturates and benzodiazepines), anticonvulsants, and skeletal muscle relaxants.^[1]

Application of supraclavicular block includes surgery of the elbow, forearm, and hand. Complication of brachial plexus block includes pneumothorax, ipsilateral phrenic nerve palsy, subclavian artery puncture, Horner syndrome, and recurrent laryngeal nerve palsy. Various local anesthetic agents are used for supraclavicular block such as lignocaine, mepivacaine, bupivacaine, ropivacaine, and levobupivacaine.^[2]

Levobupivacaine which is less toxic is a better choice for local anesthesia, bupivacaine, the widely used local anesthetic in regional anesthesia is available in a commercial preparation as a racemic mixture (50:50) of its two enantiomers, levobupivacaine, S (–) isomer and dextrobupivacaine, R (+) isomer. The levorotatory isomers were shown to have a safer pharmacological profile with less cardiac and neurotoxic adverse effects.^[3]

Recently, dexamethasone has been studied as a local anesthetic adjuvant for peripheral nerve block. As a

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Corresponding Author: Dr. Brij Mohan, 58B Lawrence Road, Amritsar - 143 001, Punjab, India. Phone: +91-9814112569.
E-mail: bmohan4849@gmail.com

perineural adjuvant, the safety profile of dexamethasone is promising. No trial reported neurotoxicity attributable to dexamethasone till date.^[4] It is effectively and widely administered for prophylaxis against post-operative nausea and vomiting.

Tramadol, a synthetic 4-phenyl-piperidine analog of codeine, exerts its central analgesic activity through activation of mu-receptor. It also has peripheral local anesthetic properties that led to its use as an additive in peripheral nerve blocks.^[5] The present study was conducted to evaluate and compare dexamethasone and tramadol as an adjuvant to levobupivacaine in supraclavicular block.

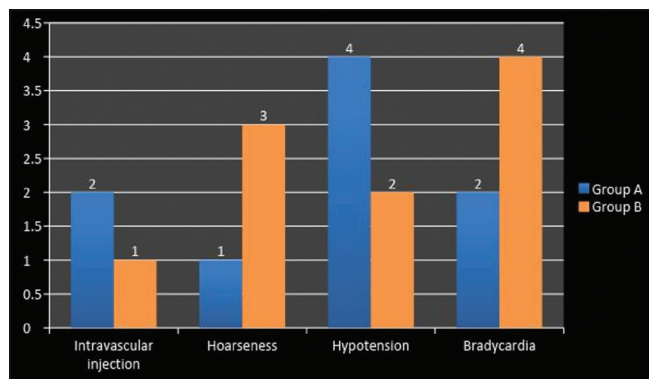
MATERIALS AND METHODS

The study protocol was a prospective, randomized, double-blind, single-center, in which 60 patients of the American Society of Anesthesiologists Grade I and II of age group of 18–60 years of either sex admitted in the Orthopedic Department of Guru Nanak Dev Hospital, Amritsar. Ethical approval was obtained from the Ethical Committee before the study.

Exclusion Criteria

Allergy to study medicine, history of significant neurological, psychiatric, neuromuscular, cardiovascular, pulmonary, renal or hepatic disease, alcohol or drug abuse, pregnant or lactating women, patient on psychotropic or adrenergic drugs, patients receiving chronic analgesic therapy, and body mass index $>35\text{kg/m}^2$ were excluded from the study.

Patients were divided into two groups, Group A ($n = 30$) in which 30 ml of 0.5% levobupivacaine hydrochloride plus 2 ml tramadol (100 mg) was administered and Group B ($n = 30$) in which 30 ml of 0.5% Levobupivacaine hydrochloride plus 2 ml dexamethasone (8 mg) was administered.



Graph 1: Complications in both the groups

A pre-anesthetic checkup of the patient selected for the study was carried out a day before surgery and was recorded as per pro forma. The interpretation of the visual linear analog scale was carried out with a 10 cm line. The end mark “0” means “no pain” and end mark “10” means “severe pain.”

All patients received tablet alprazolam 0.25 mg orally one night before surgery with 8 h of fasting. On the day of surgery, injection glycopyrrolate 0.2 mg and injection midazolam 2 mg were given 45 min before surgery. After administration of anesthesia in both the groups, various parameters such as sensory block and motor block were recorded. The data from the present study were systematically collected, compiled, and statistically analyzed after the completion of the study. Data were summarized as mean \pm standard deviation (SD) or as percentages. $P < 0.05$ was considered to be statistically significant.

RESULTS

Table 1 shows that mean age \pm SD in Group A males was 40.2 ± 12.45 years and in females was 41.3 ± 12.10 years and, in Group B, males was 42.1 ± 11.61 years and in females was 41.6 ± 11.33 years. The difference was statistically non-significant ($P > 0.01$).

Table 2 shows that mean \pm SD onset of sensory block in Group A was 5.26 ± 0.69 min and in Group B was 3.90 ± 0.75 min, motor onset was 9.00 ± 1.33 and 7.93 ± 0.73 , respectively, duration of sensory block (min) was 12.910 ± 0.815 and 15.121 ± 0.856 , respectively, motor block was 14.241 ± 0.812 and 17.901 ± 0.874 , respectively, duration of surgery (min) was 112.40 ± 16.12 and 110.32 ± 16.42 , respectively, and duration of analgesia (h) was 16.323 ± 0.825 and 19.411 ± 0.972 , respectively. There was a statistically significant difference ($P < 0.05$) except the duration of surgery. Table 2 shows that mean \pm SD onset of sensory block in Group A was 5.26 ± 0.69 min and, in Group B, was 3.90 ± 0.75 min, motor onset was 9.00 ± 1.33 and 7.93 ± 0.73 , respectively, duration of sensory block (min) was 12.910 ± 0.815 and 15.121 ± 0.856 , respectively, motor block was 14.241 ± 0.812 and 17.901 ± 0.874 , respectively, duration of surgery (min) was 112.40 ± 16.12 and 110.32 ± 16.42 , respectively,

Table 1: Age- and gender-wise distribution of patients

Groups	Male 15 (25%)	Female 15 (25%)
Group A (30)	40.2 \pm 12.45 years	41.3 \pm 12.10 years
Group B (30)	42.1 \pm 11.61 years	41.6 \pm 11.33 years

P value 0.21

Table 2: Parameters in both the groups

Parameters	Group A	Group B	P value
Sensory onset (min)	5.26±0.69	3.90±0.75	0.05
Motor onset (min)	9.00±1.33	7.93±0.73	0.01
Duration of sensory (h)	12.910±0.815	15.121±0.856	0.001
Duration of motor (h)	14.241±0.812	17.901±0.874	0.001
Duration of surgery (min)	112.40±16.12	110.32±16.42	0.698
Duration of analgesia (h)	16.323±0.825	19.411±0.972	0.001

Table 3: Baseline parameters in both the groups

Parameters	Group A	Group B	P value
RR (per min)	14.85±1.05	14.80±1.23	0.08
PR (per min)	81.46±6.05	82.30±8.17	
SBP (mm Hg)	131.70±8.24	134.10±11.18	
DBP (mm Hg)	78.36±5.63	76.57±7.20	
SpO ₂ (%)	99.27±0.23	99.80±0.20	

RR: Respiratory rate, PR: Pulse rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SpO₂: Percentage saturation of peripheral oxygen

Table 4: Intraoperative and postoperative VAS scores

Time (h)	Group A	Group B
0.5	0	0
1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
6	0	0
7	0	0
8	0	0
10	0	0
12	0	0
15	0.73±1.22	0
18	2.76±1.30	1.53±1.97
21	2.83±1.23	2.76±1.33
24	2.33±1.42	2.26±1.20

VAS: Visual analog scale

and duration of analgesia (h) was 16.323 ± 0.825 and 19.411 ± 0.972 , respectively. There was a statistically significant difference ($P < 0.05$) except the duration of surgery.

Table 3 shows baseline parameters including respiratory rate, pulse rate, systolic blood pressure, diastolic blood pressure, percentage saturation of peripheral oxygen in both the groups. The mean baseline parameters were noted preoperatively and compared statistically. The two groups were found to be comparable and insignificant with respect to the baseline parameters ($P > 0.05$).

Table 4 shows the visual analog scale (VAS) score which was significantly better in Group B as compared to Group A depicting a longer duration of analgesia in the Group B ($P < 0.05$).

DISCUSSION

The brachial plexus is a somatic nerve plexus with complex intra- and inter-neural anatomy. Upper limb regional anesthesia by brachial plexus block has become a significant anesthesiologist's armamentarium as it can be used to provide both anesthesia for surgery and analgesia thereafter.^[6] As compared to general anesthesia, brachial plexus block is relatively easy to learn and execute and does not require bulky equipment for administration. Brachial plexus block provides complete relaxation of muscles of the upper extremity, thus making approximation of tendons and reduction of fractures easier. It reduces post-operative spasm, pain, and edema due to sympathetic blockade of blood vessels. In 1884, Halsted first operated under brachial plexus block when he exposed the nerve roots in the neck and blocked them with direct application of the cocaine solution.^[7]

In the present study, Group A consisted of 15 (50%) male patients and 15 (50%) female patients, and similarly, Group B consisted of 15 (50%) male patients and 15 (50%) female patients.

We found a significant difference in onset of sensory block, motor onset, duration of sensory block, motor block, duration of surgery, and duration of analgesia in both the groups. This is in accordance with a study done by Alarasan *et al.*^[8] who found that the onset of sensory and motor block was significantly earlier in dexamethasone group (10.36 ± 1.99 and 12 ± 1.64 min) compared to control group (12.9 ± 2.23 and 18.03 ± 2.41 min). Meitei *et al.*,^[9] in their study, found that there was significantly faster onset of sensory blockade and prolonged duration of analgesia in the dexamethasone group than the saline group. Bais *et al.*,^[10] in their study, found that the mean onset of motor block in Group A was 8.04 ± 1.35 min and in Group B was 6.94 ± 0.54 min.

The surgeries were started after surgical anesthesia developed. In case, patient experienced mild pain (VAS > 3), and intraoperative supplementation was given with injection ketamine 0.5mg/kg. In our study, three patients in Group A and two patients in Group B required supplementation with injection ketamine in the first $\frac{1}{2}$ h of giving the block. The two groups were found comparable with regard to need of supplementation.

The VAS score was monitored $\frac{1}{2}$ hourly until 1 h, hourly until 8 h, 2 hourly until 12 h, and then 3 hourly until 24 h. The VAS score was 0 for all patients (except those who required ketamine supplementation) until about 15 h in Group A and 18 h in Group B, following which VAS score gradually increased, and patients were given rescue analgesia in the form of injection diclofenac sodium intramuscularly

when the VAS score >3 . VAS score was checked for 24 h after the block and rescue analgesia was given whenever it was more than three. The number of analgesic doses given within 24 h was statistically significant between two groups with Group B having less requirement of analgesic.

We observed that addition of dexamethasone to levobupivacaine increases the mean duration of sensory and motor block. This is in accordance with a study done by Choi *et al.*^[11] who found that dexamethasone prolonged the analgesic duration for long-acting intermediate-acting from 730 to 1306 min and for intermediate from 168 to 343 min. Motor block was prolonged from 664 to 1102 min. The most recent trial demonstrated equivalent prolongation with perineural or systemic administration of dexamethasone compared with placebo.

There were few adverse events in the two study groups and were statistically insignificant ($P > 0.05$). No side effects such as respiratory depression, bronchospasm, and symptoms of local anaesthetic toxicity or neurological sequelae were observed in any groups. Complications such as intravascular injection, hoarseness of voice, hypotension, and bradycardia occurred, but the differences in the two groups were statistically insignificant ($P > 0.05$) [Graph 1]. This is in agreement with various studies.^[12-15]

CONCLUSION

We conclude that dexamethasone is a better adjuvant than tramadol when added to levobupivacaine, for supraclavicular brachial plexus block used in orthopedic surgery as it is faster in onset and it prolongs the duration of sensory and motor blockade and duration of analgesia and has a better patient satisfaction score.

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Bacteriological Profile and Antibiotic Susceptibility Pattern of the Isolates among the Neonatal Septicemia in Northeast India

H Apabi¹, K H Paikhomba², J Touthang³, P Arun³, L Braja Mohon⁴

¹Associate Professor, Department of Pediatrics, Jawaharlal Nehru Institute of Medical Sciences, Imphal East, Manipur, India, ²Assistant Professor, Department of Obstetrics and Gynecology, Jawaharlal Nehru Institute of Medical Sciences, Imphal East, Manipur, India, ³Senior Resident, Department of Pediatrics, Jawaharlal Nehru Institute of Medical Sciences, Imphal East, Manipur, India, ⁴Professor, Department of Pediatrics, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Imphal East, Manipur, India

Abstract

Background: Bacterial resistance to antibiotics was a global problem. Multidrug-resistant bacteria causing neonatal septicemias were increasing in the world. It was difficult to compare the bacterial profile and antibiotic susceptibility pattern of the isolates among the neonatal septicemia between countries because the epidemiology of neonatal septicemia was extremely variable.

Objective: Timely identification of bacterial profile and antibiotic susceptibility pattern of the isolates among the neonatal septicemias are essential to guide the clinicians regarding both the empirical and definitive treatments of neonatal septicemia.

Materials and Methods: Based on the AIIMS protocol 2014 of neonatal sepsis-World Health Organization newborn CC, an operational definition of clinically diagnosed neonatal septicemia was established for the selection of participants in the study for blood culture and sensitivity test (CST). Hence, in this study, blood CST was done only among the selected patients for clinically diagnosed neonatal septicemia as recommended in the National Committee for Clinical Laboratory Standards.

Results: This study observed that there was a shift from the predominance of Gram-negative organisms to Gram-positive organisms, especially *Staphylococcus aureus*. *Acinetobacter* and *Citrobacter* were emerging organisms. In this study, aminoglycosides and fluoroquinolones were sensitive to organisms, especially in Gram-negative organisms. Imipenem and meropenem were also sensitive in both Gram-positive and Gram-negative organisms. Imipenem was more sensitive to organisms than meropenem. Tobramycin, doxycycline, gatifloxacin, and chloramphenicol were more sensitive to organisms than erythromycin, azithromycin, and clindamycin.

Conclusion: Early clinical diagnosis and prompt initiation of empirical antimicrobials therapy to patients of pending culture sensitivity reports for definitive therapy may be life-saving. Hence, periodic surveillance for bacteriological profile and antibiotic susceptibility pattern of the isolates among the neonatal septicemia for appropriate choice of antimicrobials for empirical therapy can be outlined and reevaluated in a timely manner to save the life of 5 million neonatal deaths a year, with 98% occurring in developing countries and limited resource rural areas. This study concluded that empiric therapy for clinically diagnosed neonatal septicemia should cover both Gram-negative and Gram-positive organisms. Hence, the combination of one antibiotic from each of the following two groups, (1) Imipenem/piperacillin/cefotaxime and (2) amikacin/gentamicin/netilmicin, can be included as an initial therapy for neonatal septicemia.

Key words: Antibiotic resistance, Antimicrobial susceptibility pattern, Bacterial isolates, Blood stream infection, Neonatal sepsis

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INTRODUCTION

Septicemia in neonates refers to generalized bloodstream bacterial infection documented by positive blood culture in the first 4 weeks of life and is one of the four leading causes of neonatal mortality and morbidity in India.^[1]

Corresponding Author: Dr. K H Paikhomba, Assistant Professor, Department of Obstetrics and Gynecology, Jawaharlal Nehru Institute of Medical Sciences, Porompat -795 005, Imphal East, Manipur, India. Phone: +91-7005054145. E-mail: paikhomba160@gmail.com

The incidence of neonatal septicemia varies from country to country, but it is much higher in developing countries.^[2]

According to the World Health Organization estimates, there are about 5 million neonatal deaths a year, with 98% occurring in developing countries.^[3]

The spectrum of organisms that cause neonatal sepsis changes over times and varies from region to region. This is due to the changing pattern of antibiotic use and changes in lifestyle.^[4]

According to the AIIMS Protocol 2014, neonates with sepsis may present one or more of the following symptoms and signs (1) hypothermia or fever; (2) lethargy, poor cry, and refusal to suck; (3) poor perfusion and prolonged capillary refill time; (4) hypotonia and absent neonatal reflexes; (5) bradycardia or tachycardia; (6) respiratory distress, apnea, and gasping respiration; (7) hypoglycemia and hyperglycemia; and (8) metabolic acidosis.

Antibiotic resistance is a global problem. Reports of multiresistant bacteria causing neonatal sepsis in developing countries are increasing. It is difficult to compare antibiotic resistance between countries because the epidemiology of neonatal sepsis is extremely variable.

Hence, periodic surveillance for bacteriological profile and antibiotic susceptibility pattern for appropriate choice of antimicrobials for empirical therapy can be outlined and reevaluated in timely manner to guide the clinicians.

The evaluation of organisms responsible for neonatal septicemia will be essential for the appropriate management of neonatal septicemias in the society and to save 5 million neonatal deaths a year, with 98% occurring in developing countries, especially in the limited resource rural areas.

Hence, it is rational to take up this study to determine the changing pattern of bacterial profile and antibiotic susceptibility of isolates among the neonatal septicemia in the Northeast India.

MATERIALS AND METHODS

This study was conducted in the neonatal intensive care unit (NICU), Department of Pediatrics, JNIMS, over 2 years from October 2016 to September 2018. The study was approved by the Institutional Ethical Committee of JNIMS. Based on the AIIMS protocol 2014 of neonatal sepsis-WHO newborn CC, an operational definition (OD) of clinically diagnosed neonatal septicemia was established for the selection of participants. The neonate presented with one or more of the following symptoms

and signs (1) hypothermia or fever (former is more common in preterm), (2) lethargy, poor cry, and refusal to suck, (3) poor perfusion and prolonged capillary refill time, (4) hypotonia and absent neonatal reflexes, (5) bradycardia or tachycardia, (6) respiratory distress, apnea, and gasping respiration, (7) hypoglycemia or hyperglycemia, and (8) metabolic acidosis, but cannot be diagnosed clinically by any other possible causes than neonatal sepsis which was selected for clinically diagnosed neonatal septicemia of this study.

The following inclusion and exclusion criteria were used.

Inclusion Criteria

Those neonates presented with one or more of the above symptoms and signs of OD were selected for blood culture and sensitivity test (CST) of the study. Premature and matured babies of both the sexes in the age group of 1–28 days were included in the study.

Exclusion Criteria

Those neonates presented with one or more of the above symptoms and signs but can be diagnosed clinically by any other possible causes than neonatal septicemias were excluded from the study. Babies above 28 days of age were excluded from the study. The gender, caste, ethnicity, and race were not used as inclusion or exclusion criteria.

Those neonates fulfilled the above OD of clinically diagnosed neonatal septicemia were selected for blood CST. The trained doctors in the NICU draw blood from the selected neonates for culture blood CST under strict aseptic and antiseptic precaution before starting the antibiotics. The local site to draw the blood was cleaned with povidone iodine (1%) and washed by 70% alcohol. 3 ml of blood sample was only collected from a peripheral vein under aseptic and antiseptic precautions and inoculated into 20 ml of Brain Heart Infusion broth (HiMedia, India). The blood in the culture media was immediately sent to the Microbiology Department, JNIMS, for CST. Then, the selected neonate was treated with systemic antibiotics to save the life. Antimicrobial susceptibility testing was performed for all blood culture isolates by Kirby–Bauer disc diffusion method as recommended in the National Committee for Clinical Laboratory Standards.^[5,6]

The investigator obtains the informed consent from the parents/guardian of the selected neonate. Then, only the selected neonates were enrolled in the study. The appropriate antibiotic of the neonatal septicemia was changed according to the blood CST report.

Data collection was done by the investigators. Bacteriological profile and antibiotic susceptibility pattern of the isolates

in the blood CST reports of the selected neonates were collected in a pre-designed pro forma, for observation and analysis of the study. Evaluations were done at the end of every 6 months and at the end of the study.

Data analysis was done by the statistician.

RESULTS

A total of 360 clinically diagnosed neonatal septicemia patients of both the sexes in the age group of 1–28 days were investigated for blood CST.

Table 1 shows that 33.33% (120 of 360) of blood CST were found to be blood culture positive neonatal septicemias. Of these, 61.66% (74 of 120) had early onset sepsis (EOS) and 38.33% (46 of 120) had late onset sepsis (LOS).

Table 2 shows that, of the 120 positive blood CST reports, *Staphylococcus aureus* 55% (66 of 120) was positive and was the most common isolated organism, followed by *Pseudomonas aeruginosa* 15% (18 of 120), *Acinetobacter* 15% (18 of 120), *Citrobacter* 6.66% (8 of 120), *Escherichia coli* 5% (6 of 120), and *Klebsiella pneumoniae* 3.33% (4 of 120).

Table 3 shows that *S. aureus* was the most common Gram-positive isolate. Gram-positive *S. aureus* isolates were sensitive to erythromycin (81.81%), tobramycin (78.78%), imipenem (78.78%), linezolid (72.72%), levofloxacin (75.75%), ceftriaxone (54.54%), vancomycin (48.48%), and cefotaxime (33.33%).

P. aeruginosa 15% (18 of 120), *Acinetobacter* 15% (18 of 120), *Citrobacter* 6.66% (8 of 120), *E. coli* 5% (6 of 120), and *K. pneumoniae* 3.33% (4 of 120) were the most common isolated Gram-negative organisms in this study.

Gram-negative isolates were sensitive to aminoglycosides (gentamicin, amikacin, netilmicin, and tobramycin) and fluoroquinolone (gatifloxacin, ciprofloxacin, and levofloxacin).

P. aeruginosa 15% (18 of 120) is one of the most common Gram-negative organisms and is sensitive to imipenem (88.88%), meropenem (77.77%), amikacin (77.77%), and gentamicin (77.77%).

E. coli 5% (6 of 120) is sensitive to amikacin (100%), levofloxacin (100%), tobramycin (100%), gatifloxacin (100%), imipenem (100%), and doxycycline (100%).

K. pneumoniae 3.33% (4 of 120) is sensitive to amikacin (100%), gentamicin (100%), netilmicin (100%), piperacillin (100%), tobramycin (100%), gatifloxacin (100%), imipenem (100%), meropenem (100%), and chloramphenicol (100%).

Acinetobacter 15% (18 of 120) and *Citrobacter* 6.66% (8 of 120) were emerging organisms.

Acinetobacter 15% (18 of 120) is sensitive to amikacin (44.44%), gentamicin (100%), netilmicin (88.88%), piperacillin (44.44%), tobramycin (100%), gatifloxacin (88.88%), imipenem (100%), meropenem (55.55%), and chloramphenicol (77.77%).

Citrobacter 6.66% (8 of 120) is sensitive to amikacin (100%), gentamicin (100%), netilmicin (50%), piperacillin (75%), ceftriaxone (75%), gatifloxacin (75%), levofloxacin (75%), imipenem (75%), doxycycline (100%), and chloramphenicol (100%).

Aminoglycosides and fluoroquinolones were sensitive to organisms, especially in Gram-negative organisms.

Table 1: Distribution of blood CST results into two age groups of (1) 1–7 days of age, as EOS and (2) 8–28 days of age, as LOS

Sl no.	Total number of blood CST	Total number of positive blood CST (%) n=120	Positive blood CST in EOS (%) n=74	Positive blood CST in LOS (%) n=46
1	360	33.33 (120 of 360)	61.66 (74 of 120)	38.33 (46 of 120)

CST: Culture and sensitivity test, EOS: Early onset sepsis, LOS: Late onset sepsis

Table 2: Distribution of the isolated organisms among the 120 positive blood CST in neonatal septicemia

Isolated organisms in blood CST	Total number of the specific organism out of 120 positive blood CST	Frequency of isolates (%)
<i>Staphylococcus aureus</i>	66	55 (66 of 120)
<i>Pseudomonas aeruginosa</i>	18	15 (18 of 120)
<i>Acinetobacter</i>	18	15 (18 of 120)
<i>Citrobacter</i>	8	6.66 (8 of 120)
<i>Escherichia coli</i>	6	5 (6 of 120)
<i>Klebsiella pneumoniae</i>	4	3.33 (4 of 120)

CST: Culture and sensitivity test

Table 3: Distribution of the antibiotic sensitivity pattern of the isolates among the 120 positive blood CST in neonatal septicemias

Tested antibiotics in blood CST	1 <i>Staphylococcus aureus</i> 55 % (66 of 120) %	2 <i>Acinetobacter</i> 15% (18 of 120) %	3 <i>Pseudomonas aeruginosa</i> 15% (18 of 120) %	4 <i>Citrobacter</i> 6.66% (8 of 120) %	5 <i>Klebsiella pneumoniae</i> 3.33 % (4 of 120) %	6 <i>Escherichia coli</i> 5% (6 of 120) %
Penicillin						
Ampicillin			33.33 (6 of 18)	75 (6 of 8)	50 (2 of 4)	33.33 (2 of 6)
Amoxicillin/ clavulanic	54.54 (36 of 66)					
Cefaclor	48.48 (32 of 66)					
Cefazolin						
Cefuroxime	60.60 (40 of 66)	44.44 (8 of 18)		75 (6 of 8)		33.33 (2 of 6)
Erythromycin	81.81 (54 of 66)					
Gentamicin	69.69 (46 of 66)	100 (18 of 18)	77.77 (14 of 18)	100 (8 of 8)	100 (4 of 4)	66.66 (4 of 6)
Cefixime	27.27 (18 of 66)	22.22 (4 of 18)	55.55 (10 of 18)	50 (4 of 8)		
Ceftriaxone	54.54 (36 of 66)	44.44 (8 of 18)	44.44 (8 of 18)	75 (6 of 8)	100 (4 of 4)	33.33 (2 of 6)
Ceftazidime		11.11 (2 of 18)	11.11 (2 of 18)			33.33 (2 of 6)
Cefotaxime	33.33 (22 of 66)					33.33 (2 of 6)
Levofloxacin	75.75 (50 of 66)	77.77 (14 of 18)	66.66 (12 of 18)	75 (6 of 8)	50 (2 of 4)	100 (6 of 6)
Clindamycin	57.57 (38 of 66)	11.11 (2 of 18)				33.33 (2 of 6)
Amikacin	69.69 (46 of 66)	44.44 (8 of 18)	77.77 (14 of 18)	100 (8 of 18)	100 (4 of 4)	100 (6 of 6)
Azithromycin	51.51 (34 of 66)					33.33 (2 of 6)
Vancomycin	48.48 (32 of 66)					33.33 (2 of 6)
Cefepime		33.33 (6 of 18)				33.33 (2 of 6)
Cefpirome		33.33 (6 of 18)	33.33 (6 of 18)	25 (2 of 8)		33.33 (2 of 6)
Imipenem	78.78 (52 of 66)	100 (18 of 18)	88.88 (16 of 18)	75 (6 of 8)	100 (4 of 4)	100 (6 of 6)
Meropenem	33.33 (22 of 66)	55.55 (10 of 18)	77.77 (14 of 18)	50 (4 of 8)	100 (4 of 4)	33.33 (2 of 6)
Teicoplanin	57.57 (38 of 66)					
Linezolid	72.72 (48 of 66)					
Tobramycin	78.78 (52 of 66)	100 (18 of 18)	33.33 (6 of 18)	50 (4 of 8)	100 (4 of 4)	100 (6 of 6)
Gatifloxacin	57.57 (38 of 66)	88.8 (16 of 18)	66.66 (12 of 18)	75 (6 of 8)	100 (4 of 4)	100 (6 of 6)
Piperacillin		44.44 (8 of 18)	44.44 (8 of 18)	75 (6 of 8)	100 (4 of 4)	66.66 (4 of 6)
Chloramphenicol		77.77 (14 of 18)	77.77 (14 of 18)	100 (8 of 8)	100 (4 of 4)	66.66 (4 of 6)
Doxycycline		66.66 (12 of 18)	55.55 (10 of 18)	100 (8 of 8)	50 (2 of 4)	100 (6 of 6)
Cefoperazone/ sulbactam	12.12 (8 of 66)	55.55 (10 of 18)	33.33 (6 of 18)	25 (2 of 8)	50 (2 of 4)	
Netilmicin	12.12 (8 of 66)	88.88 (16 of 18)	66.66 (12 of 18)	50 (4 of 8)	100 (4 of 4)	66.66 (2 of 6)
Ciprofloxacin	27.27 (18 of 66)	66.66 (12 of 18)	66.66 (12 of 18)	50 (4 of 8)		33.33 (2 of 6)
Ticarcillin/ clavulanate			44.44 (8 of 18)	75 (6 of 8)		33.33 (2 of 6)
Ofloxacin		55.55 (10 of 18)	33.33 (6 of 18)	50 (4 of 8)	50 (2 of 4)	66.66 (4 of 6)
Nalidixic acid		33.33 (6 of 18)				
Aztreonam			22.22 (4 of 18)	25 (2 of 8)	50 (2 of 4)	
Tetracycline		22.22 (4 of 18)				
Cotrimoxazole						

CST: Culture and sensitivity test

Imipenem and meropenem were also sensitive to both Gram-positive and Gram-negative organisms. Imipenem was more sensitive to organisms than meropenem.

Piperacillin, ceftriaxone, cefoperazone/sulbactam, and cefixime were more sensitive to organisms than cefotaxime, ceftazidime, cefepime, ceftiofime, cefuroxime, cefaclor, cefazolin, amoxicillin/clavulanic, and ampicillin.

Tobramycin, doxycycline, gatifloxacin, and chloramphenicol were more sensitive to organisms than erythromycin, azithromycin, and clindamycin.

DISCUSSION

Resistance of bacteria to antibiotics was a global problem. Multidrug-resistant bacteria causing neonatal septicemia were increasing in the world. It was difficult to compare the bacterial profile and antibiotic susceptibility pattern of the isolates among the neonatal septicemias between countries because the epidemiology of neonatal septicemia was extremely variable.

Shipra *et al.* reported that, in culture-proven septicemia, 55% of neonates presented with EOS and 45% presented with LOS. Gram-positive isolates were more as compared with Gram-negative isolates. The most common isolates were *S. aureus*, *S. epidermidis*, and *E. coli*. All Gram-positive isolates were sensitive to vancomycin and linezolid, while carbapenems and polymyxin B were the most effective drugs in the Gram-negative isolates. Mortality was higher in LOS as compared with EOS cases. Moreover, the difference was statistically significant.^[7]

The present study observed that proven sepsis was 33.33% (120 of 360). Of these, 61.66% (74 of 120) had EOS and 38.33% (46 of 120) had LOS. This study showed that, of the 120 positive blood CST reports, *S. aureus* 55% (66 of 120) was positive and was the most common organism followed by *P. aeruginosa* 15% (18 of 120), *Acinetobacter* 15% (18 of 120), *Citrobacter* 6.66% (8 of 120), *E. coli* 5% (6 of 120), and *K. pneumoniae* 3.33% (4 of 120). In this study, aminoglycosides and fluoroquinolones were sensitive, especially, in Gram-negative organisms.

West and Peterside reported that the antibiotic sensitivity testing showed that Gram-negative isolates were sensitive to meropenem and Gram-positive isolates to linezolid, netilmicin, and chloramphenicol. The most common bacteria causing neonatal sepsis was found to be *Klebsiella*. The Gram negative organisms showed the highest sensitivity to meropenem. Cefazolin was found to be most resistant antibiotic to Gram negative organisms. The Gram-positive samples showed highest sensitivity for linezolid,

and penicillin and ampicillin were found to be most resistant. Best overall sensitivity among Gram-negative isolates was to imipenem (93%), followed by amikacin (52%) and netilmicin (41%). Gram-positive isolates had a sensitivity of 91% to linezolid, 68% to tetracycline, 64% to piperacillin/tazobactam, and 52% to ciprofloxacin.^[8]

In this study, *S. aureus* was the most common Gram-positive isolate. Gram-positive *S. aureus* isolates were sensitive to erythromycin (81.81%), tobramycin (78.78%), imipenem (78.78%), linezolid (72.72%), levofloxacin (75.75%), ceftriaxone (54.54%), vancomycin (48.48%), and cefotaxime (33.33%). Aminoglycosides and fluoroquinolones were still sensitive to organisms, especially in Gram-negative organisms. Imipenem and meropenem were also sensitive in both Gram-positive and Gram-negative organisms. Imipenem was more sensitive than meropenem. Piperacillin, ceftriaxone, cefoperazone/sulbactam, and cefixime were more sensitive to organisms than cefotaxime, ceftazidime, cefepime, ceftiofime, cefuroxime, cefaclor, cefazolin, amoxicillin/clavulanic, and ampicillin. Tobramycin, doxycycline, gatifloxacin, and chloramphenicol were more sensitive than erythromycin, azithromycin, and clindamycin.

Antibiotic resistance is a global problem. Reports of multiresistant bacteria causing neonatal sepsis in developing countries are increasing. The wide availability of over-the-counter antibiotics and the inappropriate use of broad-spectrum antibiotics in the community may explain this situation.^[3] This study observed that it was difficult to compare the bacterial profile and antibiotic susceptibility pattern of the isolates among the neonatal septicemias between countries because the epidemiology of neonatal septicemia was extremely variable.

There has been a shift from the predominance of Gram-negative organisms to Gram-positive organisms *S. aureus* in the past decade throughout the world, and the reason for which is not clear.^[9-11] This present study observed a shift from the predominance of Gram-negative organisms to Gram-positive organisms (*S. aureus*).

Bhat *et al.* shown that although the Gram-negative organisms were most common in both EOS and LOS, but the incidence of Gram-positive sepsis was higher in LOS (21.89%) when compared to EOS (15.7%). *S. aureus* was the most common Gram-positive microbe in both EOS (7.3%) and LOS (17.41%). A low rate (2.24%) of enterococci infection was positive.^[11] In the present study also, *S. aureus* was the most common microbe. A low rate of enterococci infection was also observed.

Ballot *et al.*, Kaufman and Fairchild, and Hoogen *et al.* reported the isolation of general purpose buffer in 54.9%,

68.2%, and 75%, respectively.^[12-14] This study showed a preponderance of Gram-positive *S. aureus* 55% (66 of 120), which was in concordance with the previous studies.

The present study showed that *S. aureus* 55% (66 of 120) was the most common Gram-positive organisms which was high as compared to studies conducted by Agnihotri *et al.* and Sundaram *et al.*^[15,16]

Shrestha *et al.*, Jyothi *et al.*, and Nepal *et al.* reported that Klebsiella and Acinetobacter were the most common organisms attributing to LOS.^[17-19] This study showed that *S. aureus* 55% (66 of 120) was positive and was the most common isolated organism followed by *P. aeruginosa* 15% (18 of 120), *Acinetobacter* 15% (18 of 120), *Citrobacter* 6.66% (8 of 120), *E. coli* 5% (6 of 120), and *K. pneumoniae* 3.33% (4 of 120).

Tallur *et al.* observed that, among the maternal risk factors, the difficult delivery (32%) in the form of cesarean, forceps, or vacuum was the risk factors.^[20] In our study, history of fetal distress, premature rupture of membrane, prolong labor, home delivery, and instrumental deliveries were the main risk factors for neonatal septicemia.

Draz *et al.* and Tsering *et al.* reported that the greater prevalence of resistance to commonly used antibiotics has also been observed.^[1,21] Similar observations were seen in this study.

CONCLUSION

The resistance of bacteria to antibiotics was a global problem. Multidrug-resistant bacteria causing neonatal septicemias were increasing in the world. Early clinical diagnosis and prompt initiation of empirical antimicrobials therapy to patients of pending culture sensitivity reports for definitive therapy may be life-saving. Hence, a periodic surveillance for bacteriological profile and antibiotic susceptibility pattern of the isolates among the neonatal septicemias in different areas for appropriate choice of antimicrobials for empirical therapy can be outlined and reevaluated in timely manner to save the life of 5 million neonatal deaths a year, with 98% occurring in developing countries and limited resource rural areas.

This study observed that there was a shift from the predominance of Gram-negative organisms to Gram-positive organisms, especially *S. aureus*. *Acinetobacter*, and *Citrobacter* were emerging organisms. In this study, aminoglycosides and fluoroquinolones were sensitive to organisms, especially in Gram-negative organisms. Imipenem and meropenem were also sensitive to organisms in both Gram-positive and Gram-negative organisms. Imipenem was more sensitive to organisms

than meropenem. Tobramycin, doxycycline, gatifloxacin, and chloramphenicol were more sensitive to organisms than erythromycin, azithromycin, and clindamycin. This study concludes that empiric therapy for suspected neonatal septicemia should cover both Gram-negative and Gram-positive organisms. Hence, the combination of one antibiotic from each of the following two groups such as (1) imipenem/piperacillin/cefotaxime and (2) amikacin/gentamicin/netilmicin can be a choice as an initial therapy for neonatal septicemia.

This study concluded that empiric therapy for clinically diagnosed neonatal septicemia should cover both Gram-negative and Gram-positive organisms. Hence, the combination of one antibiotic from each of the following two groups, (1) imipenem/piperacillin/cefotaxime and (2) amikacin/gentamicin/netilmicin, can be included as an initial therapy for neonatal septicemia.

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Effect of Preheating on Surface Roughness and Microhardness of a Nanohybrid Composite Resin - An *In Vitro* Study

Rupali Baban Wetam¹, Sharad Basavraj Kamat², Santosh Irappa Hugar³, Girish Shankar Nanjannawar⁴, Pranav Devendra Patil⁵

¹Post Graduate Student, Department of Conservative Dentistry and Endodontics, Bharti Vidyapeeth Dental College and Hospital, Wanlesswadi, Sangli, Maharashtra, India, ²Professor and Head, Department of Conservative Dentistry and Endodontics, Bharti Vidyapeeth Dental College and Hospital, Wanlesswadi, Sangli, Maharashtra, India, ³Professor, Department of Conservative Dentistry and Endodontics, Bharti Vidyapeeth Dental College and Hospital, Wanlesswadi, Sangli, Maharashtra, India, ⁴Associate Professor, Department of Conservative Dentistry and Endodontics, Bharti Vidyapeeth Dental College and Hospital, Wanlesswadi, Sangli, Maharashtra, India, ⁵Assistant Professor, Department of Conservative Dentistry and Endodontics, Bharti Vidyapeeth Dental College and Hospital, Wanlesswadi, Sangli, Maharashtra, India

Abstract

Introduction: The success of dental composites in restorative dentistry stems from their good aesthetic properties and adequate durability. The clinical performance of composite resins is directly related to the degree of monomer conversion after photo polymerization. Placing composites at an elevated temperature reduce their viscosity and increase the efficiency of polymerization. Heating the composite prior to placement in the cavity increases monomer conversion rate and therefore the duration of the irradiation period may be reduced.

Purpose of Study: Evaluate and compare effect of pre-heating on surface roughness and microhardness of nanohybrid composite resin subjected to two different temperatures and two different durations using light emitting diode curing unit (LED LCU).

Methods: Nanohybrid composite resin was tested at two temperatures (37°C and 55°C) and pre-heating of composite was done using incubator at two durations (10 and 20 minutes) respectively. Samples were injected into cylindrical Teflon molds and the top surface of the specimens were polymerized using LED LCU for 40 s. After preservation for 24 h, specimens checked for surface roughness and Vickers hardness measurements. Statistical analysis were performed using one-way analysis of variance and Tukey *post hoc* test at a level of significance of $P < 0.05$ for both surface roughness and microhardness.

Results: Pre-heating of composite affect on microhardness and did not influence on surface roughness.

Conclusion: Pre-heating of resin composite increases microhardness and no significant effect on roughness.

Key words: Pre-heating, Nanohybrid composite, LED light curing unit

INTRODUCTION

The success of dental composites in restorative dentistry stems from their good esthetic properties and adequate durability. The clinical performance of composite resins is directly related to the degree of monomer conversion after photopolymerization.^[1]

Blue light-emitted diode-based light curing units (LCUs) have a narrow spectral range with a peak around 470 nm which coincides with the optimum absorption wavelength for CQ activation. It has also been found that blue light-emitting diode (LED) source produced a degree of monomer conversion that was significantly higher than that obtained with halogen source, even though all the sources were adjusted to produce the same irradiance (100 mW/cm²).^[2]

Nanohybrid resin composites are claimed to have the positive characteristics of macrofilled and microfilled resin composites, they are widely used as universal resin composites in both anterior and posterior

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Corresponding Author: Dr. Rupali Baban Wetam, Post Graduate Student, Department of Conservative Dentistry and Endodontics, Bharti Vidyapeeth Dental College and Hospital, Wanlesswadi, Miraj road, Sangli. Phone: +91-8600039068. E-mail: rupaliwetam8@gmail.com

teeth.^[3] Placing composites at an elevated temperature reduce their viscosity and increase the efficiency of polymerization. Heating the composite before placement in the cavity increases monomer conversion rate, and therefore, the duration of the irradiation period may be reduced.^[1]

Current one-step systems appear to be as effective as multistep systems for polishing dental composites. With the ultimate goal of achieving a smooth surface of the composite restoration in fewer steps, the one-step polishing systems are appealing to the clinician.^[4]

Hence, the purpose of the present study was conducted to evaluate and compare the effect of preheating on surface roughness and microhardness of a nanohybrid composite resin - an *in vitro* study.

MATERIALS AND METHODS

The composite resin used in this study was nanohybrid Herculite Precis (Kerr). The preheating of composite was done in a utilizing incubator (MKWO OPTIK) at 37°C and 55°C to 10 and 20 min durations, respectively. A total of 60 specimens were fabricated and divided into two groups as Group A and Group B.

- Group A: The specimens in this group were divided into two subgroups A1 and A2.
Subgroup A1: 15 specimens were preheated at 37°C for 10 min.
Subgroup A2: 15 specimens were preheated at 37°C for 20 min.
- Group B: The specimens in this group were divided into two subgroups B1 and B2.
Subgroup B1: 15 specimens were preheated at 55°C for 10 min.
Subgroup B2: 15 specimens were preheated at 55°C for 20 min.

Placement of Composite Resin and Curing

A glass slide was placed at the bottom of mold with Mylar strip covering it and preheated composite of individual subgroups was immediately injected into the mold. A second Mylar strip was placed on top of the mold with coverslip covering it. All the specimens were cured according to manufacturer's instructions using LED curing unit (Bluephase N LED, Ivoclar Vivadent) for 40 s each and embedded in acrylic resin.

The specimens of composite resin were preserved for 24 h in dark and polished using polishing discs followed by aluminum oxide impregnated polymer points (enhance finishing system, Dentsply). The surface roughness was

checked using surface roughness tester (Mitutoyo, Japan model SJ 210).

After the specimens had been checked for surface roughness, they were subjected to Vickers hardness measurements (Reichert Austria Make, Sr No. 363798).

RESULTS

The mean and standard deviation among the groups were calculated by ANOVA (One Way Analysis of Variance) and multiple comparisons among the groups were carried out by using Post Hoc Tukey's t-test. The *p*-value was taken as significant when less than 0.05. The data was analysed using Statistical package for Social Sciences (SPSS) version 17.

Analysis of Surface Roughness

The results indicated that there was statistically insignificant difference between the groups for surface roughness ($P > 0.05$) [Table 1].

Analysis of Surface Microhardness

The results indicated that there was statistically significant difference between the groups for surface microhardness ($P < 0.05$) [Table 2].

Table 1: Post hoc tests (surface roughness)

(I) Groups	(J) Groups	Mean difference (I-J)	P value
A1	A2	0.0090667	0.998
	B1	-0.0101333	0.998
	B2	0.1274667	0.113
A2	A1	-0.0090667	0.998
	B1	-0.0192000	0.986
	B2	0.1184000	0.158
B1	A1	0.0101333	0.998
	A2	0.0192000	0.986
	B2	0.1376000	0.076
B2	A1	-0.1274667	0.113
	A2	-0.1184000	0.158
	B1	-0.1376000	0.076

Table 2: Post hoc tests (surface microhardness)

(I) Groups	(J) Groups	Mean difference (I-J)	P value
A1	A2	-6.4853333*	0.008
	B1	-7.6353333*	0.001
	B2	-24.7440000*	0.000
A2	A1	6.4853333*	0.008
	B1	-1.1500000	0.933
	B2	-18.2586667*	0.000
B1	A1	7.6353333*	0.001
	A2	1.1500000	0.933
	B2	-17.1086667*	0.000
B2	A1	24.7440000*	0.000
	A2	18.2586667*	0.000
	B1	17.1086667*	0.000

DISCUSSION

The clinical use of resin composite has expanded considerably over the past few years due to increased esthetic demands by patients, new development in formulation, and simplification in bonding procedures.^[5] Studies have revealed that preheating of composite resin increases monomer conversion and reduces the duration of light exposure. The increase in the degree of polymerization of the composites may lead to better internal adaptation to cavity walls, improved mechanical properties, and increased wear resistance.^[1]

The material used in this study was nanohybrid composite (Herculite précis, Kerr company) which contains prepolymerized filler, silica nanofiller (20–50 nm), and submicron hybrid filler (0.4 μ).^[6]

The use of LED to polymerize resin composites was proposed by Mill's, in 1995.^[7] The spectral output of blue LEDs falls conveniently within the absorption spectrum of the camphorquinone photoinitiator (400–500 nm), and so no filters are required when LED LCUs are used. LED units generate minimal heat and so do not require cooling fans which have associated noise and power consumption.^[8]

The results of the present study revealed that there was no significant effect of preheating of composites on their surface roughness.

The results indicated that there was a statistically significant increase in microhardness as the temperature of composite increased from 37°C to 55°C with the increase in the duration of preheating of the composites from 10 to 20 min.

Repeated preheating procedure did not negatively influence the mechanical properties of the resin composites. Further studies might be needed to assess the clinical relevance of the other variables connected to the repeated preheating and cooling cycles.^[9]

A concern regarding preheating is the impact of this elevated temperature on the pulp tissue. According to Maeda *et al.*, the intraoral physiologic temperature range in humans is from 34.2°C to 36.6°C. Other studies reported critical temperature limit for pulpal fibroblast to be 41.5°C. According to Trujillo *et al.*,^[10] the pulp vitality may potentially be compromised by temperature rises of greater than about 5°C from the baseline level of approximately 32–34°C.^[11]

Limitations of the present study were that there was decrease in temperature of the composites during their

removal from incubator to Teflon mold stimulating clinical situation. The results of this *in vitro* study correlate to clinical situations where there are accessible and relatively flat surfaces. Future laboratory studies should be conducted to establish efficiency of one-step polishing systems on concave and convex surfaces.

CONCLUSION

A resin composite restoration can be imperceptible to the naked eyes when its surface closely resembles the surrounding enamel surface. Thus, polished restoration should demonstrate an enamel-like surface texture and gloss. Finishing and polishing procedures can be completed using single instrument, and it appears to be effective as multistep polishing systems for polishing dental composites.

There was no significant difference between the groups for surface roughness. There was significant difference between the groups for microhardness.

Preheating resin composite increases the monomer conversion rate and increases the depth of cure and microhardness of tested composite. However, further studies with larger sample size, involving various restorative materials, need to be undertaken to assess the result of preheating for optimum clinical advantage.

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Neurotoxic Snakebite in Jammu Region: Is it Cobra or Krait

Ashu Jamwal¹, Sunil Dutt Sharma¹, Ghanshyam Saini², Tarundeep Kour³

¹Associate Professor, Department of Pediatrics, Government Medical College, Jammu, Jammu and Kashmir, India, ²Professor and Head, Department of Pediatrics, Government Medical College, Jammu, Jammu and Kashmir, India, ³Dental Officer DEIC, Department of Pediatrics, Government Medical College, Jammu, Jammu and Kashmir, India

Abstract

Background: The aim of this study is to analyze the clinical profile and outcome of the neurotoxic envenomation in children in Jammu region and to identify the species based on the syndromic approach developed by WHO.

Materials and Methods: A retrospective hospital record based descriptive study which analyses the case records of children reporting to pediatric emergency with signs and symptoms of neurotoxic envenomation.

Results: A total of 22 cases of the neurotoxic envenomation reported between April 15 and October 15. These included 14 males and 8 females between the age group of 2.5 years and 16 years. The highest incidence of snakebite was observed in the age group of 4–8 years. A total of seven cases presented neuromuscular symptoms and local signs suggesting cobra bite. Bite was reported in the afternoon or evening hours between 12.30 pm and 10.30 pm and 83% bites were outdoors. A total of 15 children presented with neuromuscular symptoms with no local signs suggesting krait bite. 86% of the bites were indoor with onset of symptoms between 12 am and 7 am.

Conclusion: Both cobra and krait cause neurotoxic envenomation in children in Jammu region with krait bite accounting for 68% of the total cases. Most of these cases are brought to the pediatric emergency late. Training of the peripheral doctors regarding early recognition of neurotoxic snakebite, species diagnosis as per the WHO syndromic approach, prompt institution of initial management with neostigmine and after visit summary, endotracheal intubations and AMBU bag ventilation, and quick referral to a center with ventilator facility should help in reducing the morbidity and mortality due to krait and cobra bite in children.

Key words: Cobra bite, Envenomation, Krait bite

INTRODUCTION

Neurotoxic snakebite is a well-known pediatric medical emergency. Neurotoxic snakes belong to the family Elapidae which includes cobra and krait. Russell viper's venom has also been reported to cause neurotoxicity in some patients. Majority of snakebite-related deaths in India's rural population are caused by kraits and cobras. Russell viper's venom has also been reported to cause neurotoxicity such as ptosis, ophthalmoplegia, and respiratory distress in some patients.^[1,2]

The type of snakes found in particular area varies considerably. Furthermore, the symptoms and signs of neurotoxic envenomation vary according to the species of snake responsible for the bite and the amount of venom injected. Diagnosis of species of the snake responsible for bite is, therefore, important for optimal management and can be strongly suspected from the patient's description of the snake, the circumstances of the bite, or from knowledge of the clinical effects of the venom of that species.^[2,3]

A syndromic approach has been developed by the WHO for diagnosing the species responsible for snakebite in different parts of the Southeast Asia region. The patient should be observed closely to allow recognition of the emerging pattern of symptoms, signs, and results of laboratory tests, "the clinical syndrome," which together with the circumstantial evidence, may suggest that the species was responsible for envenomation. This information will enable

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Corresponding Author: Dr. Sunil Dutt Sharma, Department of Pediatric, SMGS Hospital Government Medical College, Jammu, Jammu and Kashmir, India. Phone: +91-9419123903. E-mail: sharmadsunil@yahoo.com

the doctor to anticipate the likely complications and manage the patient appropriately, thereby reducing the mortality associated with neurotoxic envenomation.^[3]

Cobra bites tend to occur during daytime and early darkness while going to the open toilet, playing near the loose stones, searching ball in bushes, putting sticks in grooves, and improper or careless handling while rescuing the cobra. Bite by cobra results in tender local swelling, blistering, and necrosis. Victims experience severe pain at bite site having fang marks, with rapid progression of swelling. Skin at or around the bite site is ecchymosed. Subsequent formation of tense blebs and massive damage of skin and subcutaneous tissue occurs due to myocytolysis. This rapidity of the onset of symptoms prompts the rural victim in India to seek care quickly after cobra bite.^[1,4-6]

The common krait, on the other hand, is nocturnal, terrestrial snake that enters human dwellings in search of prey such as rats, mice, and lizards during the course of hunting activity. It resides in the vicinity of human habitation, near the wattle and daub, mud, and small hut dwelling, hunts nocturnally, and is quick to bite people sleeping on the floor, often without waking their victims since venom is painless and associated with minimal local changes.^[1,7]

Cobra venom is rich in postsynaptic neurotoxins called alpha-bungarotoxin and cobratoxin, which bind, especially to postsynaptic acetylcholine receptors, preventing the interaction between Ach and receptors on postsynaptic membrane, resulting in neuromuscular blockade. Cardiotoxin content of cobra venom has direct action on cardiac and smooth muscles causing circulatory failure, cardiac arrhythmias, various heart blocks, and cardiac arrest. Cobra venom is of smaller molecular size and rapidly absorbed into circulation. Cobra unlike the krait deposits its venom deeply. This in combination with hyaluronidase allows spread of the venom rapidly and symptoms to arise abruptly. Absorption is further accelerated by running due to fear and the liberated catecholamines can kill the victim within 8 min. Interestingly, severe, irreparable local tissue is lost at the bite site of cobra envenoming due to myocytolysis. Paralysis is heralded by ptosis followed by ophthalmoplegia. Blurring of vision and loss of accommodation are earliest sign of neurological envenomation. Paralysis of facial, palatal, tongue, and neck muscles follow. Respiratory failure, precipitated by upper airway obstruction and paralysis of intercostals and diaphragm, is the usual cause of death.^[1,6,8]

Although the krait venom is 10 times more lethal than cobra, it is absorbed slowly as skin has poor circulation and reflexes are blunted during sleep. The common Indian krait

venom contains both presynaptic beta-bungarotoxin and alpha-bungarotoxin. Beta-bungarotoxin in the krait venom has a great affinity toward presynaptic Ach receptors. These toxins initially release Ach at the nerve endings, at neuromuscular junction, and then damage it subsequently preventing the release of Ach. The tissue having high concentration of these receptors is affected in the following order, such as sphincter pupillae, levator palpebrae superioris, neck muscles, bulbar muscles, subsequently limbs, and, finally, the diaphragm and intercostals muscles. Venom acts as early as 30 min and till 18 h.^[9-12]

Optimal management of neurotoxic snakebites depends on the species. Neuromuscular blockade by the short chain neurotoxin present in the cobra venom (cobra toxin, alpha-bungarotoxin) is more readily reversible than with a long chain toxin (beta-bungarotoxin). Most of the patients recover with artificial ventilation, cardiopulmonary resuscitation, and acetylcholinesterase inhibitor (AChEI). Since cobra venom is reversibly attached to postsynaptic receptors, AChEI like neostigmine is important for management. 0.5 mg neostigmine $\frac{1}{2}$ hourly preceded by atropine may help the majority of victim to recover within 24 h. This cycle may not be required >5–6 times. Local wound care is done by intravenous antibiotic, daily dressing and may require plastic surgery.^[1-3]

The common krait venom contains both pre- and postsynaptic blocker. Thus, the victims may or may not respond to neostigmine. Envenoming by krait has an early phase profound paralysis which lasts for 30–60 min followed by deep paralysis phase which lasts for 2–3 days and then recovery phase ranging from 2 to 3 weeks. Since the krait venom damages the acetylcholine receptors, prolonged period of ventilatory support, and intensive care requirements essential for recovery.^[3,13]

The epidemiology of neurotoxic snakebite in children in Jammu region has not been adequately studied. Many snakebite cases are not treated in hospitals but by traditional healers. The chances of snakebite deaths being missed are perhaps even greater than from deaths occurring from several other causes.

Aims and Objectives

This study aims to study the clinical profile and outcome of the neurotoxic envenomation in children in Jammu region and to identify the species responsible based on the WHO syndromic approach.

Settings

This study was conducted at the Department of Pediatrics, SMGS Hospital Government Medical College, Jammu.

Study Design

This was a retrospective hospital record-based descriptive study.

MATERIALS AND METHODS

Neurotoxic snakebite cases commonly report to the casualty of the Pediatrics Department, SMGS Hospital, Jammu. Since maximum number of snakebite cases occur during summer, monsoon, and post-monsoon months, we decided to carry out retrospective hospital record-based study from April to October 2015. The case records from the record section of SMGS Hospital for all the children who reported to the Pediatric Emergency with signs and symptoms of neurotoxic envenomation were evaluated. The clinical profile of patients including age, sex, residence, site of bite, time interval between snakebite and hospitalization, and clinical symptoms and signs were recorded. An attempt was made to interpret the clinical signs and identify the species based on the WHO syndromic approach. Local envenoming (swelling etc.) with paralysis = cobra or king cobra paralysis with minimal or no local envenoming/Bitten on land while sleeping on the ground = krait

RESULTS

A total of 22 cases of the neurotoxic envenomation who had been hospitalized between April 15 and October 15 were included in this study. Of these, 14 were male and 8 were female. The age group was between 2½ years and 16 years. The highest incidence of snakebite was observed in the age group of 4–8 years.

About 68% of children reported with symptoms suggestive of krait bite while 32% were cobra bites.

A total of seven cases presented neuromuscular symptoms and local signs suggesting cobra bite. Age range was from 2.5 to 13 years. 66% were male. Bite was reported in the afternoon or evening hours between 12.30 pm and 10.30 pm. 83% bites were outdoors. Patients responded well to neostigmine and after visit summary (AVS). Two patients required mechanical ventilation and mean hospital stay was 5 days. One patient died due to cardiac arrest during transportation to intensive care unit.

A total of 15 children presented with neuromuscular symptoms with no local signs suggesting krait bite. The age group was 5–16 years and 9 were male. Eight patients belonged to Jammu district, four to Kathua district, one to Samba, two to Reasi district, and one from Doda district. 86% bites were indoor. All the children started with the

symptoms at night or early morning between 12 am and 7 am. Of these, eight children were brought >6 h after the onset of symptoms while seven were brought within 6 h. In seven patients, fang marks could not be located, three children had fang marks in the upper limbs, four in lower limbs, and one in head and neck (Post-auricular region). Five children had history of sleeping on floor and two had history of sleeping outdoors. However, in 13 patients, there was no history of snakebite or having seen the snake. However, in all these cases, circumstantial evidence along with clinical signs and symptoms of a neurotoxic snakebite were found. These patients had mostly sequence of events, starting with pain throat and pain abdomen, followed by drowsiness, ptosis, and difficulty in breathing. Abdominal pain (60%), ptosis (100%), dysphagia (60%), dyspnea (50%), drowsiness (40%), blurring of vision (25%), pain throat (25%), dryness of mouth (15%), diplopia (10%), and vomiting (10%) were the predominant clinical presentations [Table 1-4].

DISCUSSION

Neurotoxic snakebite is a common pediatric emergency during the summer months. In the present study, 68% of the cases of neurotoxic envenomation appeared to be due to krait bite as per the WHO syndromic classification. Digra and Singh in their study of 37 children with neurotoxic envenomation from Jammu between 2007 and 2011 observed that 94% of the bites occurred during the months of July–October. They further observed that majority of the bites occurred during the night hours and 12 children were sleeping on the floor at the time of bite. 13 children with clinical features of neurotoxic envenomation but without a history of snakebite were admitted in emergency in early morning hours with a history of sudden onset of the abdominal pain and then gradually developing ptosis, neuromuscular paralysis, and respiratory failure.^[14]

Table 1: Age- and sex-wise distribution of neurotoxic snakebite patients

Age (years)	Male	Female	Total
0–3	1	0	1
4–8	4	4	8
9–12	4	1	5
13–15	4	2	6
16–18	1	1	2
Total	14	8	22

Table 2: Distribution of the cases studied according to the clinical syndrome

Paralysis with minimal or no local envenoming/Bitten on land while sleeping on the ground=krait	15
Local envenoming (swelling etc.) with paralysis=cobra or king cobra	7

Table 3: Characteristics of suspected cobra bite patients

Age	Sex	District	Time of bite (PM)	Time gap of bite and hospitalization	Indoor/outdoor	Site of bite	Hospital stay days	Outcome
12	M	Rajouri	4.30	4.5 h	Outdoor	LL	5	Recovered
5	F	Rajouri	10.30	5.5 h	Indoor	LL	6	Recovered
2.5	M	Jammu	12.50	2 h	Outdoor	UL	4	Recovered
7	M	Samba	1	9 h	Outdoor	LL	5	Recovered
13	M	Jammu	3	45 min	Outdoor	LL	9	Recovered
8	F	Reasi	5	6 h	Outdoor	LL	-	Died
13	M	Kathua	1	2 h	Outdoor	LL	11	Recovered

LL: Lower limb, UL: Upper limb

Table 4: Characteristics of suspected krait bite patients

Age	Sex	District	Time of bite/onset of symptoms	Time gap of hospitalization (h)	Indoor/outdoor	Site of bite	Hospital stay	Outcome
13	F	Doda	7 AM	10	Indoor	LL	15	REC
5	F	Jammu	1.30 AM	2.5	Indoor	UL	6	REC
10	M	Reasi	3 AM	12	Indoor	Left ear	4	REC
12	M	Samba	7 PM	2	Outdoor	LL	13	REC
7	M	Jammu	7 AM	4	Indoor	?	7	REC
13	M	Jammu	3 AM	4	Indoor	?	13	REC
8	F	Jammu	5 AM	2.5	Indoor	UL	15	REC
14	M	Reasi	9 AM	24	Indoor	UL	4	REC
16	M	Jammu	5.30 AM	7	Outdoor	?	24	REC
5	M	Kathua	6 AM	6.5	Indoor	?	10	REC
8	F	Kathua	5 AM	4	Indoor	?	10	REC
14	F	Kathua	4 AM	6	Indoor	?	8	REC
16	F	Kathua	1.30 AM	12.5	Indoor	UL	5	REC
8	M	Jammu	3 AM	6	Indoor	?	7	REC
10	M	Jammu	12 AM	2	Indoor	LL	10	REC

LL: Lower limb, UL: Upper limb, REC: Recovered

In the present study, most of the children with krait bite were bitten during unprovoked encounters, indoors, and mostly at night and were brought to the hospital quite late, with eight patients reporting 6 h after the onset of symptoms. This could be due to a delayed diagnosis and delayed referral as pain abdomen in early morning hours was the cardinal symptom in 60% of the cases. Timsinha *et al.* in a study of 91 cases of the snakebite observed that 46% of the patients reported to the hospital 6 h after the bite and 92.3% of the patients did not receive any first aid measures before hospitalization, which could be due to lack of transport facilities or awareness. Definite protocol for the primary health care of snakebite cases needs to be considered.^[15]

Snakes like krait, on envenomation, may not present with local signs, thereby misleading the physician to think of others possibilities and in the process allowing the golden hour to pass by. Newly posted or inexperienced doctors and inadequate facilities at primary health centre, ignorance of conventional treatment of neurotoxic snakebite by doctors, further delays appropriate treatment of victims and contribute to increasing morbidity and mortality.^[9-13,16] Studies of snakes with presynaptic neurotoxins such as kraits suggest that antivenom does not reverse established neurotoxicity, but early administration may be associated with decreased severity or prevent neurotoxicity.^[17]

In cobra bite anticholinesterases and supportive care as cornerstones of management. Faridi *et al.* reported complete reversal of envenomation symptoms in a cobra bite patient following the administration of anticholinesterase neostigmine methyl sulfate and emphasized that anticholinesterase drugs may reverse the potentially lethal neurological effects of venom.^[18] In our study, none of the children reporting to the hospital with cobra bite had received neostigmine as a part of prehospital treatment. This signifies a lack of popular awareness about current prehospital management recommendations for snakebites. Bomb *et al.* in their study reported that 12 patients of Elapid ophitoxemia with neuromuscular paralysis were administered anticholinesterase (neostigmine). In four of these patients, no antivenom and all survived. Of eight who received antivenom three were given <50 units and all three survived. Of the remaining five, despite the use of AVS in higher doses (>50 units of AVS), two died. The authors concluded that antivenom has no definite role in Elapid ophitoxemia and anticholinesterase drugs alone, with good supportive care can result in satisfactory outcome.^[19]

Availability of ventilators in tertiary care centers has improved the outcome of the snakebite patients. 65% of our patients required ventilator support as they had developed respiratory paralysis. Usually, neurotoxicity occurs within 60 min of envenomation, rapidly progressing to respiratory paralysis requiring early ventilator support.^[20]

Rapid referral to hospital for definitive care and antivenom administration is the cornerstone of the management of neurotoxic snakebite. Singh *et al.* in a study of 21 cases of the neurotoxic snakebite from a military hospital, where reporting time was between 30 min and 180 min, median dose of AVS was 180 ml and 11 (52%) of patients received neostigmine, only two patients needed ventilation. The median time of recovery from envenomation was 8 h and all patients REC.^[21]

Case fatality rate in our series was 9%. The recorded figures of snakebite deaths in hospital are regarded as underestimated of the total fatality from this cause. Data from million deaths study in India estimate that snakebite deaths are >30-fold higher than recorded in the hospital returns.^[22,23]

Limitations of syndromic approach: The more carefully the clinical effects of snakebites are studied, the more it is realized that the range of activities of a particular venom is very wide. For example, some elapid venoms, such as cobras, can rarely cause hematotoxic effects, formerly thought to be an effect only of viper venoms. In Sri Lanka and South India, Russell's viper venom causes paralytic signs (ptosis, etc.) suggesting elapid neurotoxicity. Ptosis, bulbar palsy, internuclear ophthalmoplegia, and respiratory paralysis due to presynaptic neuromuscular block in Russell viper's bite poisoning are often seen and reported from Kerala and Sri Lanka.^[24] Although there may be considerable overlap of clinical features caused by venoms of different species of the snake, a "syndromic approach" may still be useful. Medical personal throughout the region would benefit from more formal instructions on all aspects of the subject. This should include identification of medically important species of snakes, clinical diagnosis and appropriate use of antivenoms, and ancillary treatments.

CONCLUSION

Both cobra and krait cause neurotoxic envenomation in children in Jammu region with krait bite accounting for 68% of the total cases. Most of these cases are brought to the pediatric emergency late. Pain abdomen, usually during night hours without any abdominal cause, should arouse a strong suspicion of neurotoxic krait bite. Training of the peripheral doctors regarding early recognition of neurotoxic snakebite, species diagnosis, prompt institution of initial management with AChEI and AVS, endotracheal intubations and AMBU bag ventilation, and quick referral to a center with ventilator facility should help in reducing the morbidity and mortality due to krait and cobra bite in children.

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Effect of Quartz-tungsten-halogen and Light-emitting Diode-curing Units on the Depth of Cure and Flexural Strength of a Nanohybrid Composite Resin: An *In Vitro* Study

Anushri Dhananjay Shah¹, Sharad Basavraj Kamat², Santosh Irappa Hugar³, Girish Shankar Nanjannawar⁴, Pranav Devendra Patil⁵

¹Post Graduate Student, Department of Conservative Dentistry and Endodontics, Bharati Vidyapeeth (Deemed To Be University) Dental College and Hospital, Sangli, Maharashtra, India, ²Professor and Head, Department of Conservative Dentistry and Endodontics, Bharati Vidyapeeth (Deemed to be University) Dental College and Hospital, Sangli, Maharashtra, India, ³Professor, Department of Conservative Dentistry and Endodontics, Bharati Vidyapeeth (Deemed to be University) Dental College and Hospital, Sangli, Maharashtra, India, ⁴Associate Professor, Department of Conservative Dentistry and Endodontics, Bharati Vidyapeeth (Deemed to be University) Dental College and Hospital, Sangli, Maharashtra, India, ⁵Assistant Professor, Department of Conservative Dentistry and Endodontics, Bharati Vidyapeeth (Deemed to be University) Dental College and Hospital, Sangli, Maharashtra, India

Abstract

Introduction: Over the years, the demand for esthetic dentistry has grown dramatically and there has been a rapid development of new adhesive restorative materials with nanotechnology that can restore the color and characteristics of natural tooth. To polymerize these materials, light-curing dental materials extensively used are quartz-tungsten-halogen (QTH) and light-emitting diode (LED)-curing units. Literature search revealed that depth of cure and flexural strength are the most important properties of composite resin materials, relevant to the clinical technique of incremental packing and curing.

Purpose: The objectives of the present study were to evaluate and compare the depth of cure and flexural strength of a nanohybrid composite resin.

Materials and Methods: Two light-curing units were selected for this study: QTH (Bonart, Unicorn) and LED (Ivoclar Vivadent, Bluephase® N). The depth of cure was evaluated with scraping technique using digital caliper and flexural strength was evaluated using universal testing machine with a crosshead speed of 1 mm/min.

Results: Descriptive statistics was employed to measure the mean and standard deviation of the depth of cure and flexural strength. Unpaired "t"-test was used to compare the study variables. Statistical significance was fixed at ≤ 0.05 and LED-curing unit showed significantly greater depth of cure and flexural strength when compared to QTH curing unit.

Conclusion: Curing effectiveness of resin composite is dependent on the light-curing unit.

Key words: Depth of cure, Flexural strength, Light-emitting diode, Nanohybrid composite resin, Quartz-tungsten-halogen

INTRODUCTION

Resin-based composites, now used worldwide in dentistry due to their esthetic quality and good physical properties,

are either chemically activated or light activated or combination of both.^[1,2]

The most usual light-curing units (LCUs) used for composite resin polymerization are the quartz-tungsten-halogen (QTH) light and light-emitting diode (LED) LCU.^[3]

The physicommechanical properties of composite resin include compressive strength, tensile strength, elastic modulus, thermal expansion, microhardness, flexural strength, surface roughness, depth of cure, and curing

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Corresponding Author: Anushri Dhananjay Shah, Department of Conservative Dentistry and Endodontics, Bharati Vidyapeeth (Deemed to be University) Dental College and Hospital, Wanlesswadi, Miraj Road, Sangli, Maharashtra, India. Phone: +91-9049008895. E-mail: dranushreeshah@gmail.com

Table 1: Comparison between QTH and LED for the depth of cure of a nanohybrid composite resin

Groups	Number of samples	Mean depth of cure (mm)±SD	Mean difference	t value	P value
Group IA	15	5.55±0.29	-1.09	-11.385	0.001*
Group IB	15	6.64±0.21			

QTH: Quartz-tungsten-halogen, LED: Light-emitting diode, SD: Standard deviation

Table 2: Comparison between QTH and LED for flexural strength of a nanohybrid composite resin

Groups	Number of samples	Mean flexural strength (mm)±SD	t-value	P value
Group II A	15	126.6700±45.05821	-2.582	0.019
Group II B	15	173.6580±35.81040		

QTH: Quartz-tungsten-halogen, LED: Light emitting diode, SD: Standard deviation

shrinkage.^[4-6] Literature search revealed that depth of cure and flexural strength are the most important properties of composite resin materials, relevant to the clinical technique of incremental packing and curing.

However, little is understood about the interaction of these new light sources with composite resins and how they influence the depth of cure and flexural strength.^[7] Therefore, the aim of this *in vitro* study was to evaluate and compare the depth of cure and flexural strength of a nanohybrid composite resin polymerized using QTH and LED-curing units.

MATERIALS AND METHODS

The present *in vitro* study was conducted at the dental institute. Ethical clearance was obtained from BVDUMC and H, Sangli.

Experimental Design

The factors under the study were two LCUs (QTH and LED) and a nano-hybrid composite resin (Filtek™ Z250XT, 3M ESPE). The experimental units consisted of 30 resin composite molds for depth of cure assigned to two groups ($n = 15$) and 30 resin composite molds for flexural strength assigned to two groups ($n = 15$). Mean values from scraping technique and universal testing machine were analyzed by Unpaired “t”-test for the depth of cure and flexural strength, respectively.

Assessment of Depth of Cure

A cylindrical split Teflon mold measuring 5 mm in diameter and 8 mm in height was placed on a glass slide and approximated using a jig (cylindrical rubber and screw). Black paper was placed between the glass slide and the mold to prevent reflection of the light during activation. Nanohybrid composite resin (Filtek™ Z250XT, 3M ESPE) was placed into the Teflon mold in a bulk increment to obtain resin mold of 8 mm in height. A transparent mylar

strip was then placed on the resin mold, and a translucent cover slip covered it.

A total of 30 samples were prepared and divided into two groups:

- Group IA - 15 samples were cured with QTH LCU (Bonart, Unicorn).
- Group IB - 15 samples were cured with LED LCU (Ivoclar Vivadent, Bluephase® N).

All the samples were cured for the given time as per manufacturer's instructions. The depth of cure was checked using Digital Caliper 150 mm (6'') (precision measuring) after scraping (scraping technique, according to ISO 4049) the uncured composite resin using spoon excavator from the bottom surface until the resistance was felt.

Assessment of Flexural Strength

A Teflon mold measuring 25 mm in length, 2 mm in breadth, and 4 mm in height was placed on a glass slide. Black paper was placed between the glass slide and the mold to prevent the reflection of light during activation. Nanohybrid composite resin (Filtek™ Z250 XT, 3M ESPE) was placed into the teflon mold in a bulk increment. A transparent mylar strip was then placed on the resin mold and a translucent cover slip covered it.

A total of 30 samples were prepared and divided into two groups.

- Group IIA - 15 samples were cured with QTH LCU.
- Group IIB - 15 samples were cured with LED LCU.

All the samples were cured for the given time as per manufacture's instructions. Curing was performed at three points (center, right end, and left end) of the resin mold for all the samples. After being light activated, the samples were stored individually in a lightproof container for 1 week at 37°C. Then, the samples were checked for flexural strength under Universal Testing Machine (ACME, INDIA. MODEL: UNITEST. Crosshead Speed 1 mm/min).

RESULTS

The results obtained for comparison between quartz-tungsten halogen and light emitting diode curing units for depth of cure and flexural strength are as summarized in [Table 1 and 2].

Depth of cure was significantly higher for light emitting diode curing unit as compared to quartz-tungsten halogen curing unit with a *p* value of 0.001 [Table 1]. Similarly, flexural strength was also significantly higher for light emitting diode curing unit as compared to quartz-tungsten halogen curing unit with a *p* value of 0.019 [Table 2].

DISCUSSION

The popularity of tooth-colored restorations has promoted the use of light-activated resin composites, and since then, many light sources are introduced to the dental market for polymerizing light-cured restorative materials.^[1,8]

The depth of cure and flexural strength is considered essential physical properties of composite resin materials, relevant to the clinical technique of incremental packing and curing.^[3] In the present study, curing effectiveness was measured using indirect scraping method and flexural strength was measured under universal testing machine. A load was increased gradually from “0” until maximum/fracture load was obtained under 3-point Bend Test Jig with a crosshead speed of 1 mm/min.

Nanohybrid composite resin was used in this study. It has been established that the properties of composite resins are dependent on the material composition.^[9,10] In general, the monomer constituents affect the degree of conversion, viscosity, surface tension, and contact angle, and it also influences the flexural strength of composite resin.^[9] The filler characteristics affect the mechanical properties of the resin composites and it has been shown that a correlation exists between filler content and mechanical properties.^[8,11]

The better depth of cure of composite resin by LED LCU can be ascertained by the fact that spectral output falls conveniently within the absorption spectrum of camphorquinone (CQ), conversion of electrical energy into light more efficiently, operation for thousands of hours with a constant light output and spectra, etc.^[3]

LED LCU has an emission spectrum similar to the absorption spectrum of CQ photoinitiator. This spectral homogeneity allows complete usage of the emitted light by LED LCU, which otherwise does not happen with halogen light.^[8] Thus, the better flexural strength of resin composite by LED LCU can also be ascertained by the fact that the convolution of the absorption spectrum of the CQ photoinitiator present in these composites matches the emission spectrum of the LED LCU.

CONCLUSION

LED-curing unit showed greater depth of cure and flexural strength compared to QTH-curing unit.

The results obtained from this *in vitro* study may vary from the clinical outcome. Hence, further long-term clinical studies should be carried out utilizing different dimensions, materials, modes of curing units, and exposure durations to evaluate the efficiency of LCU.

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Comparative Evaluation of 0.2% Ropivacaine versus 0.125% Ropivacaine under Combined Spinal-epidural Technique for Labor Analgesia

Sujata Sharma¹, Veena Chatrath², Ranjana Khetarpal³, Puneetpal Kaur⁴

¹Professor and Head, Department of Obstetrics and Gynaecology, Government Medical College, Amritsar, Punjab, India, ²Professor and Head, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India, ³Professor, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India, ⁴Junior Resident, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India

Abstract

Background: Both pharmacological and non-pharmacological strategies for pain relief in labor have been tried and tested since long. Combined spinal-epidural analgesia (CSEA) satisfies the basic requisites of labor analgesia. Various concentrations of local anesthetics along with the addition of opioids can be used. The objective of this study is to compare the quality of labor analgesia with two different concentrations of ropivacaine (0.2% vs. 0.125%) and assess fetomaternal outcome.

Materials and Methods: A total of 60 primipara women with a singleton pregnancy in active labor were given CSEA after randomly allocating them in two groups of 30 each. Both Group A and Group B received intrathecal injection of 4 mg (2 ml) 0.2% ropivacaine + 25 µg (0.5 ml) fentanyl: Group A - epidural dose of 15 ml of 0.2% ropivacaine solution + 2 µg/ml fentanyl and Group B - epidural dose of 15 ml of 0.125% ropivacaine + 2 µg/ml fentanyl. Then, continuous epidural infusion was started at the rate of 10 ml/h which was continued until the end of delivery.

Results: Group A showed better maintenance of analgesia and better maternal satisfaction while parturients in Group B needed rescue top-up analgesia due to breakthrough pain.

Conclusions: It was concluded that ropivacaine in both concentrations (0.2% and 0.125%) with fentanyl is effective for initiation of labor analgesia. However, quality of analgesia with 0.2% ropivacaine concentration is superior to 0.125% concentration.

Key words: Combined spinal-epidural, Fentanyl, Labor analgesia, Ropivacaine

INTRODUCTION

Childbirth is a major lifetime event in the life of a woman. Labor pain has higher score on pain scale when compared to other painful life experiences.^[1] Labor pain results in maternal stress response which is harmful to the mother and fetus.^[2] It leads to maternal stress-related release of catecholamines which affect both maternal and fetal hemodynamics. Pain relief can obtund all stress responses.

With advancing times, labor analgesia is becoming more popular, but providing safe and effective analgesia has been a challenge.^[3] Combined spinal-epidural analgesia (CSEA) technique has become more popular and favored in recent years.^[4] Low-dose local anesthetics and opioids lead to rapid onset of analgesia, and also, the duration of analgesia can be extended through the use of epidural catheter.

Local anesthetics alone or with adjuvants can be used for pain relief in regional techniques. Ropivacaine, a homolog of bupivacaine, has been associated with reduced incidence of cardiotoxicity and motor blockade.^[5] It provides better sensory motor differentiation so useful when motor blockade is not needed, has a better neonatal outcome, and allows for normal progression of labor and maternal ambulation.^[6] For providing optimal labor epidural analgesia, minimal concentrations of local anesthetics

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Corresponding Author: Dr. Ranjana, Department of Anaesthesia, Government Medical College, Amritsar - 143 001, Punjab, India.
Phone: +91-9815654322. E-mail: rkhetarpal9@hotmail.com

are continuously in the search. Studies comparing the efficacy of continuous infusion of 0.2% versus 0.125% ropivacaine for labor analgesia have not been done in our institution, which leads us to undertake this study. The primary outcome of the study was the onset and quality of labor analgesia. The secondary outcome was fetomaternal outcome, complications, and maternal satisfaction score.

MATERIALS AND METHODS

Approval from the institutional ethical committee was taken, and this study was conducted in our hospital on 60 term primiparous women who were in the age group of 20–35 years with ASA Grade I and II status, having uncomplicated pregnancy in vertex presentation and scheduled for normal vaginal delivery. Parturients in active labor and on request were included in this study. Exclusion criteria included coagulation/bleeding disorder, sepsis, cephalopelvic disproportion, vertebral column deformity, or infection at the site.

It was a prospective and randomized double-blind study. The power analysis was used for a sample size of a minimum of 30 subjects per group. Sixty parturients were randomly allotted to two groups of 30 each, using computer-generated table of random numbers. Double blinding was done to remove any bias, and the drugs were made by an anesthesiologist or person who was not involved in the study.

Both the Groups A and B were given intrathecal injection of 4 mg of 0.2% ropivacaine (2 ml) + 25 µg fentanyl (0.5 ml). Group A received epidural dose of 15 ml of 0.2% ropivacaine + 2 µg/ml fentanyl (30 µg), 0.2% ropivacaine from a 20 ml ampoule (Ropin®, Neon). Group B received epidural dose of 15 ml of 0.125% ropivacaine + 2 µg/ml fentanyl (30 µg), 0.125% ropivacaine made by taking 2.5 ml of 0.75% isobaric ropivacaine and diluting it with 12.5 ml of normal saline. 30 µg of fentanyl (Trofentanyl®) was made by taking six parts from a tuberculin syringe to divide 1 ml (50 µg/ml) into 10 parts and then added to ropivacaine in both the groups. The total volume of both the solutions was made up to 16 ml with normal saline. The continuous epidural infusion was set at 10 ml/h after the epidural dose and continued until the end of delivery.

Informed consent and pre-anesthetic evaluation were done, and demographic data of the parturients including age, height, weight, gestational age, cervical dilatation, and parity were recorded. Baseline visual analog scale (VAS) score and baseline vitals, i.e., heart rate (HR), non-invasive blood pressure, respiratory rate, and oxygen saturation were recorded. After securing intravenous (i/v) line for

preloading with ringer lactate (10 ml/kg body weight) and in left lateral decubitus position and strict asepsis, 2 ml of 2% lignocaine was infiltrated at L3–L4 or L4–L5 level. With 18G Tuohy needle using the loss of resistance technique, epidural space was identified. A 27G Whitacre spinal needle introduced through the lateral eye of Tuohy's needle, and after free flow of cerebrospinal fluid (CSF), the study drug was injected for subarachnoid block and epidural catheter was inserted and secured up to the depth of 3–4 cm into the epidural space. The catheter was aspirated for the presence of blood or CSF. The clinical signs of i/v injection were checked whether parturient felt dizzy or had tinnitus, and parturient was kept in supine position with left lateral tilt. An epidural bolus of the study solution was given when the parturient reported two consecutive contractions as painful (VAS >3) or regression of the effect of spinal analgesia until T10 level. Continuous epidural infusion of the study drug was started through the catheter at the rate of 10 ml/h and maintained at constant rate until the end of delivery. Analgesia was considered adequate if pain score on VAS ≤3. The rescue bolus dose of 5 ml of the study solution in respective groups was given to the parturient on demand at any time during labor.

VAS score and continuous hemodynamic monitoring of mother and also fetal HR monitoring were done. All the readings were recorded every 2 min for 10 min, every 5 min for 30 min, and every 15 min until 300 min or the end of study or whichever was earlier. Bradycardia (defined as HR <60 bpm) was treated with injection atropine i/v and hypotension (fall in systolic blood pressure below 90 mmHg or reduction of >20% from baseline value) was treated with i/v fluid bolus and if necessary with i/v injection ephedrine. Time of onset until complete analgesia was noted. Highest sensory level and motor blockade, requirement of rescue epidural top-up, and side effects were assessed. Maternal satisfaction score was assessed after 24 h of delivery with a scale of 5 - excellent, 4 very good, 3 - good, 2 - fair, and 1 - poor. The study ended at the time of delivery and catheter was removed.

Statistical Analysis

The data from the present study were compiled and analyzed using software IBM SPSS 23.0 (Armonk, NY: IBM Corp.) to draw relevant conclusions. The patient characteristics (non-parametric data) were analyzed using the “Chi-square test,” and the “Unpaired *t*-test” was used for intergroup comparison (parametric data). $P < 0.05$ was considered as statistically significant and $P < 0.001$ was considered as highly significant. Power analysis was used to calculate the power of the study by taking α error 0.05. The power achieved was well above 90%. The results were then analyzed and compared to previous studies.

RESULTS

No statistical difference was seen in demographic and baseline hemodynamic parameters in both the groups. The difference between the two groups for mean age, height, weight, and ASA grade was found to be statistically non-significant ($P > 0.05$). Parturients in both the groups had cervical dilatation of 3–4 cm at the time of administration of CSEA. $P = 0.605$ was observed which was statistically non-significant [Table 1].

The mean VAS was statistically significant at 135 min ($P < 0.05$) and 180 min ($P < 0.05$) and statistically non-significant at all other measured intervals ($P > 0.05$) [Figure 1]. The mean number of epidural top-ups required was 0 in Group A and 1.40 ± 0.55 in Group B. The difference between the two groups was statistically highly significant ($P < 0.001$) [Figures 2 and 3].

No significant hypotension was observed in parturients in both the groups. Pruritus was present in both the groups (66.67% - Group A and 63.33% - Group B). No significant nausea, vomiting, and shivering were observed in the parturients in both the groups. No case of respiratory depression and dural puncture was seen ($P > 0.05$) [Table 2].

APGAR score was noted at 1, 5, and 10 min in both the groups after the birth of the baby. Two babies in Group A had a score of 7 at 1 min and no baby had an Apgar score of <8 at 5 and 10 min in both the groups. The difference between both the groups was statistically non-significant ($P > 0.05$) [Table 3].

Maternal satisfaction score was measured by scale in which 5 was given for excellent, 4 for very good, 3 for good, 2 for fair, and 1 for poor. It was excellent in 24 parturients in Group A and was very good in 26 parturients in Group B. The difference was found to be statistically significant ($P < 0.05$) [Table 4].

DISCUSSION

In previous years, higher concentrations of local anesthetics were used which were associated with motor blockade, resulting

in limited ambulation during labor and decreased pelvic tone which impairs the bearing down efforts in the second stage of labor. At present times, low-dose local anesthetics are being used which block the painful stimuli and preserve the motor functions.^[7] It is intriguing to strike a balance between parturients' satisfaction score with good analgesia and reduce the motor block, thus making the parturient participate in labor and reducing the rate of instrumental deliveries.^[8]

The use of opioids prolongs the duration of analgesia but with side effects of pruritus, nausea, vomiting,

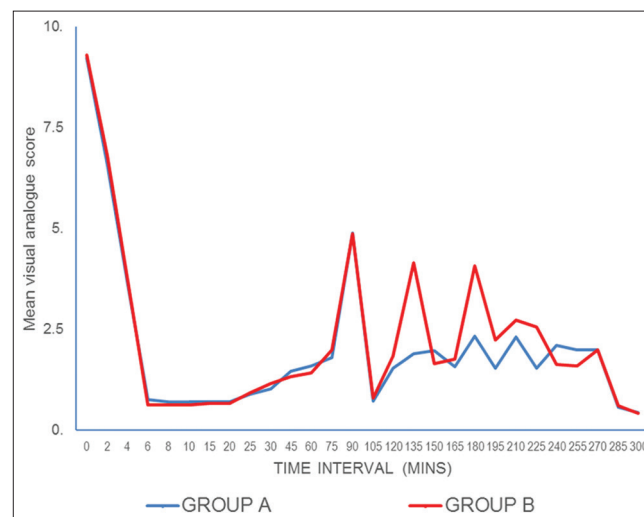


Figure 1: Mean visual analog scale score. *Showing significant difference at 135 min and 180 min

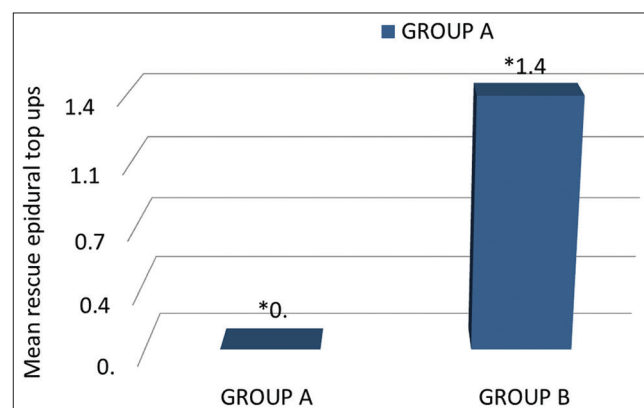


Figure 2: Mean rescue epidural top-up doses. *Showing significant difference between the two groups

Table 1: Demographic data and obstetric data

Parameters	Group A		Group B		P value
	Mean	SD	Mean	SD	
Age (years)	25.67	3.93	27.40	5.19	>0.05 (NS)
Height (cm)	152.73	2.91	153.80	8.06	>0.05 (NS)
Weight (kg)	64.47	6.11	65.40	7.83	>0.05 (NS)
Cervical dilation (cm)	3 (50%)	4 (50%)	3 (43.33%)	4 (56.67%)	>0.05 (NS)
VAS score (pre-block)	9.23	0.57	9.30	0.53	0.05 (NS)

Data are displayed as mean±SD or ratio. VAS: Visual analog scale, SD: Standard deviation

Table 2: Side effects and complications

Side effects and complications	Group A		Group B		P value	Significance
	Number of cases	% age	Number of cases	% age		
Maternal hypotension	2	6.67	1	3.33	2	>0.05 (NS)
Pruritus	20	66.67	19	63.33	20	>0.05 (NS)
Nausea/vomiting	2	6.67	1	3.33	2	>0.05 (NS)
Respiratory depression	0	0.00	0	0.00	-	-
Shivering	3	10.00	2	6.67	3	>0.05 (NS)
Dural puncture	0	0.00	0	0.00	-	-
Urinary retention	1	3.33	0	0.00	1	>0.05 (NS)
Post-dural puncture headache	0	0.00	0	0.00	-	-

Table 3: Apgar score

Groups	Apgar score		
	At 1 min	At 5 min	At 10 min
Group A			
<7	2	0	0
8	11	6	2
9	16	18	20
10	1	6	8
Group B			
<7	0	0	0
8	16	11	2
9	14	18	25
10	0	1	3
χ^2 value	4.06	5.04	2.83
P value	0.25	0.10	0.24
Significance	>0.05 (NS)	>0.05 (NS)	>0.05 (NS)

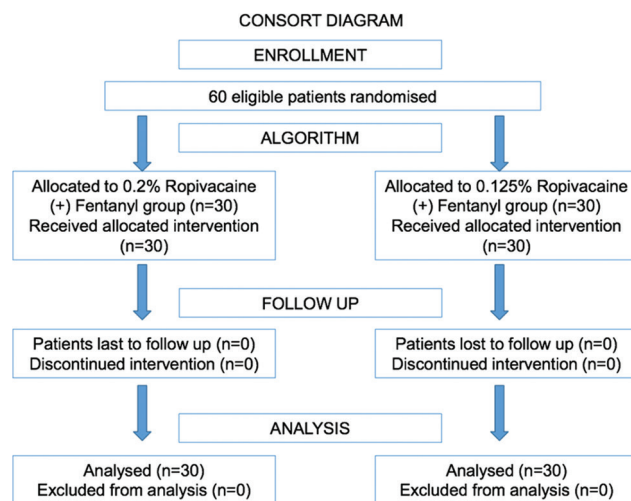
Table 4: Maternal satisfaction score

Score	Group A		Group B	
	Number of cases	% age	Number of cases	% age
5	24	80.00	-	-
4	6	20.00	26	86.66
3	-	-	4	13.34
2	-	-	-	-
1	-	-	-	-
LSCS	-	-	-	-
Total	30	100.00	30	100.00

Scale of 5 - excellent, 4 - very good, 3 - good, 2 - fair, 1 - poor. LSCS: Lower segment cesarean section

respiratory depression, fetal HR abnormalities, and urinary retention.^[9] Ropivacaine causes lesser motor blockade due to its selective action on A δ and C fibers (involved in pain transmission) rather than on A β fibers (involved in motor function) and is lesser cardiotoxic. There are a relatively fewer number of studies depicting the role of different concentrations of ropivacaine for labor analgesia. Many authors concluded that ropivacaine 0.2% offers adequate analgesia, better than 0.15% or 0.1% concentration with minimal motor block and hemodynamic side effects.^[10]

Both the groups were comparable in mean age, weight, height, and ASA grade and cervical dilatation. The mean cervical dilatation was 3.2 ± 0.52 cm in Group A and $3.53 \pm$

**Figure 3: Consort diagram**

0.6 cm in Group B ($P > 0.5$). Previously, it was believed that a higher rate of cesarean was observed with epidural being started early in labor (< 2 cm).^[11] The ACOG statement had suggested that epidural analgesia is to be delayed until 4–5 cm cervical dilatation based on the study published by Thorpe *et al.*^[12] Current ASA guidelines recommend that maternal request for labor pain relief is sufficient justification for intervention and the decision should not depend on arbitrary cervical dilation.

The mean onset of analgesia was 5.58 ± 0.5 min in Group A and 5.53 ± 0.48 min in Group B. Hughes *et al.*,^[13] in their study, compared 2.5 mg ropivacaine and 2.5 mg bupivacaine and observed the onset of analgesia to be 6.5 ± 2.3 min in ropivacaine group. The mean duration of analgesia after subarachnoid block was 90.17 ± 8.96 min in Group A and 90.00 ± 10.12 min in Group B. In a study done by Kim *et al.*,^[14] it was concluded that intrathecal ropivacaine offered shorter duration of analgesia (87 ± 47 min) as compared to levobupivacaine (122 ± 56 min). However, ropivacaine offered a greater margin of safety in systemic toxicity and favorable sensory motor differentiation. Low-dose anesthetics reduce the incidence of motor blockade. 83.34% of parturients in Group A and 86.66%

of parturients in Group B had no motor blockade. Motor block of Grade 2 or 3 was not seen in the parturients in any of the groups. Higher incidence of motor block in older studies could be due to the use of higher concentrations of ropivacaine (0.75%^[15] and 0.5%^[16]).

The mean VAS 15 min after the first epidural dose was 0.73 ± 0.68 in Group A and 0.80 ± 0.79 in Group B. The mean VAS scores were significantly higher in Group B at 135 and 180 min. Thus, breakthrough pain leads to the use of rescue top-up bolus doses (5 ml bolus of study solution) in Group B. Mean number of rescue epidural top-up in Group B was 1.40 ± 0.35 and 0 in Group A until the end of delivery ($P < 0.001$, highly significant). A study was conducted in a total of 60 term parturients by Chuttani *et al.*, for comparison of low concentrations of levobupivacaine (0.1%) versus ropivacaine (0.1%) with fentanyl, for which background infusion and on-demand bolus of the study solutions were used with patient-controlled epidural analgesia pump. It was observed that the number of manual rescue bolus doses was found to be more in ropivacaine group.^[17]

Hemodynamic parameters were also compared. All the parturients had spontaneous vaginal delivery. No statistical significance was observed in side effects and complications in both the groups. Hypotension was observed which responded to i/v fluids. Most common side effect observed was pruritus in both the groups. All cases of pruritus were mild and required no treatment. Postulated mechanism of pruritus due to fentanyl is the modulation of serotonergic pathways and medullary dorsal horn activation. In a study done by Fan *et al.*, in 60 parturients comparing tramadol and fentanyl with ropivacaine, it was found that pruritus was present in 13% of parturients in the fentanyl group alone.^[18] Nausea, vomiting, and shivering were also noted. No case of dural puncture, PDPH, and respiratory depression was observed.

There was no fetal HR abnormality detected. Apgar score was favorable at 1, 5, and 10 min and fetal outcome was good. Maternal satisfaction score was significantly better in Group A.

Our study demonstrated that 0.2% ropivacaine offered superior quality of analgesia than 0.125% ropivacaine. More breakthrough pain leading to the use of rescue epidural analgesia was observed in 0.125% ropivacaine group (Group B).

Limitations

A large sample size could give a better outlook on maternal and neonatal outcome. Furthermore, limited parturients

were willing for labor analgesia in our institution. Cord blood sampling is important for the interpretation of blood gases and pH and gives an objective idea of fetal exposure to hypoxia during labor, but it was not done in our setup (technical issues). Besides, the comparison of intermittent bolus technique with continuous infusion could give a better measure of local anesthetic and opioid consumption.

CONCLUSIONS

Our study demonstrated that both 0.2% and 0.125% ropivacaine concentrations provided effective analgesia at the onset of labor. Analgesia in 0.2% ropivacaine group was found to be superior in terms of lesser breakthrough pain that leads to significantly better quality of analgesia and no need of rescue top-up bolus requirement.

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Perineal Wounds - Worried?? - Stayfree

B. R. Sathyakrishna¹, V. Yatheendra², Kalluri Meena Reddy³

¹Senior Surgeon and Unit Chief, Department of General Surgery, St. Martha's Hospital, Bengaluru, Karnataka, India, ²Post Graduate Student, Department of General Surgery, St. Martha's Hospital, Bengaluru, Karnataka, India, ³Senior Registrar, Department of General Surgery, St. Martha's Hospital, Bengaluru, Karnataka, India

Abstract

Introduction: Perineal wounds are difficult to manage as they need much frequent dressings at the hospital. Conventional dressings are costlier and cause significant discomfort to the patient. Self-dressings using sanitary pads can be tried as an alternative as they are hygienic, easily accessible, comfortable, and cost-effective.

Materials and Methods: A total of 30 patients - 15 in conventional dressing and 15 in sanitary pad dressing compared in terms of compliance, comfort level, number of dressings required at hospital, cost, and return to work.

Results: Patients with sanitary pad dressings were more comfortable with the method of dressing and had very less number of dressings at the hospital. It was very much cost-effective and patients returned very early to work.

Conclusion: Sanitary pad can be used as a good alternative to conventional gauze pad dressings.

Key words: Conventional gauze pad dressing, Sanitary pad dressing, Perineal wounds

INTRODUCTION

Perineum is the area between the pubic symphysis up to the coccyx including the urogenital and perianal region. Wounds in this region are difficult to manage as they easily get contaminated from the urogenital or anal canal proximity. Daily dressings can be very inconvenient to the patient as it involves frequent visit to the hospital and involves a huge financial burden. The heavy padding done can cause significant discomfort to the patient. Frequent soakage of the dressing and malodorous lesions can significantly affect the quality of life of the patient.

MATERIALS AND METHODS

We conducted a prospective study at St. Martha's Hospital from a total of 30 patients were included in the study.

15 received conventional gauze pad dressing, whereas the other 15 were taught sanitary pad dressing and were advised to review in the outpatient department once weekly. The two groups were compared in terms of compliance, comfort level, number of dressings required at hospital, cost, and return to work.

Conventional Dressing

In conventional dressing, betadine and saline are used to clean the wound. Good padding is done to cover the wound and is secured with a adhesive tape Figure 1. Patient has to come daily to the hospital for dressings.

Sanitary Pad Dressing

The patient after being demonstrated self dressing from POD 1, wherein he applies the pad to his inner wear using the sticky surface of the pad and secures it with the wings of the pad. He applies the prescribed ointment over the part of the area of the pad which comes in contact with the wound and wears the inner wear along with the pad. Patient visits weekly once to the hospital for follow-up.

RESULTS

A number of dressing at the hospital for the conventional group were around 19.53, which cost the patient

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Corresponding Author: Dr. B. R. Sathyakrishna, 242, 1st B Main, WCR, 2nd Stage, Mahalakshimpuram, Bengaluru - 560 086, Karnataka, India. E-mail: dr.brsk@gmail.com



Figure 1: Soakage due to anal canal proximity



Figure 2: Pictures showing difference between the conventional and gauze pad dressing

approximately 2930 rupees. These patients took around 17.53 days to return to work. The other groups received around 8.2 dressings at hospital. Cost incurred was around 1230 rupees and they returned to work as early as 6.2 days. The above result showed sanitary pad dressing being more cost-effective and patient friendly.

15 Patients in each group	Dressings	Mean	P value
Number of dressings at hospital	Conventional	19.53	<0.001
	Sanitary pad dressing	8.20	
Total cost for dressing – in Rupees	Conventional	2,930	<0.001
	Sanitary pad dressing	1,230	
Return to work- number of days	Conventional	17.53	<0.001
	Sanitary pad dressing	6.20	

	Conventional	Sanitary pad
Fistula in Ano	3	3
Peri-anal abscess	5	2
Fournier's gangrene	2	5
Pilonidal wounds	5	5
Total	15	15



Figure 3: Sanitary pad dressing – Shows no bulge over the inner wear



Figure 4: Sanitary pad dressing done to a fistulectomy wound

DISCUSSION

Wounds in the perineum get easily soaked due to anogenital proximity. Patients with such wounds need constant care and frequent change of dressing due to early soakage. It is practically difficult to get al. dressings done at the hospital. Moreover, dressing at hospital can lead to a significant cost burden on the patient and daily travel makes it more inconvenient. Heavy padding done during the dressing makes the patient unable to wear the regular clothing's, thereby limiting one's day-to-day activities Figure 2 and 3. Whereas, dressing using sanitary pad can be done at home without anybody's help by the patient himself, thereby avoiding the cost of dressing at the hospital. The pads are very less bulky Figure 4 and have a very good absorbing capacity. They can be changed any number of times as and when it is soaked, which can help in faster healing of the wound. As they can be worn under regular garments without any discomfort, patient can return to work very early with confidence Figure 3. The pads are hygienic, easily available, and cost-effective and have already been tried as an alternative to conventional dressings.

In 1998 Smooth EC used sanitary pad as an alternative for dressing in post op wounds.^[1] Similar studies were published in 1999 and 2003 by Varon J and Demir A respectively.^[2,3] Shetty VD used sanitary pads to dress the hip and knee replacement surgery wounds in 2010.^[4]

CONCLUSION

As sanitary pads are hygienic, easily available, and cost-effective, more comfortable and self-dressing can be done by the patient, it can be used as an alternative to the conventional gauze pad dressing for perineal wounds.

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A Comparative Study to Assess Blood Loss during Abdominal Myomectomy by Tourniquet Application versus Intramyometrial Vasopressin Injection

Sujoy Dutta¹, Subrata Samanta², Subrata Lahiri³, Sudipta Samanta⁴, Agrima Mullick⁵

¹Senior Resident, Department of Gynaecology and Obstetrics, ESI PGIMS, Esic Medical College and Esic Hospital, Kolkata, West Bengal, India, ²Assistant Professor, Department of Gynecology and Obstetrics, Rampurhat Government Medical College, Rampurhat, West Bengal, India, ³Head, Department of Gynecology and Obstetrics, South Eastern Railway Central Hospital, Kolkata, West Bengal, India, ⁴Intern, Department of Gynaecology and Obstetrics, R.G. Kar Medical College and Hospital, Kolkata, West Bengal, India, ⁵Intern, Department of Gynaecology and Obstetrics, R.G. Kar Medical College and Hospital, Kolkata, West Bengal, India

Abstract

Objective: The objective of this study was to determine the efficacy of applying uterine artery tourniquet and intramyometrial vasopressin injection to reduce intraoperative blood loss during abdominal myomectomy.

Methods: A comparative interventional study comparing parameters in the two groups of patients containing 24 each where one received tourniquet application and other received intramyometrial vasopressin.

Results: Pre-operative hemoglobin (Hb) was comparable in both mean 10.5 ± 0.50 g/dl in tourniquet group and 10.5 ± 0.47 g/dl in vasopressin group. Pre-operative hematocrit (Hct) was also comparable in both mean $31.8 \pm 1.44\%$ in tourniquet group and $31.7 \pm 1.51\%$ in vasopressin group. Mean operative time was 49.0 ± 10.33 min in tourniquet group and 48.8 ± 9.62 min in vasopressin group which was statistically indifferent. Amount of mean blood loss in the tourniquet group was 467.9 ± 74.50 cc and 356.45 ± 58.35 cc in vasopressin group which is significantly higher in former. Post-operative day 3 Hb was lower in tourniquet group 8.94 ± 0.52 g/dl than 9.45 ± 0.52 g/dl in vasopressin group. Reduction in Hb postoperatively was more in tourniquet group 1.43 ± 0.45 g/dl than vasopressin group 0.92 ± 0.20 g/dl. Reduction in Hct postoperatively was more ($4.82 \pm 1.4\%$) in tourniquet group than in vasopressin group ($2.74 \pm 0.62\%$). Blood transfusion was required 5 (20.83%) cases in tourniquet group, but only in 2 (8.33%) cases of vasopressin group though it was statistically indifferent between both groups.

Conclusion: Application of tourniquet had more mean operative time, intraoperative blood loss, and requirement of blood transfusion. There is more reduction in Hb and Hct postoperatively in tourniquet application.

Key words: Hemoglobin, Hematocrit, Myoma, Myomectomy, Uterine artery, Vasopressin

INTRODUCTION

Uterine myoma (fibroid, leiomyoma, and leiomyofibroma) is the most common benign pelvic tumor in females originating from the myometrium of uterus occurring during the middle and late reproductive age group

having an incidence of 40% by age 35 Caucasian women.^[1] They are composed of large amounts of the extracellular matrix - mainly collagen type 1 and type 2 fibers.^[2] Although precise causes are unknown, the hormonal and growth factors are considered responsible for myoma.^[3]

Size and location are the main factors that determine symptoms and problems.^[4] Different locations are intramural, subserosal, and submucosal myoma. Removal is necessary in large myoma causing pain, abnormal uterine bleeding, pressure symptoms, infertility, or significant cavity distortion. Removal of submucous myoma improves fertility to near-baseline rates.^[5]

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Corresponding Author: Dr. Subrata Samanta, Department of Gynecology and Obstetrics, 152/A, Gopal Lal Tagore Road, Kolkata-700 108, West Bengal, India. Phone: +91-9433178391. E-mail: drsubratasamanta@gmail.com

Despite many options, myomectomy is important for women desiring to preserve uterus for reproduction or menstruation. Myomectomy has different routes depending on location, number of lesions, the experience, and preference of the surgeon.

Uterine myomas have more arterioles and venules causing significant blood loss.^[6] The average blood loss during myomectomy is 200–800 ml.^[7,8] Myoma distorts normal vascular architecture.^[9,10]

Traditional abdominal incision during myomectomy may transect these vessels causing profuse hemorrhage. Other options are laparoscopy or by robotic surgery, but robotic surgery is not superior to laparoscopy.^[11] A submucous myoma <5 cm may be removed by hysteroscopy.^[12] Open approach is often preferred for large myomas. Despite different methods, recurrence of new myomas occurs in 42–55% of cases.^[13] Furthermore, these methods do not prevent the rupture of uterus in later pregnancy.^[14]

Each myoma is surrounded by a dense vascular layer separated from the myometrium by a narrow avascular cleft.^[15] Bleeding can be prevented if dissection is done through the avascular cleft or decreased with mechanical or pharmacological methods. Intramyometrial vasopressin injected into the planned uterine incision site for each myoma reduces blood loss. Vasopressin acts by constricting the smooth muscles in the capillaries, small arterioles, and venules. It also causes retention of water in the body.^[16,17]

Another method to reduce blood loss is to apply a uterine artery tourniquet. Using uterine artery tourniquet compared without tourniquet resulted in a significant decrease in blood loss in the tourniquet group.^[18] Previous randomized trials showed that blood loss during myomectomy was reduced significantly with intramyometrial vasopressin use than with placebo (299 ml less)^[19] and also less than or comparable to using uterine artery tourniquet.^[20,21] Till date, there are few studies comparing the effect of intramyometrial vasopressin injection versus tourniquet application to reduce intraoperative blood loss. There are also very few clear inferences regarding which one is better method to reduce blood loss. Therefore, this study aims to compare the effectiveness of intramyometrial vasopressin injection versus using uterine artery tourniquet in reducing blood loss during myomectomy.

METHODS

Study Area

This study was conducted at the Department of Obstetrics and Gynaecology, South Eastern Railway Hospital, Garden Reach, Kolkata.

Study Period

The study duration was from December 15, 2013, to December 14, 2014.

Study Population

Women of reproductive age group are attending at the outpatient department (OPD) of gynecology and admitted for myomectomy.

Study Design

A comparative interventional study in which comparison of parameters was made in the two groups of patients.

Sample Design

Patients were allocated randomly in two groups “A” and “B” groups - “A” group receiving conventional tourniquet application and “B” group receiving intramyometrial vasopressin injection.

Sample Size

This is a comparative interventional study comparing parameters in a total of 48 subjects made in the two groups of 24 each. Subjects were randomly chosen from women of reproductive age group attending at gynecology OPD and were admitted for myomectomy between December 15, 2013, and December 14, 2014.

Inclusion Criteria

The following criteria were included in the study:

- Women of reproductive age group having symptomatic myoma, not responding to medical therapy.
- Women of reproductive age group having asymptomatic myoma, sonologically diagnosed, with desire for fertility.
- The size of uterus is 10–16 weeks.
- The total number of myoma not more than three (sonologically diagnosed)

Exclusion Criteria

The following criteria were excluded from the study:

- Women of above and below reproductive age group (15–45 years).
- Women not desiring to preserve their uterus.
- Women having myoma >16 weeks size.
- Women having more than three (sonologically diagnosed).
- Women having severe anemia or hemodynamic instability.
- Women unfit for anesthesia.
- History of a bleeding disorder, heart disease, renal disease, etc.
- Women on concurrent anticoagulant therapy.
- Pre-operative hemoglobin (Hb) level of <9.0 g/dl.
- Women having other concomitant conditions such as pregnancy or any malignancy or endometriosis having impact on blood loss.

- The intraoperative time for removal of myoma >2 h.
- History of previous myomectomy.

Study Variables

- Pre-operative Hb and hematocrit (Hct)
- Immediate and 3rd post-operative Hb and Hct
- Duration of surgery
- Blood loss during surgery
- Requirement of blood transfusion

Study Tools

- Clinical history and detailed examination - Uterine size and shape (multiple or single myoma).
- USG of pelvic organs: Pre-operative sonographic evaluation size, number, location, and volume of myomas.
- Pre-operative investigations: Pre-operative Hb and Hct values.
- Intraoperative uterine size by direct examination

Estimation of Blood Loss in Both Groups

1. Weighing of all dry mops before operation and all blood-soaked mops after operation
2. Collecting blood from the suction machine collection bottle (at the starting, the bottle was empty every time)
 - Total blood loss during operation = X + Y ml
 - (Weight of blood-soaked mops – weight of dry mops) = X gm \approx X ml
 - 1 g blood \approx 1 ml of blood
 - Blood collected from suction bottle = Y ml
3. Intra- and post-operative blood transfusion
4. Reduction of Hb and Hct (measured immediate post-operative day and day 3 uniformly) from pre-operative values
5. Blood transfusion requirement in post-operative period
6. Operative time

Study Technique

- Approval from the Ethical Committee, Central Hospital, S.E. Railway, Garden Reach, was obtained.
- After admission for myomectomy, written informed consent of the patient was taken after proper counseling for either of the procedures.
- Patients are allocated randomly in two groups, i.e.,
- Group A (Tourniquet group): 24 women randomized for myomectomy with tourniquet application.
- Group B (Vasopressin group): 24 women randomized for myomectomy after vasopressin administration.
- Detail clinical examination and pre-operative investigations were done - Hb, Hct, abdominal ultrasonography, etc.
- Operative methods:
- The skin incision was Pfannenstiel incision. The uterus

was exteriorized, bowels packed away with two large dry mops.

- 20 units of vasopressin, diluted in 100 ml of normal saline, were injected intramyometrial and surrounding myoma before giving incision over myoma; but the volume of vasopressin injected varied depending on the number of myomas to be removed.
- In the other group, tourniquet was applied to occlude the uterine vessels:
 - Palpate the broad ligament just above the level of internal OS to identify a space that is free of vessels and the ureter, lateral to uterine artery.
 - Make 1 cm incision in this clear space bilaterally.
 - Pass the tourniquet (A latex-free tourniquet in a latex allergic patient) through the incisions with the ends protruding anteriorly.
 - Pull the tourniquet tight and secure by securing the ends with a clamp. Tightness was assured by blanching of uterus after tourniquet application. Take care to avoid enlarging the broad ligament incisions and damaging the surrounding structures.
 - Simultaneously atraumatic clamps or tourniquets were applied over infundibulopelvic ligaments bilaterally to reduce blood flow from ovarian vessels, especially in fundal fibroids. Every 15–20 min clamps or tourniquets were released to maintain blood flow to ovaries. Care was taken for not to damage tubes, ureters, ovaries, and vessels.
- Intraoperative blood loss estimation by:
 - Weighing of all dry mops before operation and all blood-soaked mops after operation.
 - Collection of blood from the suction machine collection bottle (at the starting of the operation, the bottle was empty every time).
- Intraoperative blood transfusion.
 - Reduction of Hb and Hct (measured immediate post-operative day and day 3 uniformly) from pre-operative values.
 - Blood transfusion requirement in post-operative period.
 - Operative time and complications are noted.

Pre-operative, intraoperative, and post-operative data were collected in prescribed pro forma. Data were collected during a span of 1 year and were charted in Excel worksheet; then, the data were analyzed using Epi Info™ 3.5.3 to detect effectiveness of both methods in reducing blood loss.

Statistical Analysis

Statistical analysis was performed with the help of Epi Info™ 3.5.3., a trademark of the Centers for Disease

Control and Prevention. Using this software, basic cross-tabulation, inferences, and associations were performed.

Descriptive statistical analysis was performed to calculate means with corresponding standard deviations (SD). Test was used to test the association of different study variables with the study groups. Z-test (standard normal deviate) was used to test the significant difference between two proportions. *t*-test was used to compare the means. Odds ratio (OR) with 95% confidence interval had been calculated to find the risk factors. Multivariate logistic regression was used to estimate the OR after adjusting the confounding factors. $P \leq 0.05$ was considered statistically significant.

RESULTS

Mean Hb and Hct (Hct) Level in Pre-operative, Immediate, and 3rd Post-operative Period [Table 1]

Chi-square test showed no significant association between the groups in terms of pre-operative Hb ($= 0.62$; $P = 0.73$) and Hct ($= 0.43$; $P = 0.80$). However, Chi-square and *t*-test showed significant association between Hb level in two groups in both immediate ($= 8.58$; $P = 0.013$) and 3rd post-operative period ($= 11.37$; $P = 0.003$). Similarly, significant association between Hct levels in two groups in both immediate ($= 20.97$; $P = 0.00001$) and 3rd post-operative period ($= 19.76$; $P = 0.0001$). *t*-test showed that Group B had significantly higher mean Hb and Hct level in both immediate and 3rd post-operative day.

Mean Fall of Hb in Immediate and 3rd Post-operative day [Figure 1]

t-test showed that mean fall of Hb both in immediate ($t_{46} = 4.63$; $P < 0.00001$) and 3rd post-operative period ($t_{46} = 3.17$; $P < 0.0001$) in two groups was significantly higher for Group A.

Mean Fall of Hct in Immediate and 3rd Post-operative Day [Figure 2]

t-test showed that the mean fall of Hct both in immediate ($t_{46} = 6.07$; $P < 0.00001$) and 3rd post-operative day ($t_{46} = 4.82$; $P < 0.0001$) in two groups was significantly higher for Group A.

Intraoperative Blood Loss [Table 2]

Chi-square test showed that there was a significant association between loss of blood during surgery between groups ($P = 0.0002$).

t-test showed that mean amount of blood loss during surgery in Group-A was significantly higher than that of Group-B ($t_{46} = 5.26$; $P < 0.0001$).

Duration of Surgery (Table 3)

Chi-square test showed that there was no significant association between duration of surgery and groups ($P > 0.05$). The mean duration of surgery (mean \pm SD) of the patients of Group-A was 49.00 ± 10.33 min with range 30.0–65.0 min and the median was 49.0 min. The mean duration of surgery (mean \pm SD) of the patients of Group-B was 48.79 ± 9.62 min with range 30.0–65.0 min and the median was 46.5 min.

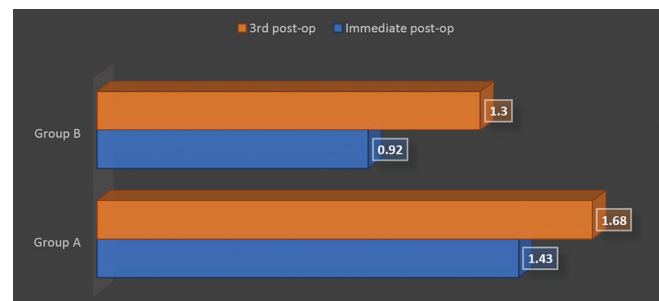


Figure 1: bar diagram showing the mean fall of Hb (in gm%) in immediate and 3rd post-operative day after intervention in each

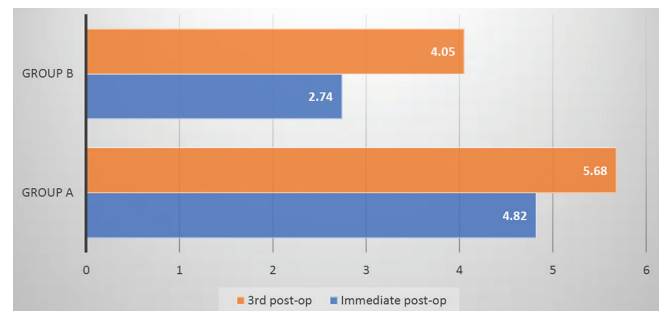


Figure 2: Bar diagram showing the mean fall of Hct (in %) in immediate and 3rd post-op period after intervention in each group

Table 1: Mean Hb and Hct level in pre-operative, immediate, and 3rd post-operative day

Period	Parameter*	Group A (Mean \pm SD)	Group B (Mean \pm SD)
Pre-operative	Hb	10.54 \pm 0.5	10.45 \pm 0.46
	Hct	31.80 \pm 1.44	31.69 \pm 1.51
Immediate post-operative	Hb	9.11 \pm 0.51	9.52 \pm 0.48
	Hct	26.97 \pm 1.51	28.95 \pm 1.57
At 3 rd post-operative	Hb	8.94 \pm 0.52	9.45 \pm 0.52
	Hct	26.45 \pm 1.55	28.74 \pm 1.69

*Hb levels are expressed in "gm%" and Hct levels are expressed in "%." Hb: Hemoglobin, Hct: Hematocrit, SD: Standard deviation

Table 2: Distribution of patients according to their loss of blood during surgery

Blood loss (in ml)	Group A (n=24)	Group B (n=24)	Total
300–400 ml	7	21	28
401–500 ml	8	2	10
501–600 ml	9	1	10
Total	24	24	48
Mean±SD	467.91±74.49	356.45±58.35	

$P=0.0002$, S - Significant. SD: Standard deviation

Table 3: Distribution of patients according to their duration of surgery

Duration of surgery (in min)	Group A (n=24)	Group B (n=24)	Total
30–45	11	12	23
46–60	12	11	23
>60	1	1	2
Total	24	24	48
Mean±SD	49.00±10.33	48.79±9.62	

$P=0.95$, NS - Not significant. SD: Standard deviation

Table 4: Distribution of patients according to the requirement of blood transfusion

Requirement of blood transfusion	Group A (n=24)	Group B (n=24)	Total
Yes	5	2	7
No	19	22	41
Total	24	24	48

t -test showed that there was no significant difference between the mean duration of surgery of the two groups ($t_{46} = 0.06$; $P > 0.05$).

Requirement of Blood transfusion (Table 4)

Test of proportion showed that proportion of patients with requirement of post-operative blood transfusion was significantly higher in Group-A than that of Group-B ($Z = 2.51$; $P < 0.05$).

DISCUSSION

The total number of patients was 48. 24 of them were recruited in each group (tourniquet group or Group A and vasopressin group or Group B). No one was lost from the study.

In literatures, various methods are described to reduce blood loss during myomectomy,^[18–21] but studies comparing intramyometrial vasopressin versus tourniquet application were minimum.^[21]

Pre-operative Hb values were comparable in both groups, i.e., mean 10.5 ± 0.50 g/dl in tourniquet group (Group A) and 10.5 ± 0.47 g/dl in vasopressin group (Group B)

($P = 0.515$) [Table 1]. Pre-operative Hct values were also comparable in both groups, i.e., mean $31.8 \pm 1.44\%$ in tourniquet group (Group A) and $31.7 \pm 1.51\%$ in vasopressin group (Group B) ($P = 0.808$) [Table 1]. These are important parameters required for the calculation of the reduction of Hb and Hct postoperatively. Taylor *et al.* included all patients having pre-operative Hb ≥ 10.5 g/dl.^[22]

Immediate mean post-operative Hb was lower in tourniquet group (Group A) 9.11 ± 0.51 g/dl than 9.52 ± 0.48 g/dl in vasopressin group (Group B) ($P = 0.00001$) [Table 1]. There was a significant mean reduction in Hb in post-operative period in both groups ($P \leq 0.00001$), but it was more in tourniquet group (Group A) (1.43 ± 0.45 g/dl) in comparison to vasopressin group (Group B) (0.92 ± 0.20 g/dl) [Figure 1].

Immediate post-operative Hct was lower in tourniquet group (Group A) $26.45 \pm 1.55\%$ (R: 24.5–31%) in comparison to $28.95 \pm 1.57\%$ (R: 25.5–32%) in vasopressin group (Group B) ($P \leq 0.0001$) [Table 1]. Mean reduction in Hct value in post-operative period was $4.82 \pm 1.4\%$ in tourniquet group (Group A) versus $2.74 \pm 0.62\%$ in vasopressin group (Group B) ($P \leq 0.0001$), and it was more in tourniquet group [Figure 2].

Post-operative day 3 Hb was lower in tourniquet group (Group A) 8.94 ± 0.52 g/dl (R: 8.1–10.4 g/dl) than 9.52 ± 0.48 g/dl (R: 8.4–10.6 g/dl) in vasopressin group (Group B) ($P = 0.001$) [Table 1]. There was significant mean reduction in Hb in post-operative period in both groups ($P \leq 0.00001$), but it was more in tourniquet group (Group A) (1.68 ± 0.16 g/dl) in comparison to vasopressin group (Group B) (1.31) [Figure 1].

Post-operative day 3 Hct was lower in tourniquet group (Group A) $26.45 \pm 1.55\%$ (R: 24.5–31%) in comparison to $28.74 \pm 1.69\%$ (R: 25.5–32%) in vasopressin group (Group B) ($P \leq 0.0001$) [Table 1]. Mean reduction in Hct value in post-operative period was $5.68 \pm 0.45\%$ in tourniquet group (Group A) versus $4.05 \pm 0.07\%$ in vasopressin group (Group B) ($P \leq 0.0001$), and it was more in tourniquet group [Figure 2]. Frederick *et al.* showed in his study 1.7 g/dl fall in Hb and 5 % fall in Hct at post-operative period with the use of vasopressin.^[23] Recently, in a study done in Japan, in 26 patients who underwent myomectomy, the intraoperative blood loss was reduced by the vasopressin administration, and their treatment results were compared with seven patients who underwent only myomectomy. The vasopressin was administered by the intramyometrial injection. There was no difference in the operation time between both groups, but intraoperative blood loss was lower in vasopressin group.^[24]

An average intraoperative blood loss of 540 ml was reported in a review of abdominal myomectomy for

uterine size exceeding 14 weeks despite the use of different non-mechanical techniques to reduce blood loss during surgery.^[25] In our study, the amount of mean blood loss in the tourniquet group (Group A) was 467.9 ± 74.50 cc versus 356.45 ± 58.35 cc in vasopressin group (Group B) which is significantly higher in the tourniquet group ($P \leq 0.001$) [Table 2], and it was almost nearly comparable with the review report of Royal Australian and New Zealand College of Obstetricians and Gynaecologists where also showed the superiority of intramyometrial vasopressin administration.^[26]

The mean operative time was 49.0 ± 10.33 min (R: 30–60 min) in tourniquet group (Group A) and 48.8 ± 9.62 min (R: 30–65 min) in vasopressin group (Group B) which was statistically indifferent ($P = 0.943$) [Table 3].

Blood transfusion was also required more, i.e., 5 (20.83%) cases in tourniquet group (Group A) and only in 2 (8.33%) cases of vasopressin group (Group B) though it was statistically indifferent between both groups ($P = 0.416$) [Table 4]. However, despite the use of one or more of these techniques to reduce blood loss during abdominal myomectomy up to one-third of the United Kingdom gynecologists use blood transfusion,^[22] but it was comparatively less in our study.

Histological examination of the resected tissue showed leiomyoma tissue in all patients and confirmed the diagnosis as myoma uteri.

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Concurrent Hyperfractionated Chemoradiation Versus Conventional Fractionated Chemoradiation with Low-dose Weekly Paclitaxel in Locally Advanced Non–Small-Cell Lung Cancer in a Tertiary Cancer Center in Kashmir: A Prospective Study

Wani Y Nahida¹, Subiya Kaneez², Bhat Tanveer³, Mohd Ashraf⁴, Muhib UI Haq⁵, Abdul Majeed⁶, Sanaullah Kuchay⁷

¹Registrar, Department of Radiation Oncology, Government Medical College, Srinagar, Jammu and Kashmir, India, ²Assistant Professor, Department of Radiation Oncology, Government Medical College, Srinagar, Jammu and Kashmir, India, ³Senior Resident, Department of Plastic and Reconstructive Surgery, SKIMS, Srinagar, Jammu and Kashmir, India, ⁴Chairman Tumor Board, ⁵Department of Oncology, Noora Hospital, Srinagar, Jammu and Kashmir, India, ⁶Professor and RSO, Department of Medical Physics, SKIMS, Srinagar, Jammu and Kashmir, India, ⁷Professor, Department of Cardiovascular and Thoracic Surgery, SKIMS, Srinagar, Jammu and Kashmir, India, ⁸Professor, Department of Radiation Oncology, Government Medical College, Srinagar, Jammu and Kashmir, India

Abstract

Introduction: Lung cancer is the most common cancer worldwide and has a poor prognosis but integration of chemoradiation has led to an increase in overall survival time and percentage of cured patients with acceptable toxicity.

Purpose: The purpose of this study was to compare the efficacy of hyperfractionated (HFX) radiotherapy with conventional radiotherapy and weekly concurrent paclitaxel in stage IIB/III non-small-cell lung cancer (NSCLC).

Materials and Methods: A total of 60 patients were enrolled, of which 30 patients were given twice daily radiotherapy (1.2 Gy each) to a total of 72 Gy over 5–6 weeks and 30 patients were given single daily fraction (2 Gy) to a total of 66 Gy for the same duration to achieve a comparable biological effective dose. Both groups received weekly 50 mg/m² paclitaxel.

Results: An overall response of 83.3% versus 56.6% with a partial response of 70% versus 53.3% and complete response (CR) of 13.3% versus 3% was seen in HFX radiotherapy versus conventional radiotherapy which was statistically significant ($P = 0.04$). 10 of 25 patients and 11 of 17 patients who achieved response in study and control groups, respectively, progressed. The median survival of patients in HFX radiotherapy arm was 18 months, compared to 9 months in conventional radiotherapy arm. The median time to local recurrence was 19 versus 11 months with local recurrence-free survival of 72% versus 66% at 1 year follow-up. The 1 and 2 year survival rates were 76% and 40% in study arm and 50% and 26% in control arm ($P = 0.005$). Esophagitis (70% vs. 63.3%), skin reaction (70% vs. 63.3%), and radiation-induced pneumonitis (50% vs. 43.3%) were the common toxicities with no statistical significance between the two groups. Overall, there was mild chemotherapy-related toxicity.

Conclusions: The combination of HFX radiation with weekly paclitaxel is effective treatment with a moderate degree of toxicity in stage IIB/III NSCLC. An average response to treatment and the use of lesser drugs have made us to consider this therapy in locally advanced NSCLC.

Key words: Conventional radiotherapy, Hyperfractionated radiotherapy, Non-small-cell lung cancer, Paclitaxel

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INTRODUCTION

Lung cancer is the most common cancer worldwide, accounting for 13% of all new cases and 19% of cancer-related deaths worldwide.^[1] Lung carcinoma is the second most common cancer diagnosis by gender, behind prostate cancer for men and breast cancer for women.^[2] The

Corresponding Author: Dr. Subiya Kaneez, House no. 45 Azad Colony, 90 feet Road, Soura, Jammu and Kashmir, India.
Phone: +91-9419421053/+91-7006604634. E-mail: subiyakaneez79@gmail.com

estimated new cases of lung cancer in the US for 2018 are 234,030.^[2] In India, lung cancer constitutes 6.9% of all new cancer cases and 9.3% of all cancer-related deaths in both the sexes.^[3] GLOBOCAN estimate of lung cancer in India would indicate that the incidence of lung cancer in India is 70,275 (for all ages and both the genders).^[4] In Kashmir, the annual crude incidence rate of lung cancer was 4.005 per 100 000 population, being 6.55/100 000 in males and 1.18/100 000 in females.^[5]

Survival of people with lung cancer varies depending on the stage of cancer at presentation. Despite advances in imaging techniques and treatment modalities, the prognosis of lung cancer remains poor, with 5-year survival of 14% in early stages and <5% in locally advanced stages.^[6,7] Unfortunately, only 20–30% of patients present with an operable disease, while most of the patients present in advanced stages II and III.^[8]

There are two main types of lung cancers. Around 20–25% are small-cell lung cancers (SCLCs) and 75–80% are non-SCLCs (NSCLCs).^[9] The main types of NSCLC are squamous cell carcinoma (32%), adenocarcinoma (26%), and non-small-cell not otherwise specified (35%).^[10] In India as well as Kashmir Valley, in particular, squamous cell lung cancer predominates still over adenocarcinoma.

Patients with stage III NSCLC are those who after clinical or surgical staging (or both) have no demonstrable distant metastasis but, at the same time, have locally extensive or invasive disease or involvement of mediastinal lymph nodes. If tumor can be completely resected, surgery provides the best chance of cure, but majority of patients are inoperable/unresectable at presentation. This group typically includes those with bulky stage IIIA disease and IIIB disease, excluding malignant pleural effusion.

Chemotherapy (CHT) has widely been used along with radiation, as multimodality therapy in the treatment of locally advanced NSCLC. Integration of chemoradiation has led to an increase in overall survival time and percentage of cured patients. Chemotherapeutic agents cover systemic disease while radiation treats the locoregional disease. Besides, many chemotherapeutic agents have radiosensitizing action even at low doses. Several phase III trials testing simultaneous (concurrent) chemoradiation versus radiation alone showed an increased survival in concurrent chemoradiation arm.

Platinum-based agents, especially cisplatin, have traditionally been used as chemotherapeutic agents concurrent with radiation. These can be used as weekly or daily basis. Although radiosensitizing action of cisplatin is well documented, it has many toxicities. Introduction of newer

drugs has demonstrated high response rates with favorable toxicity profiles.^[11] The role of paclitaxel as radiosensitizer has been widely appreciated due to its comparative low toxicity profile when given at low doses and good activity against NSCLC. Paclitaxel, a plant product, promotes microtubule assembly and stabilizes microtubules.^[12] It causes cell arrest in G2M phase which is the most radiosensitive phase in cell cycle. Hence, it gives more time for radiation to act on cancer cell and increase the overall efficacy of radiotherapy.

Fraction size is also a dominant factor in determining late effects; overall treatment time has little influence. By contrast, fraction size and overall treatment time both determine the response of acutely responding tissues. The delivery of total dose in a large number of fractions than conventional fractionation is called hyperfractionation. The rationale underlying hyperfractionated (HFX) radiotherapy is that late responding tissues are generally more sensitive to large fraction sizes (low alpha/beta ratio), but many rapidly growing tumors remain sensitive even at low fraction sizes. This is offset by the increased tumor repopulation that occurs after 3–5 weeks. Hyperfractionation treatments are generally delivered as two treatments per day, often with a slightly higher overall dose than conventional fractionation to account for the reduction in cell kill that occurs with smaller fraction sizes.

MATERIALS AND METHODS

A total of 60 patients with histologically documented non-small-cell (non-adenoca) lung cancer with locally advanced/unresectable stage II (unresectable) and stage III A/B lung cancer were included in the trial (30 each in study and control group) prospectively between December 2012 and July 2016. Pre-treatment evaluation included history, physical examination, complete blood count (CBC), liver function test, kidney function test, contrast-enhanced computed tomography (CECT) chest and abdomen, pulmonary function test, and bone scan.

The inclusion criteria were histologically documented stage II (unresectable) and stage III A/B NSCLC (non adeno), age >18 years, the Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , adequate bone marrow function at presentation, serum chemistry within normal range, and optimal lung function, namely forced expiratory volume in 1 s/vital capacity ratio $\geq 75\%$ and weight loss <5% during 3 months before diagnosis. The exclusion criteria were synchronous second malignancy, pregnancy or lactation, any comorbidity, distant metastasis, previous history of CHT or thoracic radiation, and malignant pleural effusion.

The control group comprised of cases who received conventional radiation with concurrent paclitaxel. To make study and control groups, comparable inclusion and exclusion criteria for both groups were the same.

After enlisting the patients, written consent was taken from all the patients. In the study arm (Group I), treatment schedule comprised of HFX radiation therapy (RT) concurrent with paclitaxel. HFX treatment consisted of two daily fractions of 1.2Gy/Fr, 5 days/week, with a minimum interfraction interval of 6 h. The initial target volume was treated with a dose of 48 Gy/4 weeks, after which a supplement dose of 24 Gy/2 weeks was delivered by reduced portals. CHT comprised of weekly injection paclitaxel at 50 mg/m² (1 h infusion) given with premedication on day 1 of every week of radiation. Radiation was delivered on a cobalt-60 teletherapy machine. The primary tumor with a margin of 2 cm, the ipsilateral hilum with 2 cm margin, contralateral hilum with 1cm margin and mediastinum was irradiated in phase 1. the ipsilateral hilum encompassed with a 2-cm margin and the contralateral hilum with a 1 cm margin. The ipsilateral supraclavicular fossa was included in the treatment field only when the primary tumor was located in the upper lobe. In the control arm (Group II), CHT was given in similar manner and radiation was delivered by conventional fractionation, i.e., initial target volume by 2 Gy/Fr for a dose of 46 Gy/23 Fr, followed by supplement dose of 20 Gy/10 Fr by reduced fields. In both groups, the biological effective dose was comparable and treatment was completed within 6–8 weeks. During the period of chemoradiation, patients were monitored for signs and symptoms of toxicity. Treatment was stopped at Grade 3 non-hematological and Grade 4 hematological toxicity. At completion of treatment, patients showing progressive disease, stable disease, or partial response (PR) were assessed for consolidation CHT /salvage surgery as per departmental protocol, depending on their performance and disease status.

After completing treatment, patients were followed up every month for 3–4 months and then examined after every 10–12 weeks for late toxicities (as per RT oncology group [RTOG] criteria) along with assessment for local and systemic recurrences. On each follow up the common expected toxicities like pneumonitis, esophagitis, mucositis, and neutropenia were checked. On each follow-up, CBC, blood chemistry, and chest-X ray were done. Treatment response was assessed by clinical examination, CT chest, and abdomen. The criteria for treatment response were performed as per the RECIST 1.1 criteria.^[13]

Statistical Analysis

The results of the two groups were compared using statistical analysis.

Differences, if any, between pairs of groups in patient characteristics, response rates, and incidence of toxicity were evaluated by Chi-square test. Overall and relapse-free survival rates were calculated the Kaplan–Meier method. $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 60 patients were available for final analysis, 30 in study arm and 30 in control arm; The mean age was 62.5 ± 12.5 years in study group and 60.2 ± 11 years in control group. 26 of 30 (86.7%) patients in study arm were smokers. Cigarette smoking was predominantly found in 17 patients (56.6%), of which 10 patients (33.3%) smoked only cigarettes and 7 patients (23.3%) were addicted to both huqa and cigarettes. In the control arm, 90% of patients were smokers. Cigarette smoking was seen in 16 patients (53.3%), of which 10 (33%) smoked only cigarettes and 6 (20%) were addicted to both huqa and cigarettes. ECOG score was I in 56.6% and II in 33.3% in study group and was I in 50% and II in 36.6% in control group. Well-differentiated squamous cell carcinoma (W/D Sq cell ca) was slightly more than moderately D Sq cell ca (M/D Sq cell ca) (46.7% vs. 40%) in study arm, whereas M/D Sq cell ca was more than (66.7% vs. 38.3%) W/D Sq cell ca in control group. Poorly differentiated squamous cell carcinoma was only 13.3% and 3% in study and control groups, respectively. Right lung disease was seen more (53.3%) compared to the left lung (46.6%) in study group, whereas there was no difference (50% in each group) in control arm. The most common symptoms in both the study and the control arms were a cough with expectoration (70%) followed by hemoptysis (61.7%). 80% (24 of 30) in study group had a cough with expectoration as compared to 60% (18 out of 30) in control group. However, many cases had more than one symptom in both the groups. In both arms, stage IIIB was predominant, accounting for 46.6% and 50% in study and control arms, respectively, compared to stage IIIA (40% vs. 36.6%) and stage IIB (13.3% vs. 13.3%). Most of patients belonged to T2 subset (40% in study arm and 36.6% in control arm) and N2 subset (53.3% in study arm and 40% in control arm) in both the arms. The main patient and tumor characteristics are presented in Table 1.

Survival, Response, and Relapse

To evaluate objective response, radiological tests (chest X-ray and/or CECT chest) were done using RECIST 1.1 criteria.^[13] In the HFX arm, 21 patients showed a PR (70%) and four patients had CR (13.3%) with an overall response of 83.3% (25 of 30). The remaining 5 patients (16.6%) failed to show response, of which three patients (10%) had stable disease (SD) and 2 patients (6%) had a progression of disease (PD) during chemoradiation. In the conventional

group, only 17 patients (56.6%) showed overall response, of which 16 patients (53.3%) showed PR and one patient (3%) showed CR. Of the 13 patients (43.3%), 9 patients (30%) had SD and 4 patients (13.3%) had PD. After comparing both groups by Chi-square analysis, overall response was statistically significant ($P = 0.04$) in the study group than control group. In the study group, of 25 patients who achieved response, 10 patients (40%) developed recurrence of disease in the form of local PD or distant metastasis during follow-up (6 patients had intrathoracic PD, 2 had only distant metastasis, and 2 patients had both local recurrence and distant metastasis). In the control group, of 17 patients who achieved response, 11 patients (64.7%) had PD during follow-up (8 patients had local recurrence, 2 patients had distant metastasis, while 1 patient had both local and distant metastasis [Tables 2 and 3].

Survival analysis was performed using Kaplan–Meier method. The log-rank test was used for between-group

comparisons. The median survival of patients in study arm was 18 months with 95% confidence interval (CI) of 9.98–26.02 months, whereas median survival of controls was 9 months with 95% CI of 6.96–11.03 months. Overall median survival of both groups was 12 months with 95% CI of 5.23–18.76 months. The 1-year survival rate in study arm was 76%, whereas in control group, it was 50%, and 2-year survival rate was 40% in study group and 26% in control group. The log-rank test between the two did reveal a statistical significance with a $P = 0.005$ [Figure 1].

Prognostic Factors for Response

Analysis of 25 patients who achieved treatment response (PR+CR) in concurrent HFX arm showed that group of patients with ECOG performance score 2 had a response of 60%. Patients with lower ECOG score had better response rate: 100% for ECOG of 0 and 88.2% for ECOG of 1. The trend was the same in concurrent conventional arm with only 18.1% response in patients with ECOG 2 and 73.3% in ECOG 1. Similarly, patients in stage IIB showed better response (100% in study and 75% in control arm). Stage IIIB patients achieved a comparatively poor response in both the arms (78.5% vs. 46.7%) than stage IIIA (83.8% and 63.6%) in study and control groups, respectively. The patients with younger age groups also achieved better response, and it decreased with increasing age.

Toxicity

Treatment-related toxicity was assessed by RTOG toxicity scoring criteria. Esophagitis was the most common complication seen in both the study and control arms. In the study arm, 70% of patients suffered from esophagitis (Grade 1 - 30%, Grade 2 - 30%, and Grade 3 - 10%), whereas, in control arm, 63.3% of patients suffered from esophagitis, of which 20% had Grade 1 and 40% had Grade 2 esophagitis. Radiation-induced skin reaction was seen more (70%) in study arm than control arm (63.3%). Grade 3 skin toxicity was also more in study arm than control arm (13.3% vs. 0%).

Table 1: Patient characteristics

Characteristics	Study arm	Control arm
Total number of patients	30	30
Age (years)		
Mean	62.5	60.2
Range	44–74	42–72
Sex		
Male	28	25
Female	2	5
Smoking habits		
Smokers	26	27
Non smokers	4	3
Histology		
W/D squamous	14	9
M/D squamous	12	20
P/D squamous	4	1
Stage		
IIB	4	4
IIIA	12	11
IIIB	14	15
ECOG (performance status)		
0	3	4
1	17	15
2	10	11

WD: Well-differentiated, MD: Moderately differentiated, PD: Poorly differentiated

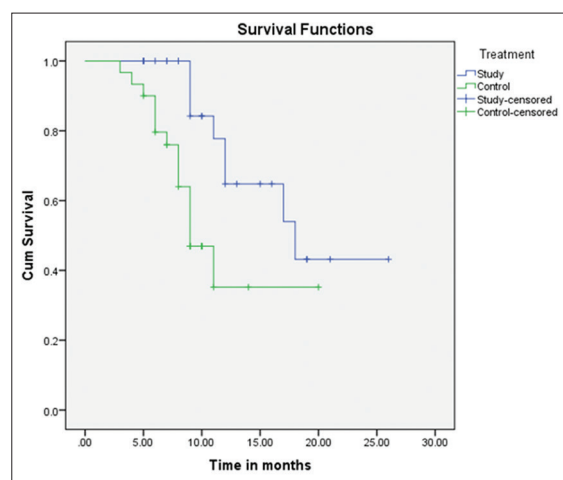
Table 2: Distribution of patients according to their response to treatment

Response to treatment	Study group, n=30 n (%)	Control group, n=30 n (%)	Statistical remarks (P value)
Overall response			
Partial response, PR	21 (70)	16 (53.3)	0.075(NS)
Complete response, CR	4 (13.3)	1 (3)	
Stable disease, SD	3 (10)	9 (30)	0.04 (Sig.)
Progression of disease, PD	2 (6)	4 (13.3)	
Overall response (PR+CR)	25 (83.3)	17 (56.7)	
PD+SD	5 (16.7)	13 (43.3)	
Total	30 (100)	30 (100)	

PR: Partial response, CR: Complete response, SD: Stable disease, PD: Progression of disease

Table 3: Distribution according to the pattern of failure in patients who achieved initial response

Failure pattern	Study group, n=25	Control group, n=17	Statistical remarks (P value)
	n (%)	n (%)	
Intrathoracic progression of disease			
Intrathoracic progression only	6 (24)	8 (47.0)	0.44 (NS)
Intrathoracic progression+distant metastasis	2 (8)	1 (5.8)	
Distant metastasis only	2 (8)	2 (11.7)	
Total	(10)	11 (64.7)	

**Figure 1: Disease free survival (months)**

Stomatitis was seen more in control arm than study arm (43.3% vs. 33.3%). The incidence of upper GI toxicity (nausea and vomiting) was also low (43.3%) in study arm than in control arm 33.3% with no Grade 3 toxicity. Overall, hematological toxicities were mild and were almost similar in both the arms with no Grade 3 toxicity in any arm. Radiation-induced pneumonitis was more in study group than control group. Neuropathy was almost similar in both study and control groups.

There was no Grade 4 toxicity or toxicity-related death (Grade 5 toxicity) in any group [Table 4].

DISCUSSION

Locally advanced (stage IIB and stage III) NSCLC is considered to be non-resectable in majority of patients. The role of surgery with or without CHT or RT has been placed under scrutiny in recent trials, and it seems to offer no clear advantages in terms of survival.^[14,15] Although some patients might benefit from it, these patients represent a very small proportion. Once surgery has been ruled out, the best treatment currently available is CHT combined with RT. The superiority of this combination

over RT alone was demonstrated several years ago.^[16-18] The first trial to demonstrate a survival advantage with the addition of CHT to radiation was reported by Dillman *et al.* and was conducted by cancer and leukemia Group B-8433.^[19] It showed a median survival of 13.8 months in chemoradiation arm and 9.7 months in radiation only arm ($P = 0.0066$). The respective 1-, 2-, and 3-year survival rates in chemoradiation arm were 55%, 26%, and 23%, respectively. The same survival rates in radiation only group were 40%, 13%, and 11%, respectively. In 7 years' follow-up, this improved survival in chemoradiation arm was shown to persist.^[19] After several other studies confirmed the superiority of adding CHT to radiation, combined chemoradiation became the standard in locally advanced NSCLC which led the American Society of Clinical Oncology to issue guidelines in 1997 and recommended the use of chemoradiation in locally advanced NSCLC.^[20]

After the advantages of chemoradiation were established beyond doubt, next question was the timing and sequencing of CHT with respect to radiation, whether to give CHT before, after, or even during radiation (sequential/concurrent). The main advantage with concurrent chemoradiation is an effect on micrometastasis as well as enhances radiotherapeutic effect on local tumor through radiosensitization. The most recent randomized trials studying the integration of CHT and RT have shown an improved survival with concurrent CHT and RT regimens.^[16,17]

On the basis of radiobiological considerations, different investigators introduced alternative fractionation schedules for the treatment of locally advanced NSCLC so as to further intensify the local efficacy of radiotherapy. Being influenced largely by the RTOG study 8311 design,^[21] various studies were done on HFX radiotherapy in NSCLC, showing better local control and overall survival. To investigate the efficacy of concurrent HFX RT and low-dose CHT in stage III NSCLC, a study was conducted by Jeremic *et al.*^[22] showing a median survival of 22 versus 14 months and 4-year survival rates of 23% versus 9% ($P = 0.021$). The two groups showed a similar incidence of acute and late high-grade toxicity ($P = 0.44$ and 0.75 , respectively). No treatment-related deaths were observed during this study.

Although the benefit of concurrent chemoradiation over sequential chemoradiation was established, concurrent modality was associated with higher toxicity rates. The main toxicities observed were hematological toxicities and radiation-induced esophagitis.^[23] Thus, efforts were made to decrease the overall toxicity in concurrent modality with newer drugs like platinum compounds. The other issue is the optimal dose in concurrent modality, whether to give

Table 4: Distribution of patients according to toxicity observed (RTOG criteria)

Toxicity	Grade	Study group, n=30	Control group, n=30	Statistical remarks
		n (%)	n (%)	
Stomatitis	1	5 (16.7)	8 (26.7)	0.563 (NS)
	2	4 (13.3)	5 (16.7)	
	3	1 (3.3)	0 (0)	
	4	0 (0)	0 (0)	
	Total	10 (33.3)	13 (43.3)	
Esophagitis	1	9 (30)	6 (20)	0.551 (NS)
	2	9 (30)	12 (40)	
	3	3 (10)	1 (3.3)	
	4	0 (0)	0 (0)	
	Total	21 (70)	19 (63.3)	
Upper GIT (nausea/vomiting)	1	5 (16.7)	8 (26.7)	0.563 (NS)
	2	5 (16.7)	5 (16.7)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	10 (33.3)	13 (43.3)	
Skin reaction	1	11 (36.7)	13 (43.3)	0.198 (NS)
	2	5 (16.6)	4 (13.3)	
	3	4 (13.3)	0 (0)	
	4	0 (0)	0 (0)	
	Total	20 (70)	17 (56.6)	
Hematological Leucopenia	1	3 (10)	7 (23.3)	0.378 (NS)
	2	2 (6.7)	2 (6.7)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	5 (16.6)	9 (30)	
Neutropenia	1	5 (16.7)	4 (13.3)	0.718 (NS)
	2	0 (0)	0 (0)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	5 (16.6)	4 (13.3)	
Anemia	1	2 (6.7)	4 (13.3)	0.431 (NS)
	2	1 (3.3)	0 (0)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	3 (10)	4 (13.3)	
Thrombocytopenia	1	0 (0)	1 (3.3)	0.313 (NS)
	2	0 (0)	0 (0)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	0 (0)	1 (3)	
Pneumonitis	1	8 (26.7)	6 (20)	0.685 (NS)
	2	6 (20)	7 (23.3)	
	3	1 (3.3)	0 (0)	
	4	0 (0)	0 (0)	
	Total	15 (50)	13 (43.3)	
Neuropathy	1	4 (13.3)	5 (16.7)	0.936 (NS)
	2	1 (3.3)	1 (3.3)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	5 (16.6)	6 (20)	

RTOG: Radiation therapy oncology group, GIT: Gastrointestinal

lower radiosensitizing dose or standard dose of systemic CHT. Although the latter dose is associated with better response rates but very high toxicity, it might be better to give lower doses of CHT with good radioenhancing action. In this regard, paclitaxel has demonstrated promising results.

Paclitaxel, a complex plant product (diterpene) extracted from the bark of *Taxus brevifolia*, has demonstrated

substantial anticancer activity in patients with advanced (stage IIIB or IV) non-small-cell lung cancer. In addition to the radiosensitizing effect, it produced a response rate of 20–25% when given alone, as described by investigators from three different institutions.^[24] Paclitaxel has a unique mechanism of action, binds to tubulin, enhances rate and extent of microtubular polymerization, and stabilizes formed microtubules, hence causing cell arrest.^[25] The cell

arrest caused by paclitaxel happens in G2 and M phase of cell cycle which are most sensitive to radiation effect. The dose of paclitaxel was weekly 50 mg/m², although phase I trials have demonstrated that up to 60 mg/m² of paclitaxel can be given with quite acceptable side effects in concurrent settings.^[26] The activity of paclitaxel in advanced NSCLC and its strong radiosensitizing properties provided the basis for its use in concurrent chemoradiation in locally advanced NSCLC.^[27]

In our setup, patients present mostly in a cachexic state with poor performance status. In an earlier study conducted to assess the profile of lung cancers in our hospital, it was found that 23% of patients opted for no treatment at all 22.4% received radiation alone followed by chemoradiation (14.9%) and CHT alone (9.4%).^[28] Patients may be reluctant to receive CHT due to morbidities involved. For this reason, an attempt was made to demonstrate the benefits of concurrent chemoradiation with acceptable toxicity profile, the aim being minimal toxicity apart from attaining maximal benefit to patients.

In our study, majority of the patients were in the age group of 50–70 years, majority being males in both study and control groups (93.3% and 88.3%), respectively. The male-to-female ratio which is coming down in western literature due to an increasing trend of smoking in females was not seen in our study. Our study showed a ratio of 14:1 and 5:1 in study and control groups, respectively, possibly because smoking in females has not increased as in developed countries.^[28,29] In our study, 86.7% were smokers in the study arm and 90% in the control arm. Smoking has long been established as a risk factor for lung cancer.^[28-32]

Although approximately 10% of lung cancers are detected in asymptomatic patients on routine chest radiograph, most patients are symptomatic when diagnosed. The most common symptoms in our patients were cough with expectoration (80% in study and 60% in control arm), hemoptysis (66.7% in study and 56.7% in control), and breathlessness (36.7% in study and 40% in control arm) which were similar to other studies.^[28-35] The right lung was involved in 16 patients (53.3%) in study arm and 15 patients (50%) in control arm as compared to left lung which was involved in 14 (46.6%) in study arm and 15 patients (50%) in control arm, respectively. These results have been reported by other investigators as well.^[28,33]

While studying a large group of 600 patients of NSCLC using concurrent HFX chemoradiation in stage II patients, Jeremić *et al.* have shown better outcome in squamous cell histology.^[36] In our study, we had included only squamous histology. Well-differentiated squamous cell histology was more (46.7% vs. 40%) in study group, whereas moderately

differentiated histology was more than well-differentiated (66.7% vs. 38.3%) in control group. Furthermore, most of the patients belonged to stage IIIB in both the groups, 46.6% in study group and 50% in control group. Patients with ECOG performance status of 2 or less were included in the present study. Most of the patients belonged to ECOG 1 category, 56.6% in study group and 50% in control group. Similarly, since pre-treatment weight loss is an important prognostic factor^[37] and patients with weight loss of >5% carry a bad prognosis, patients with weight loss <5% were taken into the study.

Bronchoscopy was the main diagnostic modality and was positive for malignancy in 76% patients. There were only three patients (10%) positive for malignant cells (M cells) in bronchoalveolar lavage (BAL) in study group and 5 patients (16.6%) in control group which are quite low as compared to other studies where BAL was positive for M cells in 68% of patients.^[33,38]

The short overall treatment time improved patient compliance for completing treatment as within 2 months whole radical CCRT was over. In our study group, only six patients defaulted early in study group and only 4 patients defaulted in control group; 30 patients in each group completed full treatment which was assessed for response and toxicity.

The present study showed an objective response rate (ORR) of 83.3% (25/30) patients in concurrent HFX chemoradiation arm, of which 4 (13.3%) patients showed CR, 21 (70%) patients showed PR, and 16.60% of patients failed to show response, i.e., they had either SD (10%) or their disease progressed (6%) locally during treatment. In the control arm, ORR was achieved in 56.6% (17/30) patients, of which only 1 (3%) patient showed CR and 16 (53.3%) had PR. The difference in overall response rates between the two arms was 26.7% in favor of concurrent HFX arm which was statistically significant ($P = 0.04$).

The median survival of patients in concurrent HFX chemoradiation arm was 18 months, compared to 9 months in concurrent conventional radiation arm. The survival advantage was 9 months in favor of concurrent HFX arm. The median time to local recurrence seen in study group was 19 months with local recurrence-free survival of 72%, whereas median time to local recurrence in control group was 11 months with local recurrence-free survival of 66% at 1 year follow-up. The 1-year survival rate in study arm was 76%, whereas, in control arm, it was 50% and a 2-year survival rate was 40% in study group and 26% in control group. The 3-year survival rate was 25% in study arm and 14% in control arm. The log-rank test between the two did reveal a statistical significance with $P = 0.005$.

After analyzing the response rates in different subsets of patients, it was noticed that ECOG status, age, and stage did have a bearing on it. Young patients with good ECOG, and lower stage of disease at presentation had better response in both groups. This was in consistent with other studies.^[37]

Any treatment protocol is assessed by its toxicity profile which in turn determines patient compliance and subsequent response and survival rates. Radiation-related toxicities were assessed by RTOG toxicity scoring criteria. As far as our study is concerned, due to lower dose of paclitaxel, the toxicities were quite acceptable, and consequently, patient compliance was better. There was no Grade 4 toxicity and few Grade 3 toxicities. In particular, hematological toxicities were mild. This is in contrast to patients who receive conventional full-dose CHT, which is associated with high morbidity,^[39] resulting in frequent disruptions and discontinuation of treatment. Esophagitis, induced by thoracic radiation, was the main complication observed, more in study group than control group (70% vs 63.3%) with no statistical significance ($p=0.55$) on comparison. This was inconsistent with most of the studies involving thoracic radiation. Chandra and Belani,^[40] in 1999, have reported 26% of Grade 3–4 esophagitis and 16% pneumonitis in HFX radiation concurrent with paclitaxel and carboplatin. However, our study showed only 10% Grade 3 toxicity in study arm. Radiation-induced pneumonitis was also more in study arm than control arm (50% vs. 43.3%) with no significance ($P = 0.685$). In a multicenter phase II study, the RTOG enrolled 79 patients onto a protocol of HFX accelerated RT (1.2 Gy bid, total dose of 69.6 Gy) and their results showed Grade ≥ 3 lung toxicity in 19 patients (25%) accounting for two of three treatment-related deaths.^[41] In contrast to that, our study had only one (3.3%) Grade 3 reaction in study arm. In our study, radiation-induced skin reaction was seen more (70%) in concurrent HFX arm than concurrent conventional arm (63.3%) with 13.3% Grade 3 toxicity in study arm compared to 0% in control arm. However, overall, no statistical significance was seen ($P = 0.198$).

In the present study, our results were comparable to other studies.^[36,42] However, controversies remain over the most effective combination of drugs, their optimal mode of administration, optimal sequencing of radiation and CHT as well as details of thoracic radiation; these important issues have not been properly defined. A clinical trial cannot provide exact “prescription” of how to treat individual case; ultimately, treatment modality is to be decided by clinician and patient together and will depend on many factors: Survival, toxicity, quality of life, and economic burden.

CONCLUSIONS

The combination of HFX radiation with weekly paclitaxel is effective for the treatment of patients with advanced NSCLC. The moderate degree of toxicity, an average response to treatment, and use of lesser drugs have made us to consider this therapy in locally advanced NSCLC.

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Compare Onset Time of Cisatracurium for Tracheal Intubation with and without Priming Dose of Rocuronium

Veena Chatrath¹, Harpreet Kaur², Reena Makhni³, Jaspreet⁴, Ojaswani Rai Sood⁵

¹Professor and Head, Department of Anaesthesia, Government Medical College, Amritsar Punjab, India, ²Professor, Department of Anaesthesia, Government Medical College, Amritsar Punjab, India, ³Associate Professor, Department of Anaesthesia, Government Medical College, Amritsar Punjab, India, ⁴Junior Resident, Department of Anaesthesia, Government Medical College, Amritsar Punjab, India, ⁵Junior Resident, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India

Abstract

Background: Priming is one of those techniques in which a small dose of non-depolarizing muscle relaxants is administered followed by a large intubating dose. Cisatracurium is the newly introduced drug with Hoffman elimination. The problem with its use is delayed onset of action. The present study was conducted to compare the onset of cisatracurium for tracheal intubation with and without priming dose of rocuronium.

Materials and Methods: A total of 60 American Society of Anesthesiologist physical Status I and II patients undergoing surgery under general anesthesia were included in the study. Patients were divided into two groups of 30 each. Patients in Group R received priming dose of rocuronium 0.06 mg/kg before intubating dose of cisatracurium (0.14 mg/kg). Group C patients did not get any priming, only normal saline was given before intubating dose of cisatracurium (0.15 mg/kg).

Results: Time gap between administration of the cisatracurium and complete loss of T_1 was recorded as intubation time. The intubation time was significantly less in Group R, i.e., 130 ± 11.02 s as compared to Group C, i.e., 230.33 ± 12.82 s. The intubating conditions were similar in both the groups. The hemodynamic changes were statistically insignificant. The time to 25% recovery of the T_1 response is defined as the clinically effective duration of neuromuscular block. The rate of recovery is described by the recovery index, which is defined as the time from 25% to 75% T_1 recovery.

Conclusion: Priming with rocuronium decreased the onset time without increasing the clinical duration of action or recovery index.

Key words: Non-depolarizing muscle relaxants, Priming, Cisatracurium, Rocuronium

INTRODUCTION

Endotracheal intubation is one of the important components of general anesthesia. The non-depolarizing muscle relaxants (NDMRs) act by competitively binding at the neuromuscular junction to provide muscle paralysis.^[1] Cisatracurium besylate is a newly NDMR, an isomer of atracurium.^[2] The problem with cisatracurium is its delayed onset of action. Priming is the technique in which a small

dose of NDMR is administered which is followed by a large intubating dose of same or different NDMR. This produces rapid and profound blockade.^[3] The present study was conducted to compare the onset of cisatracurium for tracheal intubation with and without priming dose of rocuronium.

MATERIALS AND METHODS

A randomized prospective double-blind study was conducted in the Department of Anesthesia, Government Medical College, Amritsar, Punjab, India. The randomization was done using the computer generated software. A total of 60 American Society of Anesthesiologist (ASA) Grade I and II between the age of 18 and 65 years with Mallampati grading 1 and 2

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Corresponding Author: Dr. Reena Makhni, Department of Anaesthesia, Government Medical College, Amritsar-143 001, Punjab, India.
Phone: +91-9814063758. E-mail: reenamakhni22@yahoo.co.in

requiring elective surgery under general anesthesia were included in the study. After approval from the institutional ethical committee, an informed written consent was taken. Patients who were <18 years or >65 years, pregnant patients, emergency cases, those allergic to drugs, anticipated difficult airway, morbidly obese, and ASA more than II had a history of neuromuscular disease and who refused to give consent were excluded from the study. A thorough pre-operative checkup was done. A detailed history was taken. The complete general physical and systemic examination including airway assessment was done. Relevant investigations were done. Demographic data including age, sex, and ASA status were collected. Patients were randomly divided into two groups of 30 each. Patients in Group R received priming dose of rocuronium 0.06 mg/kg before intubating dose of cisatracurium (0.14 mg/kg). Patients in Group C received no priming, only normal saline was given before intubating dose of cisatracurium (0.15 mg/kg). Routine fasting guidelines were followed.

In the operating room, multipara monitor was attached. Two stimulating electrodes were placed over the ulnar nerve at the wrist and acceleration transducer attached to the thumb with adhesive tape. Baseline heart rate, blood pressure (BP), and oxygen saturation were recorded. Intravenous line was set on the hand opposite to the electrodes and fluid started. All patients were premedicated with inj. midazolam 0.04 mg/kg, inj. glycopyrrolate 0.2 mg, and inj. butorphanol 40 µg/kg. After preoxygenation with 100% oxygen, anesthesia was induced with inj. propofol 2 mg/kg. After loss of eyelash reflex, O₂-N₂O in the ratio of 4:6 and isoflurane 1% started for the maintenance of anesthesia using closed circuit. Supramaximal stimulus was given (2 Hz for 2 s) through nerve stimulator. Baseline train of four (TOF) was recorded. T₄/T₁ percentage, i.e., the percentage between the fourth and first twitch recorded. Priming dose of rocuronium (0.06 mg/kg IV diluted to 1 ml with 0.9% normal saline) is given in Group R patients. Group C patients received 1 ml of 0.9% of normal saline. After 3 min of priming interval, intubating dose of cisatracurium 0.14 mg/kg was given to patients of priming group (Group R) and 0.15 mg/kg to patients of non-priming group (Group C) over 5 s. The intravenous line was flushed by rapid flow of fluid for 15 s. TOF was recorded every 10 s till complete loss of T₁. At this point, intubation was attempted by the senior anesthesiologist. Time gap between administration of the NDMR and complete loss of T₁ was recorded as the intubation time. The time of onset of the neuromuscular block is defined as the time to maximum suppression of the T₁ response.

Variable	Excellent	Good	Poor
Laryngoscopy	Easy	Fair	Difficult
Vocal cord position	Abducted	Intermediate/ moving	Closed
Reaction to insertion of the tracheal tube and cuff inflation (diaphragmatic movement/coughing)	None	Slight (1–2-week contractions or movement for <5 s)	Vigorous/sustained (More than two contractions and/or movement for longer than 5 s)

Assessment of intubating conditions (According to Fuchs-Buder *et al.*)^[4]

Type of Laryngoscopy

- Easy: Jaw relaxed, no resistance to blade insertion,
- Fair: Jaw not fully relaxed slight resistance to blade insertion,
- Difficult: Poor jaw relaxation, active resistance of the patient to laryngoscopy.

From above-mentioned Intubating Conditions

- Excellent: All qualities are excellent,
- Good: All qualities are either excellent or good,
- Poor: The presence of single quality listed under “poor.”

Clinically acceptable are excellent and good conditions. Poor conditions were those who were not clinically acceptable.

After checking position of endotracheal tube and securing it, anesthesia and monitoring continued with total fresh gas flow with O₂-N₂O in 4:6 ratio with isoflurane 1% using closed circuit. Hemodynamics were recorded every 5 min during surgery. The inhalational anesthetic vaporizer switched off 6–8 min before the end of surgery. Neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg IV were administered after the T₄/T₁ percentage became 75%. The trachea extubated once T₄/T₁ percentage became 90% of baseline.

The time to 25% recovery of the T₁ response is defined as the clinically effective duration of neuromuscular block. The rate of recovery is described by the recovery index, which is defined as the time from 25% to 75% T₁ recovery. The recovery profile was maintained using Aldrete scoring system. The patient was monitored for 24 h for any side effects and complications.

Statistical Analysis

Sample size was calculated keeping in view at most 5% risk, with minimum 85% power and 5% significance level (significant at 95% confidence interval). Raw data were recorded in a Microsoft Excel spreadsheet and analyzed using the Statistical Package for the Social Sciences (SPSS version 23.00). The continuous data were presented as mean with standard deviation (mean ± SD). Number of patients

and/or percentage of cases expressed discrete categorical data. Categorical variables were analyzed using Chi-square test. Normally distributed continuous variables were analyzed using independent sample *t*-test. *P* value was determined finally to evaluate the levels of significance. $P > 0.05$ was considered statistically non-significant; $P = 0.01$ to 0.05 was considered statistically significant and $P < 0.01$ was considered highly statistically significant. The results were then analyzed and compared to previous studies.

RESULTS

As shown in Table 1, the demographic data of both the study groups including age, sex, and ASA grade were comparable as $P > 0.05$ and statistically insignificant.

The time gap between administration of the NDMR and complete loss of T_1 was recorded as intubation time. The intubation time was recorded and compared in both the groups. In Table 2, the two groups are compared in terms of the onset/intubation time, intubation conditions, duration of action and recovery index. The difference in intubation time is highly significant as in Group R, the intubation time was 130.67 ± 11.02 s as compared to Group C where it was 230.33 ± 12.82 s showing that priming with rocuronium decreases the onset time of cisatracurium ($P > 0.01$).

In Group R, 28 (93.3%) of 30 patients had excellent intubating conditions and two (6.67) patients had good intubating conditions. The intubating conditions were rated excellent in 27 (90%) patients and good in three (10%) patients in Group C. The difference between the two groups was statistically insignificant ($P > 0.05$).

The time to 25% recovery of the T_1 response is defined as the clinically effective duration of neuromuscular block. The mean duration of the action of cisatracurium in Group R was 55.17 ± 2.16 min and Group C was $53.77 \pm$

2.14 min. The mean duration of the action of cisatracurium was comparable in both the groups as the difference among them being statistically insignificant ($P > 0.05$).

The recovery index is defined as the time from 25% to 75% T_1 recovery. The mean recovery index of cisatracurium in Group R was 15 ± 0.83 min and Group C was 14.27 ± 1.11 min. The two groups were comparable in terms of recovery index as the difference is statistically insignificant ($P > 0.05$).

The hemodynamic profile (heart rate, systolic BP, diastolic BP, and mean arterial pressure) of both the groups was observed and recorded. It was found to be comparable with no statistically significant difference as $P > 0.05$.

DISCUSSION

Many NDMRs have been studied till today. However, the problem with NDMR is their delay in onset of action. Various techniques have been studied to decrease the onset time of various NDMRs. Some of them are - priming principle, timing principle, administering large doses, and combining different neuromuscular blocking agents.

Priming principle is the technique in which a small dose of NDMR is administered followed by a large intubating dose. This produces rapid and profound neuromuscular block for suitable intubating conditions.

The studies conducted by Gergis *et al.*^[5] and Hutton *et al.*^[6] reported that the onset of neuromuscular block could be hastened by administering small dose before the intubating dose. The term priming dose was coined by Foldes.^[7] After that, several studies were conducted based on the priming principle.

The mechanism underlying the shortening of the time interval between intubating dose and achieving intubating conditions by priming can be explained by two theories. The first theory proposed that the priming dose occupies a proportion of post-synaptic nicotinic receptors necessary for clinical paralysis. According to this theory, the priming dose is of more importance as compared to the priming interval as it has to occupy critical mass of receptors. The other theory suggests that the priming dose blocks the

Table 1: Demographic profile

Variables	Group R	Group C	P value
Age (years)	40.30±10.65	39.20±11.3	0.724
Sex (M/F)	17/13	14/16	0.438
ASA (I/II)	22/8	21/9	0.77

$P > 0.05$ (non-significant), mean±SD. ASA: American Society of Anesthesiologist

Table 2: Onset, intubation conditions, duration of action, and recovery index

Variables	Group R	Group C	P value	Statistical significance
Onset/intubation time (s)	130.67±11.02	230.33±12.82	0.001	Significant
Intubation conditions (excellent/good/poor)	28/2/0	27/3/0	0.640	Insignificant
Duration of action (min)	48.18±0.66	47.93±0.37	0.075	Insignificant
Recovery index (min)	15.00±0.83	14.27±1.11	0.093	Insignificant

$P > 0.05$ (non-significant), mean±SD

presynaptic nicotinic receptors, reducing the mobilization and release of acetylcholine so that paralysis is produced rapidly using the intubating dose.^[8] Cisatracurium is an NDMR having potency almost 4 times more than atracurium. It has no histamine release and is cardio stable. It is metabolized by Hoffmann elimination so can be used in patients with decreased hepatic or renal function. The problem with this NDMR is the delayed onset of action. Several studies have been conducted to establish the method for decreasing the onset time of cisatracurium.

The combinations of NDMR with different structures are considered to have synergistic effects. The synergism is said to be maximized if two molecules have different roles in prejunctional and postjunctional effect. There are different binding sites at presynaptic and postsynaptic receptors and different binding affinities of 2- α subunits of the acetylcholine receptor.^[9,10] There occurs potentiation of the neuromuscular block due to synergism of combined NDMRs and different binding affinities.

The synergism has been found for pairs of cisatracurium and rocuronium.^[11] A study conducted by England suggested that rocuronium has higher affinity for the presynaptic sites than other NDMR.^[12] Furthermore, rocuronium has fast onset and short duration of action. As the combinations of rocuronium and cisatracurium have synergistic effects, so rocuronium may be used as priming agent to decrease the onset time of cisatracurium.^[13]

Thus, the present study was designed to compare the onset time of cisatracurium for tracheal intubation with and without priming dose of rocuronium.

We observed that the intubation time in Group R was 130.67 ± 11.02 s and Group C was 230.33 ± 12.82 s which was statistically significant. Hence, the intubation time in priming group was less than the non-priming group. This shows that the priming with rocuronium decreases the onset time of the cisatracurium. The studies conducted by Lin *et al.*^[14] and Jung *et al.*^[15] showed similar results, i.e., the priming decreases the onset time of cisatracurium.

In our study, to assess the intubating conditions, three parameters, laryngoscopy, vocal cord position, and response to insertion of tracheal tube and cuff inflation, were studied and results compiled to note intubating conditions in both groups. Laryngoscopy was easy in 29 patients of 30 in Group R and 28 patients in Group C. There was one case in Group R and two cases in Group C in which laryngoscopy was fair in grading. There was no statistically significant difference in both the groups.

Vocal cord position was noted, i.e., whether abducted, intermediate or closed, and also on the movement of vocal

cords during intubation. In all intubations of Group R, the vocal cords were abducted, and in 29 intubations of Group C, the vocal cords were abducted. Only in one intubation of Group C, the vocal cords were moving. However, statistically no significant difference in both the groups was found.

Response to intubation was noted on the basis of the movements of limbs and coughing in response to insertion of tracheal tube or cuff inflation. 29 patients in Group R and 28 patients in Group C had no response to intubation. One patient in Group R and two patients in Group C had slight coughing in response to cuff inflation.

Hence, our study showed that the intubating conditions were similar in both the groups, i.e., with or without priming with rocuronium. Johann *et al.*^[16] and Deepika *et al.*^[17] showed similar results that the intubating conditions were similar in priming and non-priming group.

The duration of action and recovery index in Group R 48.18 ± 0.66 and 15.00 ± 0.83 and Group C were 47.93 ± 0.37 and 14.27 ± 1.11 , respectively. Both were comparable in both priming and non-priming groups. Hence, priming of cisatracurium with rocuronium will not result in any prolonging of the action of cisatracurium.

We observed that the heart rate, systolic BP, diastolic BP, and mean BP readings were comparable in both the groups. Hence, both rocuronium and cisatracurium are hemodynamically stable drugs.

Both the groups had similar recovery profile of cisatracurium when compared in terms of duration of action and recovery index.

CONCLUSION

From our study, we concluded that the onset time of cisatracurium for tracheal intubation decreases when priming is done with rocuronium. The intubating conditions were excellent or good with cisatracurium alone or after priming with rocuronium. The priming dose of rocuronium does not prolong the duration of action and recovery index of cisatracurium. Both cisatracurium and rocuronium are hemodynamically stable drugs and produce no complications in the intraoperative or post-operative period.

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Angiographic Profile of Patient with Unstable Angina: An Observational Study

J. M. Ravichandran Edwin¹, C. Balachandran², Heber Anandan³

¹Head and Professor, Department of Cardiology, Tirunelveli Medical College Hospital, Tirunelveli, Tamil Nadu, India, ²Senior Assistant Professor, Department of Cardiology, Tirunelveli Medical College Hospital, Tirunelveli, Tamil Nadu, India, ³Clinical Epidemiologist, Department of Clinical Research, Dr. Agarwal's Healthcare Limited, Tamil Nadu, India

Abstract

Introduction: Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in the world. In CAD, atherosclerotic plaque builds up inside the coronary arteries and restricts the flow of blood and, therefore, the delivery of oxygen to the heart.

Aim: This study aims to study the relationship of the clinical profile with coronary angiographic profile in patients with unstable angina.

Materials and Methods: A total of 50 patients underwent coronary angiogram through femoral or radial access using Judkins technique. Demographic variables included age and gender, history of smoking, and family history were collected. Electrocardiogram and echocardiogram were done.

Results: Smoking, diabetes, hyperlipidemia, and hypertension (HTN) are major risk factors for unstable angina. ST elevations in aVR are seen in nine patients. The left ventricular dysfunction was seen in 13 patients, who showed the left main coronary artery lesion in three patients, three-vessel disease (3VD) in nine patients. 13 patients had a single VD, 12 patients had two VD, 13 patients had 3VD, and 12 patients had normal/insignificant coronary lesions.

Conclusion: Major risk factors of CAD are the same around the world. Tobacco use, dyslipidemia, and HTN are the main determinants of population attributable risk worldwide.

Key words: Angiographic profile, Coronary artery disease, Risk factors

INTRODUCTION

Coronary artery disease (CAD) is one of the important causes of cardiovascular morbidity and mortality globally, giving rise to >7 million deaths annually.^[1] An increasing burden of CAD in India is a major cause of concern with angina being the leading manifestation. It is posing a devastating health epidemic in South Asia, as more than half of the worldwide cardiovascular disease risk burden is estimated to be borne by Indian subcontinent

by 2020. It has been observed that individuals in Indian subcontinent develop CAD at a higher rate and also at an early age, which should be considered as the “tip of the iceberg” as young, asymptomatic patients usually do not undergo medical investigations.^[2,3] The incidence rate of CAD in India remains high with 47 million cases per year and mortality due to CAD in 2.3 million cases.^[4] In the past three decades, the prevalence of CAD has increased from 1.1% to 7.5% in the urban population and from 2.1% to 3.7% in the rural population.^[5,6] It has also been observed that CAD tends to occur at a younger age in Indians than in other groups, with more severe and extensive angiographic involvement.^[7]

Aim

This study aims to study the relationship of the clinical profile with coronary angiographic profile in patients with unstable angina.

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Corresponding Author: Dr. C. Balachandran, Department of Cardiology, Tirunelveli Medical College Hospital, Tirunelveli, Tamil Nadu, India.
E-mail: chandruchidambaram@yahoo.com

MATERIALS AND METHODS

In prospective observational study was conducted in the Department of Cardiology at Tirunelveli Medical College Hospital. Inclusion criteria: Patient undergoing coronary angiography was included in the study. Risk stratification was made clinically, electrocardiogram (ECG) and enzymes, and all these patients were subjected to a coronary angiogram. Demographic variables included age and gender, history of smoking, and family history were collected. ECG and echocardiogram were done. All patients underwent coronary angiogram through femoral or radial access using Judkins technique. The procedure was performed within 72 h of admission to hospital. All obstructive lesions were visualized in multiple planes. Qualitative morphological analysis of all angiograms is performed. In each case, we attempted to identify the ischemia-related artery and a culprit lesion with a visual diameter stenosis of $>70\%$ on the basis of anatomy (left anterior descending coronary artery [LAD], left circumflex [LCx], and right coronary artery [RCA] lesions), 50% for the left main coronary artery (LMCA or LM) equivalent lesions which were taken as significant anatomical stenosis.

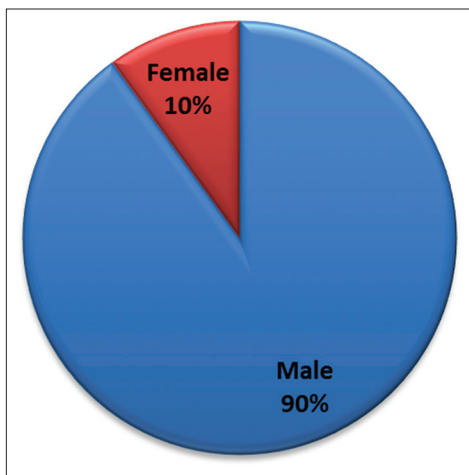


Figure 1: Distribution of gender

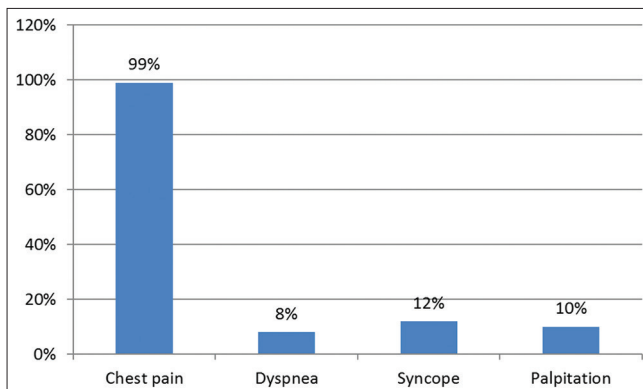


Figure 2: Distribution of complaints

RESULTS

In 50 patients, 56% of patients were in 56–60 years followed by the age group of 61–75 years (24%). Males outnumber females in this study. 90% of 100% of cases are males Figure 1. Almost all patients presented with a history of chest pain. Other symptoms such as dyspnea, syncope, and palpitation were present in $<12\%$ of patients Figure 2. Smoking, diabetes, hyperlipidemia, and hypertension (HTN) formed the major risk factors in this study. Majority of the patients are smokers and diabetes, hyperlipidemia, and HTN Table 1. 4% of patients had a family history of heart diseases. ST elevations in aVR are seen in nine patients. Normal ECG was seen in 46% of patients Table 2. The left ventricular dysfunction was seen in 13 patients, who showed LMCA lesion in three patients, three-vessel disease (3VD) in nine patients Table 3. LMCA

Table 1: Distribution of risk factors

Risk factors	Number of cases	LMCA	SVD	DVD	TVD	Normal
Smoking	23	3	6	6	7	4
DM	15	4	3	5	5	2
HTN	15	4	2	4	4	5
High lipid	18	4	3	5	5	2
Family history	2	0	1	1	0	0

DM: Diabetes mellitus, HTN: Hypertension, LMCA: Left main coronary artery, SVD: Single-vessel disease, DVD: Double-vessel disease, TVD: Triple-vessel disease

Table 2: Distribution of ECG findings

ECG findings	Number of cases	LMCA	SVD	DVD	TVD
ST-T	18	8	3	6	9
AVR	9	7	1	1	7
Normal	23	0	0	0	0

ECG: Electrocardiogram, LMCA: Left main coronary artery, SVD: Single-vessel disease, DVD: Double-vessel disease, TVD: Triple-vessel disease

Table 3: Distribution of echo finding

Echo findings	Number of cases	LMCA	SVD	DVD	TVD
LVD	13	2	3	4	4
Normal	37	4	9	8	9

Echo: Echocardiogram, LVD: Left ventricular dysfunction, LMCA: Left main coronary artery, SVD: Single-vessel disease, DVD: Double-vessel disease, TVD: Triple-vessel disease

Table 4: Distribution of angiographic findings

Category	Number of cases
LMCA	6
SVD	13
DVD	12
TVD	13
Normal	12
Thrombus	4
Total occlusion	2

LMCA: Left main coronary artery, SVD: Single-vessel disease, DVD: Double-vessel disease, TVD: Triple-vessel disease

was seen in six patients in this study. 13 patients had a single VD (SVD), 12 patients had two VD, 13 patients had 3VD, and 12 patients had normal/insignificant coronary lesions Table 4.

DISCUSSION

CAD and its risk factors are increasing at a rapid pace in Indian population. However, lack of health screening programs and lack of preventive measures have remained major challenges related to the increasing prevalence of CAD. Heart diseases are occurring in Indians 5–10 years earlier than in other populations around the world.^[8] According to the INTERHEART study, the median age for the first presentation of acute myocardial infarction in the South Asian (Bangladesh, India, Nepal, Pakistan, and Sri Lanka) population is 53 years, whereas that in Western Europe, China, and Hong Kong is 63 years.^[9] Studies on epidemiological data from angiographically proven cases of premature CAD (≤ 40 years) in native Indians suggest hyperlipidemia as the most prevalent risk factor.^[10,11]

Khadkikar *et al.* observed SVD, double VD (DVD), triple VD (TVD), and no VD in 50%, 13.6%, 4.5%, and 31.8% of cases, respectively, and association of risk factors such as smoking 25%, HTN 15.6%, diabetes 11%, dyslipidemia 32.1%, and family history 37.5% of cases.^[12] Arumugam *et al.* observed diabetes mellitus (DM) 10.5%, HTN 14.8%, dyslipidemia 2.4%, smoking 2.8%, and alcohol consumption 0.5% of cases and observed SVD in 24.5% of patients, DVD in 12.5% of patients, TVD in 11.5% of patients, and non-obstructive/minimal lesion in 20% of patients.^[13] Saghir *et al.* had also observed SVD as the most common type of CAD in patients <40 years of age in 39% of cases followed by DVD in 20%, TVD in 12%, and LMCA in 2% of cases. They also observed smoking as the most common risk factor being seen in 62% of cases followed by dyslipidemia in 51%, HTN in 34%, family history of CAD in 30%, and diabetes as the least common association seen in 14% of cases studied in young patient group and LAD as the most common artery involvement in obstructive type of CAD in patients <40 years of age seen in 47% of RCA in 43% and LCx in 10% of cases.^[14] Colkesen *et al.* in their study on CAD in young adults under 35 years of age also found that LAD was the most commonly involved vessel, followed by RCA, LCx, and LMCA.^[15] Weber and Maurer *et al.*, 11 in a study of 30 patients who risk stratified according to the severity of ECG changes which subsequently underwent coronary angiogram showed the more severe the ECG changes, the more extensive the coronary lesions.^[16] Shah *et al.*, 44 in a study on angiographic analysis in unstable

angina showed 18.9% had SVD, 26% had DVD, and 45% had TVD, 3% had LM disease, and 7% had normal coronaries.^[17]

CONCLUSION

The present study reveals a high prevalence of most of the modifiable cardiovascular risk factors, especially HTN, DM, smoking, and dyslipidemia. The study strongly suggests the importance of patient education by providing awareness classes about the importance of smoking cessation to avoid long-term complications in these patients and better control of cardiovascular risk factors is expected to have a favorable impact on the incidence of the acute coronary syndrome and thereby improving the quality of life of the patients.

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Assessment for Performance of Middlebrook 7H9 with Oleic-Albumin-Dextrose-Catalase Culture Media for Isolation of *Mycobacterium tuberculosis* in Ziehl–Neelsen Smear-positive Sputum Samples in Clinically Suspected Cases of Tuberculosis

Nitika Saini¹, Rajendra Kumar Saini², Varsha A Singh³

¹Student, Department of Microbiology, Maharishi Markandeshwar (Deemed to be University), Ambala, Haryana, India, ²Student, Department of Forensic Medicine and Toxicology, Maharishi Markandeshwar (Deemed to be University), Ambala, Haryana, India, ³Professor and HOD, Department of Microbiology, Maharishi Markandeshwar (Deemed to be University), Ambala, Haryana, India

Abstract

Introduction: Pulmonary tuberculosis (TB) is a second foremost cause of death from a communicable disease, after the HIV. Being communicable should be diagnosed at the earliest. Smear examination is preliminary step for the confirm diagnosis, but culture is still a gold standard method.

Materials and Methods: The present study was carried out in the Department of Microbiology on a total of 600 smear sputum samples from clinically suspected cases of pulmonary TB attending the outpatient and inpatient departments of MMIMSR, Mullana, Ambala, from December 2016 to June 2018. Specimens were subjected to ZN and LED staining before and after decontamination. After microscopy, specimens were subjected to culture on LJ and Middlebrook 7H9.

Results: *Mycobacterium tuberculosis* was isolated in 23.33% of samples. 110 (78.57%) were detected by microscopy (ZN and LED), respectively. ZN smear positivity before and after decontamination was maximum in mucopurulent 78% and 76.63% and LED 73.63% and 72.03%. Culture positivity on Middlebrook 7H9 was 100% while 87.85% on LJ media. The rate of contamination was 5% and 7% on Middlebrook 7H9 and LJ media, respectively.

Conclusions: Middlebrook media was superior to the conventional LJ medium in being rapid, easy to use and interpret, and significantly low time-to-growth detection and had lesser contamination rate because the liquid media contains growth supplement oleic-albumin–dextrose-catalase, provides additional nutrition.

Key words: LJ media, Middlebrook media, Pulmonary tuberculosis

INTRODUCTION

For numerous centuries, tuberculosis (TB) has been the very important of the infections in its global incidence. In ancient days, TB remains one of the world's deadliest transmissible diseases. Newer diagnostic facility, modern

treatment, and better preventive measures have almost controlled the disease in the past decade. However, after the arrival of HIV, coinfection of HIV and TB created the havoc. On the top of it, the advent of multidrug resistant (MDR) and extensively drug-resistant tuberculosis has agitated the situation further. MDR accounts for 5% of the global TB burden; however, <5% of existing MDR-TB patients are currently being diagnosed as a result of serious laboratory capacity constraints.^[1]

Laboratory confirmation and proper follow-up are extremely significant. TB may look like clinically to other respiratory diseases such as pneumonia; similarly,

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Corresponding Author: Dr. Nitika Saini, Department of Microbiology, Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala, Haryana, India. Phone: 91-9992449887. E-mail: dr.nitikasaini2019@gmail.com

common radiological finding in pneumonia and pulmonary aspergillosis has almost same radiological finding. That is why it is very difficult to differentiate, thus confirmation of TB can only be done after microbiology examination. According to Revised National Tuberculosis Control Program (RNTCP), microscopic examination of sputum is, as a rule, the only way by which the diagnosis of pulmonary TB can be confirmed. ZN microscopy is still the most useful among all methods and even done at PHC and CHC level due to its simplicity, speed, low cost, and minimal requirement of equipment and technical skills. Only disadvantage is that it requires 103–104 organisms/ml and acid-fast bacilli (AFB) and each smear examination requires on average 5–10 min, creating considerable workload for laboratories with limited resources. An alternative technique to ZN smear microscopy, LED staining gives better result as compared to ZN. Fluorescent microscopy is little bit expensive and complexity of the microscope, it reduces laboratory workloads.^[2]

During the past two decades, several methods for achieving early growth of *Mycobacterium tuberculosis* have been developed. Sputum sample contains normal flora, which may overgrow on culture, and makes the detection of mycobacteria difficult, this emphasizes the importance of a good decontamination technique before culture, chemical agents employed for this purpose should be able to effectively destroy non-tubercular organisms in sputum and release the intracellular tubercle bacilli from the epithelial cells.

In the current study, Middlebrook 7H9 liquid media is used to prevent the contamination or unwanted growth, Middlebrook 7H9 and oleic-albumin-dextrose-catalase (OADC) provide additional nutrition, it offers a more conducive environment, for helping the growth of tubercular bacilli and whereas liquid media contains polymyxin, amphotericin B, nalidixic acid, trimethoprim, and azlocillin (PANTA). A series of antimicrobial agents, namely PANTA, which prevent contamination and LJ medium, was used. In the present study, we tried to compare the Middlebrook 7H9 and LJ for shorter turnaround time and feasibility for use in smaller laboratories.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Microbiology, Maharishi Markandeshwar (Deemed to be University), Mullana, district Ambala. The study was conducted on 600 smears from clinically suspected cases of pulmonary TB after ethical clearance from ethical committee. A detailed clinical history was taken from clinically suspected patients. Sputum samples

were collected in sterile wide-mouthed, screw-capped translucent container (at least 35 mm in diameter) so that the patient can expectorate easily inside the container without contaminating the outside and to observe specimen volume and quality without opening the container. Samples were transported to the laboratory as soon as possible after collection. If unavoidable delay, the samples were refrigerated at 4° to inhibit the growth of unwanted microorganism. After processing of samples, growth detection was observed.

Processing of the Sample

The sputum samples, which are at least 2 ml, were selected for the study. The specimen was split approximately into three equal parts and was processed by digestion, decontamination, and concentration by cetylpyridinium chloride (CPC) and sodium chloride as per standard protocol.

Inoculation

About 500 microliters of the samples processed by all three methods will be then inoculated on LJ medium and Middlebrook 7H9 OADC.

Incubation

All inoculated LJ medium and Middlebrook 7H9 OADC media were incubated at 37°C.

Growth Detection

LJ medium and Middlebrook 7H9 OADC medium were checked twice weekly for the first 2 weeks and then every week for a maximum of 8 weeks.

The colony characteristics were noted and confirmed by acid-fast staining from culture.

Inclusion Criteria

Smear-positive sputum samples from clinically suspected cases of pulmonary TB were included in the study.

Exclusion Criteria

Smear-negative sputum samples from clinically suspected cases of pulmonary TB were excluded from the study.

Results were observed and compared statically.

RESULTS

Table 1 demonstrates that out of 600, *M. tuberculosis* was isolated in 23.33% of samples while 76.66% of samples showed invalid results including contamination.

Table 2 illustrates that out of 140 culture isolates, 110 (78.57%) were detected by microscopy (ZN and LED) among the culture-positive cases.

Table 3 shows by direct smear examination, fluorescent (100%) staining was better than ZN microscopy (90.90%). Sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) of conventional ZN microscopy and LED microscopy were 90.82%, 98%, 99%, and 98%, respectively.

Table 4 depicts the correlation between nature of sputum and smear positivity. Mucopurulent samples showed maximum correlation, i.e., Zn (39%) as well as LED (40.5%) followed by blood tinged Zn (7%), LED (9%), and least with salivary Zn (15) and LED (6.66%).

Table 5 depicts the correlation, on ZN staining, nature of sputum and smear positivity before and after

decontamination in salivary were 15% and 15.8%, mucopurulent 78% and 76.63%, and blood tinged 7% and 7.47%, whereas on LED, smear positivity before and after decontamination was maximum in mucopurulent 73.63% and 72.03% followed by salivary 18.18% and 19.49% and blood tinged 8.1% and 8.4%.

Table 6 shows that the grading of smear by ZN staining before and after decontamination showed decrease in number in scanty and 1+ grade from 15% to 4.67% and 23% to 9.34%, respectively, while in Grade 2+ and Grade 3+ increase in number 25% to 32.7% and 37% to 53.27%, respectively, as well as the grading of smear by LED staining before and after decontamination showed decrease in number in scanty and 1+ grade from 6.36% to 0% and 27% to 11.02%, respectively, while in Grade 2+ and Grade 3+ increase in number 30% to 36.44% and 39.09% to 52.54%, respectively.

Table 7 depicts that out of 140 cases, culture positivity on Middlebrook 7H9 was 100% while 87.85% on LJ media. Sensitivity, specificity, PPV, NPV of culture positivity on LJ media and Middlebrook 7H9 were 97.56%, 96.43%, 85.34%, and 99.35%, respectively.

Table 8a shows comparison of the isolation of mycobacteria on LJ media isolated mycobacterial strains from 81.30% ZN smear positive to 18.9% ZN smear negative and 90.24%

Table 1: Distribution of culture-positive cases among clinically suspected cases of pulmonary tuberculosis

Total cases studied	Culture positive (%)	Culture negative (%)
600	140 (23.33)	460 (76.66)

Table 2: Correlation of culture with microscopy

Total culture positive	Positive by microscopy (%)
140	110 (78.57)

Table 3: Outcome from conventional ZN microscopy (100%) and from LED microscope (110%) from the 110 smear-positive samples

ZN microscopy (n=100)	LED microscopy (n=110)		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	+ve	-ve				
+ve	99	1	90.82	98	99	98
-ve	10	490				

Table 4: Correlation of macroscopic appearance of sputum with direct ZN positivity and LED positivity in clinically suspected cases of pulmonary tuberculosis

Macroscopic examination of sputum	n=600 (%)	ZN positivity (%)	LED positivity (%)
Salivary	300 (50)	15 (5)	20 (6.66)
Mucopurulent	200 (33.33)	78 (39)	81 (40.5)
Blood tinged	100 (16.66)	7 (7)	9 (9)
Total	600	100	110

Table 5: Rate of detection of mycobacteria by ZN and LED stains before and after decontamination in relation to gross examination

Macroscopic examination of sputum	ZN positivity (%)		LED positivity (%)	
	Before decontamination	After decontamination	Before decontamination	After decontamination
Salivary	15 (15)	17 (15.8)	20 (18.18)	23 (19.49)
Mucopurulent	78 (78)	82 (76.63)	81 (73.63)	85 (72.03)
Blood tinged	7 (7)	8 (7.47)	9 (8.1)	10 (8.47)
Total	100	107	110	118

LED smear positive to 9.75% LED smear-negative samples as well as on Middlebrook media isolated mycobacterial strains from out of 71.42% ZN smear positive and 28.57% ZN smear negative and 79.28% LED smear positive and 29.71% LED smear-negative samples.

Table 8b shows that sensitivity, specificity, PPV, and NPV on LJ Media in relation with ZN and LED smear for the recovery of mycobacteria were 81.30%, 99.37%, 97.08%, and 95.37%, respectively.

Table 8c shows that sensitivity, specificity, PPV, and NPV on Middlebrook media in relation with ZN and LED smear for the recovery of mycobacteria were 71.42%, 98.91%, 95.23%, and 91.91%, respectively.

DISCUSSION

Concentration and decontamination techniques play an important and critical role in the detection and isolation

Table 6: Detection of smear grading with direct and after decontamination by ZN staining and fluorescent staining

Grades	ZN direct (%)	Staining after decontamination (%)	LED direct (%)	Staining after decontamination (%)
3+	37 (37)	57 (53.27)	43 (39.09)	62 (52.54)
2+	25 (25)	35 (32.7)	33 (30)	43 (36.44)
1+	23 (23)	10 (9.34)	27 (24.54)	13 (11.02)
Scanty	15 (15)	5 (4.67)	7 (6.36)	0 (0)
Total	100	107	110	118

Table 7: The statistical analysis on 100% was culture positive on LJ media, whereas 87.85% were culture positive for Middlebrook 7H9

Culture media	Middlebrook 7H9		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
LJ media						
+ve	120	17	97.56	96.43	85.34	99.35
-ve	3	460				

Table 8a: Correlation of culture with ZN microscopy and decontamination technique

Culture media	Culture-positive samples	ZN microscopy (%)		LED microscopy (%)	
		After decontamination		After decontamination	
		Positive	Negative	Positive	Negative
LJ	123	100 (81.30)	23 (18.9)	111 (90.24)	12 (9.75)
Middlebrook 7H9	140	100 (71.42)	40 (28.57)	111 (79.28)	29 (20.71)
Chi-square (<i>P</i> value)		3.503 (0.031)		5.975 (0.007)	

Table 8b: The statistical analysis on LJ media in relation with ZN and LED smear for the recovery of mycobacteria

On LJ media	LED after CPC		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	+ve	-ve				
ZN after CPC						
+ve	100	3	81.30	99.37	97.08	95.37
-ve	23	474				

CPC: Cetylpyridinium chloride, PPV: Positive predictive value, NPV: Negative predictive value

Table 8c: The statistical analysis on Middlebrook media in relation with ZN and LED smear for the recovery of mycobacteria

On Middlebrook media	LED after CPC		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	+ve	-ve				
ZN after CPC						
+ve	100	5	71.42	98.91	95.23	91.91
-ve	40	455				

CPC: Cetylpyridinium chloride, PPV: Positive predictive value, NPV: Negative predictive value

of mycobacteria. In samples such as sputum mycobacteria and normal flora are habitually present but are confined within the mucus. Liquefaction by mucolytics and vortex of the specimen disrupts the mucus and releases the mycobacteria. Thus, increasing the rate of detection. Likewise, in the current study showed that *Mycobacterium TB* was isolated in 140 (23.33%) from 600 specimens of clinically suspected patients of pulmonary TB [Table 1] which was in accordance with studies conducted by Shinu *et al.*,^[3] in 2013, who observed a isolation rate of 23.07% and 19.88%, respectively. Morcillo *et al.*^[4] (2008) also supported this study. The lower the percentage in this study may be because it was conducted in Haryana which is among the rich states of India.

The objective of the present study was to compare the two different types of staining and examination LED microscopy and ZN microscopy which is standard diagnostic procedure in urban, semi-urban, and rural settings, 78.57% smear positivity were detected with two methods, i.e., light microscopy by staining the smears with ZN staining and LED microscopy after staining with auramine stains among the culture-positive cases. [Table 2] in accordance with Kelamane *et al.*, who has reported ZN positive cases were 17.6% and on LED microscopy 82%. when both methods of microscopy were combined. Overall, culture positivity from cases of pulmonary TB shows wide variation and the present study excluded all the patients already on ATIT, so the recovery on culture remained on a higher side. Furthermore, culture considers as an the gold standard in the diagnosis of TB and yields higher positivity when compared to smears, findings of the present study were in accordance to Dhingra *et al.*,^[5] who in their study also revealed that the culture yielded more positivity 32.7% as compared to microscopy (20.2%).

In existing study by direct smear examination, LED microscopy (100%) showed better results than Zn microscopy (90.90%) and sensitivity is 90.82%, specificity is 98%, PPV is 99%, and NPV is 98% of conventional ZN microscopy and LED microscopy [Table 3] supported by Kelamane *et al.*^[6] (2016) showed that sensitivity and specificity of Zn microscopy when compared to culture were 98.50% and 62.70%, respectively.

In the current study, the maximum samples processed were grossly salivary (50%) followed by mucopurulent (33.33%) and blood tinged (16.66%). On evaluation of smears by direct ZN staining, mucopurulent samples yielded the maximum result, i.e., 39% followed by salivary (5%) and minimum results were seen with blood tinged (7%) samples as well as in fluorescent microscopy. Mucopurulent samples yielded the maximum result, i.e., 40.5% followed by salivary (6.66%) and minimum results were seen with

blood tinged (9%) samples [Table 4]. This outcome is in concordance with results of Yoon *et al.*,^[7] who also found minimum results with salivary and maximum with mucopurulent samples. The reason behind it may be due to the fact that purulence is due to infection which consists of excessive pus cells where the mycobacteria intracellularly yielding more smear positivity, i.e., why RNTCP considers mucopurulent sputum as an ideal sample to be processed for yielding higher number of mycobacteria.

In the current study, CPC was used as decontamination techniques. CPC is better for the detection of mycobacteria because it causes disturbance of cell membrane and seepage of cell contents ultimately cell death of epithelial cells causing release of intracellular mycobacterial bacilli, hence, useful as an aid in detection. During infection, due to immune response, there is chemotaxis of pus cells, thus purulent sample comprises excessive pus cells; as mycobacteria are intracellular organism, such specimens yield maximum smear positivity. During decontamination, there is dissolution of mucous by mucolytics and release of intracellular AFB from the pus cells. In the current study, the effect of CPC method on positive sputum samples was better, this may be because overnight treatment of specimens with CPC causes digestion of all cells and debris, which must have cleared during staining process, hence, aiding in better viewing of the bacilli against a clear background under ZN microscopy and LED microscopy. LED smear positivity and culture goes hand in hand, especially in multibacillary cases as auramine O stain can detect bacilli up to 104/ml of sputum. By this method in the present study, maximum samples processed were grossly mucopurulent (78%) followed by salivary (15%) and blood tinged (7%) before contamination. However, after decontamination, mucopurulent (76.63%) followed by salivary (15.8%) and blood tinged (7.47%). On evaluation of smears by LED microscopy, before decontamination, mucopurulent (73.63%) followed by salivary (18.18%) and blood tinged (8.1%) and after decontamination by CPC mucopurulent (72.03%) followed by salivary (19.49%) and blood tinged (8.47%). Mucopurulent yielded maximum result, respectively. Minimum results were seen with blood tinged [Table 5]. This conclusion was in concordance with Yoon *et al.*,^[7] who also found that mucopurulent (33.3%) yielded maximum followed (24%) blood stained and least in salivary (2.4%). Decontamination and concentration procedures break down the cell releasing the intracellular bacilli outside, thereby increasing the positivity rate on microscopy as revealed by Hooja *et al.*^[8] in their study that the sensitivity increased by 6.67% for ZN microscopy after decontamination

In ZN microscopy, the present study found a decrease in the number of scanty samples from 15% on direct

microscopy to 5% after CPC and while in LED microscopy, number of scanty samples decreased from 6.36% on direct microscopy to 0%. As well as in 1+ grade found 23% on direct microscopy to 10% after CPC and while in LED microscopy decrease from 27% to 11.02% respectively. There was a significant increase in rest of the grades after decontamination [Table 6]. According to grading of smears. Scanty samples were 15% and 6.36% on ZN and LED microscopy, respectively, and as the load increases to Grade 3+, the rate of detection in LED increases as compared to ZN. After CPC, scanty samples were 5 (4.67%) and 0% on Zn and LED microscopy. It depends on various factors such as time of collection, number of samples taken, nature of sample, antitubercular treatment, and observer's competency. The present study according to the grades of direct ZN microscopy showed highest result for 3+37 (37%) and 43 (39.09%) and lowest for scanty 15 (15%) by direct examination after ZN staining [Table 6] which is in accordance with the study conducted by Hellen *et al.*,^[9] who observed that 58.8% were 3+ and 8.8% were scanty. Scanty samples were only 10% and 7% on ZN and LED microscopy, respectively, and as the mycobacterial load increases to 3+, the rate of detection on smears increases.

In this current study, LED microscopic and ZN microscopic result after decontamination, compared with culture on LJ and Middlebrook 7H9 for diagnosis of TB. Culture is the ultimate diagnostic tool for TB. LJ is the internationally accepted media used as the gold standard. In the present study, 100% and 87.85% showed growth on the LJ and Middlebrook; sensitivity, specificity, PPV, and NPV of biphasic media for the recovery of mycobacteria were 97.56%, 96.43%, 85.34%, and 99.35%, respectively [Table 7]. A study by Pawar *et al.*^[10] in culture positive on Middlebrook and LJ showed isolation rates of 23% and 62.9%, respectively, as well the study of Naveen and Peerapur^[11] culture positive on Middlebrook and LJ showed isolation rates of 34.74% and 26.27% correspondingly. Compared to LJ medium, Middlebrook 7H9 is a liquid medium, OADC provides additional nutrition, it offers a more conducive environment, for helping the growth of tubercule bacilli and whereas biphasic media contains PANTA which has antibacterial and antifungal activity which prevents contamination. In this study, few patients were on antitubercular treatment for variable time periods so that are why some drugs target the cell wall of mycobacteria, as a result dead bacilli take uneven stain, therefore, give beaded appearance and can be differentiated from uniformly stained live bacilli. However, in patients on recently started ATT, it may be difficult to differentiate live and dead bacilli on microscopy. The dead bacilli do not grow on culture media but may show its presence in microscopy, hence, giving false-positive results. This also

reveals that microscopy does not always give accurate results for the diagnosis of TB, and all positive smears should be confirmed by culture.

In the present study shows comparison of isolation of mycobacteria on LJ media and Middlebrook with LED microscopy after decontamination and Zn microscopy and concentration techniques. On LJ media, of total 140 isolates, 81.30% and 18.9% were Zn positive and Zn negative after CPC, whereas in LED microscopy, 90.24% and 9.75% were LED positive and LED negative after CPC. Similarly, of 123 isolates on Middlebrook, 71.42% and 28.57% were Zn positive and Zn negative after CPC, whereas in LED microscopy, 79.28% and 29.71% were LED positive and LED negative after CPC. Statistical analysis on LJ media, sensitivity 81.30%, specificity 99.37%, PPV 97.08%, NPV 95.33% and on middle brook Sensitivity 71.42%, Specificity 98.91%, PPV 95.23%, NPV 91.91% [Table 8], whereas 1 (14.28%) and 1 (25%) samples showed no growth on LJ and Middlebrook correspondingly. As far our knowledge is concern, none of the researcher had done similar research.

In existing study, Middlebrook liquid media provided early growth of isolates, i.e., within 3–4 weeks, 25% were positive on Middlebrook and rest of 75% were positive on 4–6 weeks as compared to 20% were positive on LJ by 4 weeks and rest 80% were on 5–6 weeks on LJ. This is attuned with Pawar *et al.*^[10] in their study. All 41 samples growth was obtained on the 5th week of incubation on Middlebrook, whereas only 13 cultures were positive on LJ by the 5th week for rest 21 it took 6 weeks for the bacteria to grow on LJ medium. Middlebrook liquid medium could be adapted for early recovery of *Mycobacterium* with better of performance and reliability. Due to high growth supplements in Middlebrook 7H9, it detects more number of mycobacteria other LJ media.

CONCLUSIONS

RNTCP considers staining as an effective method for the preliminary diagnosis of TB. ZN staining is still a popularly used method, especially in resource-limited laboratories. However, LED microscopy after fluorescent staining yields better results than the conventional ZN staining and is recommended by the WHO. In the present study examination, fluorescent LED (18.33%) staining was better than Zn microscopy (16.66%). Gross examination has played an important role in diagnosis of TB. Mucopurulent specimens of sputum yielded the best results and were more relevant and beneficial in diagnosis as the mycobacteria are concentrated in the thick part of the sputum and it is the specimen suggested by RNTCP as ideal.

Decontamination and concentration are a key step, thus it is important to choose an efficient decontamination method. In the present study, CPC method was used, the overnight treatment of specimens with CPC causes digestion of all cells and debris gives better result. In the present study in ZN smear positivity, before and after decontamination was maximum in mucopurulent 78% and 76.63% and LED smear positivity, before and after decontamination was maximum in mucopurulent 73.63% and 72.03%.

Culture is still considered as the gold standard. Solid and liquid culture media has been used nowadays for isolation. Though LJ is internationally accepted media. Liquid culture has become routine microbiology practice and its introduction has improved the sensitivity for detection and reduced the time to result by more than a week in comparison to conventional culture on LJ medium.

The Middlebrook 7H9 medium could be well adapted for early recovery of *M. tuberculosis* with ease of performance and reliability. It does not require gas supplies or radioactive tracers and enable recovery of the mycobacteria without special equipment in small and peripheral laboratories. Whereas Middlebrook media had lesser contamination rate, because the liquid media contains growth supplement OADC, provides additional nutrition, it offers a more conducive environment, for helping the growth of tubercule bacilli and antibiotic mixture contains PANTA which has antibacterial and antifungal activity which prevents contamination.

It is not only comparable with the conventional LJ medium but significantly better for recover and growth

of *M. tuberculosis*. It is safer and self-contained and can be used easily in rural laboratories.

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Correlation between Fundamental Speech Frequencies (F0) and Serum Testosterone Levels in Patients with Puberphonia Attending a Tertiary Care Hospital

B. Baby Sai Rani¹, Md. Naveed Ahmed²

¹Assistant Professor, Department of Physiology, Government Medical College, Anantapur, Andhra Pradesh, India, ²Professor, Department of ENT, Government Medical College, Anantapur, Andhra Pradesh, India

Abstract

Background: voice in humans is susceptible to the hormonal changes throughout life right from the puberty until old age. Thyroid, gonadal, and growth hormones have varied impact on the structure and function of the vocal apparatus. Voice changes are observed during physiological states such as puberty and menstruation. Puberphonia is defined as an inappropriate use of high-pitched voice beyond pubertal age in males which is usually seen in the immediate postpubescent period when the male vocal mechanism has undergone significant changes in size and function caused by hormonal changes. Endocrine evaluations in puberphonia by astute clinical observers who make out the changes in the voice are required to develop a system of diagnosis and assessment of prognosis.

Aim of the study: The aim of the study was to analyze the relationship between serum testosterone levels and fundamental frequencies (F0) of patients with puberphonia.

Materials and Methods: A total of 43 patients aged between 14 and 18 years with puberphonia were included in the study. They were subjected to pubertal history taking and an ENT evaluation with a stroboscope to obtain visual assessment of the vocal cords. The mucosal wave, vibratory symmetry, and amplitude; type of glottic closure; hyperfunction; arytenoids movement and symmetry; ventricular movement, etc., were evaluated using stroboscopy including patient's fundamental frequency (F0) during sustained phonation. The relationship between circulating levels of serum testosterone and the fundamental frequencies of puberphonia patients was analyzed. Serum testosterone was evaluated by quantitative high-performance liquid chromatography-tandem mass spectrometry method in this study. Serum levels of testosterone more than 165 ng/dL in children aged 14–15 years; testosterone levels higher than 619 ng/dL in children aged 15–16 years; and higher than 733 ng/dL in children aged 16–17 years were taken as abnormal. All the data were analyzed using standard statistical methods.

Observations and Results: Among the 43 patients, the incidence was equal in all age groups between 14 and 17 years. There was no statistical significance in relation to socioeconomic status, the presence of secondary sexual features, personality, and parent domination among the groups. However, residing in urban locality was statistically significant over residence in the rural locality among the patients with puberphonia with $P = 0.042$ and 0.038 , respectively. The overall F0 mean value for the study group was 196.56. The relationship between mean F0 values and mean serum Testosterone levels were analyzed using Chi-square test and observed that there was statistical significance between the values in all the age groups of the study ($P < 0.05$).

Conclusions: There was a negative relationship between circulating levels of serum testosterone and fundamental frequency (F0). Higher testosterone levels are indicating lower fundamental frequency, although the magnitude of the relationship was larger than previously observed studies in literature. It is thought that male voices may have deepened over the course of evolution to signal dominance and/or to increase the speaker's attractiveness. Findings confirm that vocal frequencies may provide an honest signal of the speaker's hormonal quality.

Key words: Frequency, Hormone and vocal cords, Puberphonia, Speech therapy, Voice

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INTRODUCTION

Voice is an important component that imparts self-confidence and socially acceptable behavior of an individual. The quality of the voice is an essential component of the self-assessment tool and reduces the social and physiological handicap of an individual.^[1]

Corresponding Author: Dr. Md. Naveed Ahmed, Department of ENT, Government Medical College, Anantapur, Andhra Pradesh - 515 001, India. Email: naveedahmed60@gmail.com

The pitch of the voice is considered as the main factor influencing the perception of the gender based on the voice.^[2] The relationship between voice and hormones was appreciated even in the medieval era. In earlier centuries, in Central Asia and European countries, it was a practice to castrate young male singers with exceptionally good voice to prevent the cracking of their voice during puberty, giving them a long professional life. This practice was prevalent in 17th and 18th centuries and the popular castrated stars during that era include Baldassare Ferri (1610–1680) and Alessandro Moreschi (1858–1922).^[3] The physical properties of speech include the voice (audible sound waves), pitch (rate of vibration of the vocal folds), resonance (quality and depth of voice), intonation (variation of pitch without distinguishing of words), tone (pitch variation with distinguishing of words), intensity (pressure of sound), timbre (characteristic tone or quality), and articulation (production of vowels and consonant sounds).^[4] The fundamental frequency (F0) corresponds to the number of vocal fold vibration cycles per second (Hz) and perceived as the pitch of the voice. The vocal cords in females are short and thin, leading to fast vibration, giving a higher pitch to their voice. There are changes in the F0 with age with the first change happening at puberty in males. Thereafter, with advancing age, the pitch gets reduced in females and increases in males. The short vocal tract in the females gives the voice a higher resonance than male voice.^[5] Voice is an important secondary sexual characteristic giving an independent imprint to the character and personality of an individual. The deep influence of sex hormones on the characteristics of voice is mediated by the hormonal receptors present within the vocal folds and apparatus.^[6] The sexual differences about the voice change are observed during puberty.^[7] Increased testosterone and dihydrotestosterone in males lead to increased bulk of laryngeal muscles and ligaments. This leads to drop in the higher octaves in the pitch of voice and frequent cracking. Puberphonia is defined as an inappropriate use of high-pitched voice beyond pubertal age in males which is usually seen in the immediate postpubescent period when the male vocal mechanism has undergone significant changes in size and function caused by hormonal changes. The patients resent with a complaint of a high-pitched voice which is deemed inappropriate for their age and sex. The incidence of puberphonia in general population is 1 in 900,000.^[8] The most common symptoms are pitch breaks, hoarseness, breathiness, difficulty in vocal projection, and visible laryngeal muscle tension. The various theories put forth in literature^[9] regarding the development of puberphonia are increased laryngeal muscle tension causing laryngeal elevation, embarrassment of the newly achieved vocal pitch, failure to accept the new voice, social immaturity, etc. In elderly males, the levels of estrogen

play an important role in influencing the voice. In a study conducted in an elderly population compared the voice characteristics in patients with and without hypogonadism the patients with low estrogen levels, there was an increase in the mean fundamental frequency and a shift of the frequency ranges with alterations in the highest and lowest frequencies.^[10] In the case of females, the elevated levels of estrogens and progesterone have no or minimal effect on the voice during puberty. The importance of hormonal influence on the female voice is appreciated during the cyclical changes of the menstrual cycle. The voice changes associated with the premenstrual syndrome are grouped under dystrophia premenstrualis.^[11] During this period, the classical manifestation is the difficulty in singing high notes. There is also laryngeal edema due to the high estrogenic state before the ovulation. The slight drop in pitch of voice after menopause may be due to a relative excess of androgens. Other voice changes observed after menopause include huskiness, vocal fatigue, and inability to reach high harmonics which are appreciated more in professional singers and teachers. Hormone replacement therapy has shown to reverse most of the observed voice changes in postmenopausal females.^[12] The present study was conducted with an aim to analyze the relationship between salivary testosterone hormone levels and their fundamental frequencies in patients with puberphonia.

Type of Study

This was a prospective cross-sectional and analytical clinico-physiological study.

Period of Study

The period of study was from October 2016 to September 2018 (2 years).

Institute of Study

This study was conducted at Government Medical College, Anantapur.

MATERIALS AND METHODS

In this prospective study conducted in the department of ENT of a tertiary hospital over a period of 2 years, 43 patients with history of high-pitched voice (perceptually) and found to have high F0 (Fundamental Frequency) on Multi-dimensional Voice Program (Kay Pentax) were diagnosed as puberphonia and were included in the study. All the patients were aged between 14 and 18 years.

Inclusion Criteria

- (1) Patients aged between 14 and 17 years were included.
- (2) All the patients were males.
- (3) Patients with fundamental frequency (F0) >200 KHZ were included.
- (4) Patients

consenting to collect blood samples for estimation of early morning serum testosterone levels were included.

Exclusion Criteria

(1) Patients <14 years and >17 years were excluded. (2) Patients with vocal cord lesions were excluded. (3) Patients with a history of surgeries on the throat were excluded. All the patients were subjected to detailed pubertal history taking by a physiologist, and an ENT evaluation by an ENT surgeon with a stroboscope was done using Kay Pentax 9105 System. Stroboscopy was used to obtain a visual assessment of the vocal cords. The stroboscopic evaluation provided measures of vibratory behavior of the vocal folds such as presence or absence of mucosal wave, vibratory symmetry, and amplitude; type of glottic closure; hyperfunction; arytenoids movement and symmetry; ventricular movement, etc. Stroboscopy also yielded a measure of the patient's fundamental frequency (F0) during sustained phonation. The relationship between circulating levels of serum testosterone and the fundamental frequencies of puberphonia patients who recorded their voices and provided blood samples at 9 am on a single day was studied. Serum testosterone was evaluated by quantitative high-performance liquid chromatography-tandem mass spectrometry method in this study. Serum levels of testosterone more than 165 ng/dL in children aged 14–15 years; testosterone levels higher than 619 ng/dL in children aged 15–16 years; and higher than 733 ng/dL in children aged 16–17 years were taken as abnormal. All the data were analyzed using standard statistical methods.

OBSERVATIONS AND RESULTS

A total of 43 patients with a diagnosis of puberphonia and evaluation were included in this study. The incidence of age groups and demographic data was analyzed and found that the incidence was equal in all age groups among the children aged between 14 and 17 years and not statistically significant ($P < 0.05$ was taken as significant) [Table 1]. Similarly, socioeconomic status, presence of secondary sexual features, personality, and parent domination were also not significant statistically. However, residing in urban locality was statistically significant over residence in the rural locality among the patients with puberphonia with $P = 0.042$ and 0.038 , respectively [Table 1].

Stroboscopy findings among the patients with puberphonia in this study showed normal features in regard with a mucosal wave, vibratory symmetry, and amplitude, type of glottic closure, arytenoids movement symmetry, and ventricular movement. Fundamental frequency (F0) showed variable expression and was tabulated in Table 2. The overall F0 mean value for the study group was 196.56.

Table 1: The age incidence and demographic data of patients with Puberphonia (n=43)

Observation	Number	Percentage	P value
Age group (years)			
14–15	17	39.53	Not significant
15–16	15	34.88	
16–17	11	25.58	
Socioeconomic status			
Low	9	20.93	Not significant
Middle	20	46.51	
High	14	32.55	
Residence			
Urban	26	60.46	0.042 (significant)
Rural	17	39.53	
Sibling status			
First	7	16.27	0.038 (significant)
Second	22	51.16	
Third	14	32.55	
Other secondary sexual features			
Present	39	90.69	Not significant
Absent	4	09.30	
Personality			
Timid	20	46.51	Not significant
Introvert	6	13.95	
Extrovert	17	39.53	
Parental domination			
Mother	24	55.81	Not significant
Father	19	44.18	

The relationship between mean F0 values and mean serum testosterone levels was analyzed using Chi-square test and observed that there was statistically significant difference between the values in all the age groups of the study ($P < 0.05$) [Table 3].

DISCUSSION

Voice production in humans is a complex function depending on multiple systems such as properly functioning neurological system, the respiratory system and an anatomically sound, and physiologically active upper airway tract. Production of normal voice is possible only with the coordination of complex systems such as various laryngeal muscles. There should be a temporary cessation of the vital functions of the upper aerodigestive tract such as breathing and deglutition.^[7] The larynx *per se* being a dynamic structure alters its shape and lumen by a system of articulated cartilages controlled by the vagus nerve. Voice is produced by the vibration of a closed glottis during expiration. The expiratory blast of air from the lungs induces a vibration in the vocal cords producing voice which, in turn, gets articulated in the lubricated supralaryngeal airway to form speech. Any change in any of these systems brought about by endocrine disorders would have an impact on the physiology of voice production. The characteristics of speech include the voice (audible sound waves), pitch

Table 2: The incidence of F0 ranges in the study group (n=43)

Frequency (KHz)	14–15 years (17)		15–16 years (15)		16–17 years (11)		Overall mean
	Number of patients	Mean F0	Number of patients	Mean F0	Number of patients	Mean F0	
100–150	4	123.30	2	121.45	1	119.40	
150–200	7	168.95	6	157.35	5	155.50	
200–250	5	215.55	3	205.20	3	240.30	
>250	1	265.40	4	253.15	2	261.25	
Mean F0		193.30		184.28		194.11	196.56

Table 3: The correlation between F0 and testosterone levels in the study groups (n=43)

Age groups (years)	Mean values of F0	Mean testosterone levels (ng/dL)	P value
14–15 (17)	193.30	194	0.035
15–16 (15)	184.28	658	0.045
16–17 (11)	194.11	759	0.371

(rate of vibration of the vocal folds), resonance (quality and depth invoice), intonation (variation of pitch without distinguishing of words), tone (pitch variation with distinguishing of words), intensity (pressure of sound), timbre (characteristic tone or quality), and articulation (production of vowels and consonant sounds).^[4] The fundamental frequency (F0) corresponds to the number of vocal fold vibration cycles per second (Hz) and perceived as the pitch of the voice. The vocal cords in females are short and thin, leading to fast vibration, giving a higher pitch to their voice. There are changes in the F0 with age with the first change happening at puberty in males. Thereafter, with advancing age, the pitch gets reduced in females and increases in males. The short vocal tract in the females gives the voice a higher resonance than the male voice.^[5] Voice is considered by many as an important secondary sexual characteristic which gives an independent imprint to the character and personality of an individual. The profound influence of sex hormones on the characteristics of voice is mediated by the hormonal receptors present within the vocal folds and apparatus.^[6] There are certain sexual differences in the voice change observed during puberty.^[10] Increased testosterone and dihydrotestosterone in males lead to increased bulk of laryngeal muscles and ligaments. This leads to a drop in the higher octaves in the pitch of the voice and frequent cracking. In elderly males, the level of estrogens has a major influence on the voice rather than the prevailing androgens. A study done in an elderly population compared the voice characteristics in patients with and without hypogonadism. In patients with low estrogen levels, there is an increase in the mean fundamental frequency and a shift of the frequency ranges with alterations in the highest and lowest frequencies.^[11] Whereas in females the higher levels of estrogens and progesterone have minimal effect on the voice during puberty. The importance of hormonal influence on the female voice is appreciated during the cyclical changes of the menstrual cycle. The voice changes associated with the premenstrual syndrome are

grouped under dystrophia premenstrualis.^[12] The classical manifestation is the difficulty in singing high notes during the premenstrual period. There is laryngeal edema due to the high estrogenic state before the ovulation. However, the relative excess of androgens after menopause may lead to a slight drop in the pitch of the voice. Other voice changes observed after menopause include huskiness, vocal fatigue, and inability to reach high harmonics. These changes are appreciated more in professional singers and teachers who use the voice for a living. Hormone replacement therapy has shown to reverse most of the observed voice changes in postmenopausal females.^[13] Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In males, testosterone is secreted by the testicular Leydig cells and to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated through pituitary-gonadal feedback involving luteinizing hormone and to a lesser degree, inhibins, and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which in males also is called testosterone-binding globulin. A lesser fraction is albumin-bound and a small proportion exists as a free hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is, therefore, considered bioavailable. In male children around puberty, larynx undergoes deep modifications resulting in voice mutation. The vocal folds suffer a pronounced growth, doubling in size. As a result, voice decreases one octave, and the adult

voice is established. In women, whereas this growth is less significant, and voice decreases only two to three notes around 12–14-year-old.^[14,15] These voice changes, along with all the other secondary sexual characteristics, allow the differentiation of gender through voice, something that does not occur during childhood.^[15] These changes take few months to 1 year and the male child's voice may become mildly rough, weak, and unstable, with some variations and bitonality, but tending to low sounds.^[15] If this mutation does not occur correctly and adequately, a mutational dysphonia or puberphonia occurs. The cause is rarely organic, and it is usually part of the psycho-emotional sphere. Mutational dysphonia may be didactically classified into prolonged, incomplete, excessive, premature, retarded, and mutational falsetto.^[14] Among them, the mutational falsetto is considered the most frequent, representing 2% of the functional dysphonia.^[15] In this study, an attempt was made to find the relationship between the serum testosterone levels and fundamental frequency of puberphonia patients which is an effect of the mutational failure of the larynx. Stroboscopy findings among the patients with puberphonia in this study showed normal features kin regard with a mucosal wave, vibratory symmetry, and amplitude, type of glottic closure, arytenoids movement symmetry, and ventricular movement. Fundamental frequency (F0) showed variable expression and was tabulated in Table 2. The overall F0 mean value for the study group was 190.56. The relationship between mean F0 values and mean serum testosterone levels was analyzed using Chi-square test and observed that there was statistical significance between the values in all the age groups of the study ($P < 0.05$) [Table 3]. A study with 10 teenagers with mutational falsetto in pre- and post-therapy conditions showed mean F0 values of 221 Hz and 119 Hz, respectively. These values are very close to those found in this study 190.56.^[16] It is thought that male voices may have deepened over the course of evolution to signal dominance and/or to increase the speaker's attractiveness.^[17] Findings confirm that vocal frequencies may provide an honest signal of the speaker's hormonal quality.

CONCLUSIONS

There was a negative relationship between circulating levels of serum testosterone and fundamental frequency (F0).

Higher testosterone levels indicating lower fundamental frequency, although the magnitude of the relationship was larger than previously observed studies in literature. It is thought that male voices may have deepened over the course of evolution to signal dominance and/or to increase the speaker's attractiveness. Findings confirm that vocal frequencies may provide an honest signal of the speaker's hormonal quality.

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Tattoo Removal using Surgical Techniques: Experience with 350 Cases

Samira Sharma¹, Kavita Kumari², Reena Makhni³

¹Assistant Professor and Head, Department of Plastic Surgery, Government Medical College, Amritsar, Punjab, India, ²Assistant Professor, Department of Blood Transfusion, Government Medical College, Amritsar, Punjab, India, ³Associate Professor, Department of Anaesthesia, Government Medical College, Amritsar, Punjab, India

Abstract

Introduction: There has been an exponential increase in the number of young adults seeking tattoo removal in recent years. The main reason is a prohibition of any form of tattoo in recruitment of army, paramilitary force, police, and other jobs. Most studies done on tattoo removal are either on laser removal or have established results of only one particular surgical method of tattoo removal. However, almost all known surgical methods of tattoo removal have been performed in the present study.

Aims and Objectives: The aim is to study the clinical outcome of various surgical methods of tattoo removal to search for an ideal one.

Materials and Methods: A study was conducted in 350 patients. Tattoo removal was done with surgical methods. The various surgical techniques used were excision and primary closure, serial excision, tangential split thickness excision, tangential excision with dermal over grafting, and excision with grafting. The factors which determined the choice of procedure were size, site, shape, depth of tattoo, skin laxity, and presence of complication of tattooing or previously attempted tattoo removal. Patients were followed for 3 months.

Results: Excision and primary closure were done in 26 tattoos. Serial excision in 9, split thickness tangential excision in 2, tangential excision with dermal over grafting in 179, and excision with grafting in 134 tattoos were done. Scar stretching, minimal color changes, and hypertrophy were seen after tattoo removal. Post-operative marginal hypertrophy was seen lesser in tangential excision with dermal over grafting (60%) than in excision with grafting (75%) though it could be managed conservatively. Patient satisfaction levels were well achieved.

Conclusion: All procedures resulted in complete tattoo removal, and each had its own application and limitations. It was difficult to label one procedure superior to the other.

Key words: Dermal over grafting, Serial excision, Tangential excision

INTRODUCTION

The problem of tattoo removal is not new. Bromberg suggested that tattooing is frequently a sign of emotional immaturity.^[1] The term tattoo is derived from “tattau,” a Tahitian word which translates essentially “to mark” and is

a process of implantation of permanent pigment granules in the skin.^[2] Although tattooing is an ancient practice, there has been a dramatic increase in recent times among teenagers and young adults, as a cosmetic and decorative body art form. A tattoo is a permanent reminder of a temporary feeling.^[3] Many people eventually want to get rid of their tattoos because of emotional reasons, change of religious faith, as a requirement for jobs and careers and as a result of complications of tattooing.

All methods of tattoo removal involve some element of tissue destruction of the skin to ablate the pigment design.^[4] The approach to remove tattoos may be divided into two categories.

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Corresponding Author: Dr. Kavita Kumari, Department of Blood Transfusion, Government Medical College, Amritsar – 143 001, Punjab, India. Phone: +91-9876055376. E-mail: drjpatri@gmail.com

Non-surgical Methods

These utilize local application of chemical and physical agents. Salabrasion,^[5] trichloroacetic acid application,^[6] cryosurgery, and electrosurgery^[7] have been used. However, depth control and scarring due to deep dermal injuries are the problems with these methods. Laser removal of tattoos has also gained a lot of popularity, and excellent results have been claimed.^[8,9]

Surgical Methods

Various surgical techniques to remove tattoos are excision and primary closure, serial excision,^[10] split thickness tangential excision,^[4] derma abrasion,^[11] and tangential excision with dermal over grafting and excision with grafting.^[12] Derma abrasion is time-consuming and pigment removal may be irregular requiring repetitions followed by scarring in case of deep dermal involvement of pigment.^[4]

Most studies conducted on tattoo removal have established only one method of tattoo removal, and of late, laser removal has become a popular trend. No author in the past has included all surgical methods of tattoo removal in his study. In the present study instead of restricting to one or two methods, almost all surgical methods have been used. The aim was to study clinical outcome and find the most ideal surgical method of tattoo removal.

MATERIALS AND METHODS

A prospective study was conducted on 350 tattoos removed between January 2012 and December 2017 at the Department of Plastic Surgery, Guru Nanak Dev Hospital, attached with Government Medical College, Amritsar. The small-to-moderate-sized tattoos which were not crossing the neutral lines of limbs and neck were included in the study.

Routine laboratory investigations were done in all patients, especially, viral markers for hepatitis B, hepatitis C, and HIV. Any person found to be HIV, HCV or HBs positive was not included in the study. Size, site, shape, and depth of tattoo skin stretchability and the presence of previous intervention or not were the deciding factors in the selection of surgical technique in a particular patient. All of these factors had to be taken into consideration.

Tattoos of the same dimensions might have to undergo different methods of removal if they were situated on different sites or even in different orientations. Similarly, tattoos of the same surface area might have to undergo different methods of removal depending on their length and breadth ratios. Tattoos which had one dimension narrow enough or those situated where the skin was easily stretched could be excised and closed primarily.

Split skin graft was required if primary closure was not possible due to large size of tattoo or inextensible skin. Such tattoos were removed by excision or tangential excision. In cases who presented with hypertrophic scarring over tattoos as a result of improper attempts of tattoo removal or complications of tattooing such as allergic reactions, tangential excision was avoided. Tangential excision was not done for tattoos where pigment was infiltrating deep in to the subcutaneous tissue or when tattoos present on the web spaces of the hand. These underwent excision with grafting. The tattoos were excised completely so that pigment was not visible at the margins of the grafted area. It was sometimes possible to deal with a large tattoo by serial excision, removing only a part of tattoo at the first operation and removing the rest after a delay of 3–6 months.

Aseptic preparation of area to be operated on was done with 10% povidone-iodine. All cases were operated under local anesthesia. The tattoos were removed with either of the following methods.

Excision and Primary Closure [Figure 1]

Twenty-six tattoos were treated by this method. The tattoo was marked and local infiltration of 0.5% Lidocaine with 1:200,000 adrenaline was done. Full-thickness skin-bearing tattoo was excised. Undercutting of skin margins was done. Tension-free wound closure was obtained in two layers using Vicryl 4-0 for subcutaneous and Ethilon 4-0 or Ethilon 5-0 subcuticular sutures as well as interrupted sutures for the skin. Wound was dressed. Post-operative interrupted sutures were removed on the 5th day and subcuticular sutures between 10 and 14 days. From the 21st post-operative day, all patients were advised coconut oil massage on scar twice a day for 2 min and silicone gel application twice a day for 3 months.

Serial Excision [Figure 2]

Nine tattoos were treated in this manner. In the first stage, a part of tattoo was removed to achieve primary closure easily. Rest of tattoo was removed after 3 months' interval, and closure, suture removal, and scar management protocol were the same as done in the previous method.

Split-Thickness Tangential Excision [Figure 3]

Two tattoos underwent split-thickness tangential excision. An intermediate split-thickness portion of the skin was excised using manual skin graft knife. Once it was ensured that total pigment removal had been achieved at the level of superficial dermis level only, the wound was dressed using Sofra-Tulle grass and Bulky Gauze dressing. The dressing was removed on the 7th post-operative day. The area was



Figure 1: Excision and primary closure of tattoo.
(a) Pre-operative and (b) post-operative

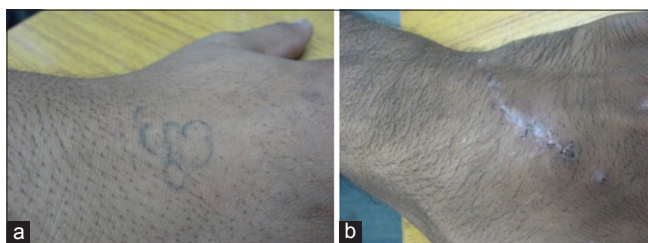


Figure 2: Serial excision (a) pre-operative and (b) post-operative

allowed to reepithelialize just like a donor skin graft area. On the 21st day, coconut oil massage and pressure garment were advised for 3 months.

Tangential Excision and Dermal Over Grafting [Figure 4]

One hundred seventy-nine tattoos were included in this group. Multiple tangential excisions of skin bearing tattoo were done with manual skin graft knife (Humby's knife handle with Down's skin grafting blade) up to the depth where the pigment was completely removed. Deep dermis level had to be reached mostly to achieve full clearance of the pigment. In some cases, a few small specks of pigment were seen which were scooped out with 11 no surgical blade.

Donor area (thigh of patient) was dressed with non-adherent padded dressing. The graft was applied to recipient area after achieving homeostasis with epinephrine gauze. The graft was secured with minimal sutures or staplers. Tie overdressing was done. Splint was given where the recipient area was on hand dorsum or very near to wrist joint on the forearm.

Recipient area was dressed after 8 days. Donor area usually healed in 14–21 days. Grafts usually settled in 15–20 days. Patients were instructed about graft care such as massage with coconut oil, pressure garment, and avoidance of sun exposure.

Excision and Grafting [Figure 5]

One hundred thirty-four tattoos were included in this group. Excision was done with 15 no surgical blade ensuring complete removal of the tattoo. The rest of the procedure and post-operative protocol was similar to the

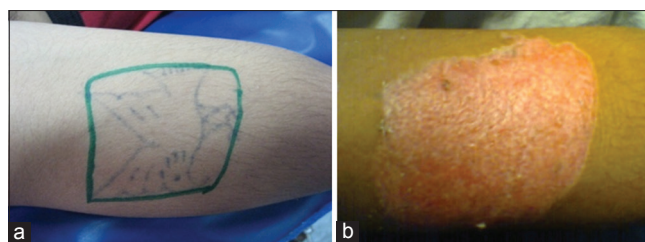


Figure 3: Tangential split skin excision without skin grafting.
(a) Pre-operative and (b) post-operative, complete pigment removal was achieved

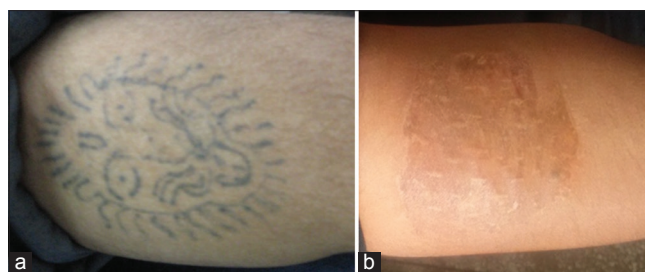


Figure 4: Tangential excision with dermal over grafting of tattoos. (a) Pre-operative and (b) post-operative

previous procedure. All patients were discharged on the same day. All patients were followed for a minimum of 3 months.

Patients were assessed for pigmentation, vascularity, pliability, and height through physical examinations on scar after 3 months of surgery by applying Vancouver Scar Scale (VSS).^[13]

Pigmentation
0=Normal color
1=Hypopigmentation
2=Hyperpigmentation
Vascularity
0=Normal
1=Pink (slight increase in blood supply)
2=Red (significant increase in blood supply)
3=Purple (excessive local blood supply)
Pliability
0=Normal
1=Supple (flexible with minimal resistance)
2=Yielding (giving way to pressure offering moderate resistance)
3=Firm (solid/inflexible unit, not easily moved, resistant to manual pressure)
4=Banding (rope-like tissue that blanches with extension of scar does not limit a range of motion)
5=Contracture (permanent shortening of scar-producing deformity or distortion limit range of motion)
Height
1=Normal
2<2 mm
3≥2 mm and <5 mm
4≥5 mm
Vancouver scar scale

After 3 months, patients were asked to select one of five responses which were very satisfied, satisfied, neutral, unsatisfied, and very unsatisfied.^[14]

RESULTS

In our study, we found that tattoos were more prevalent in males (325 cases, i.e., 93%) than in females (25 cases, i.e., 7%). The age of patients ranged between 18 and 26 years, and the average age is 19.5 years. Size of tattoos ranged from 3 cm × 1 cm to 15 cm × 7 cm.

One hundred ninety tattoos were on the upper arm (54%), 108 on the forearm (30.9%), 48 on the dorsum of hand (14%), and 4 on the neck (1.1%).

The most common indication for tattoo removal was recruitment in army, paramilitary, and police force (302 cases, 86%), followed by emotional reasons such as divorces and breakups (23 cases, 7%), complications of tattooing (14 cases, 4%), and other jobs and careers (11 cases, 3%). Complications of tattooing which needed tattoo removal were in the form of allergic reaction to pigments.

One hundred twenty-seven (36%) cases were those where some intervention was already done by the patients themselves or by ignorant medical practitioners in the form of chemical application or cauterization leading to incomplete tattoo removal and hypertrophied scars bearing tattoo pigments [Figure 6]. Of these, two patients had themselves shaved off their tattoos with the knife leading to partial tattoo removal and presented with non-healing raw areas still bearing tattoo impressions [Figure 7]. One patient presented with infection with frank pus discharge after application of some chemical on tattoo [Figure 8]. He was operated on after infection got settled with

conservative treatment. Seven patients of these 127 could be managed with excision and primary closure [Figure 9] and one with tangential excision and dermal over grafting and rest underwent excision and grafting.

Excision and primary closure were possible only in a few patients because only linear tattoos could be managed by this method.

Serial excision was a staged procedure. Some scar stretching was seen in all patients who underwent serial excision [Figure 10]. This procedure obviated the need of skin grafting and was suitable for neck and hand dorsum.

Tangential split-thickness excision was possible only in two cases where penetration of pigment was found to be limited to superficial dermis only. Soon we left this method for the fear of scarring and incomplete pigment removal.

In 102 (60%) cases, who underwent tangential excision and dermal over grafting, marginal hypertrophy was seen [Figure 11].

In patients who underwent excision and grafting, 100 patients (75%) developed marginal hypertrophy [Figure 12] which was managed with coconut oil massage and pressure garment wearing. Hyperpigmentation was seen in all patients who underwent skin grafting, but it



Figure 5: Excision and grafting of tattoo. (a) Pre-operative and (b) Post-operative



Figure 6: Partially removed tattoo with hypertrophy underwent excision and grafting. (a) Pre-operative, (b) Post-operative

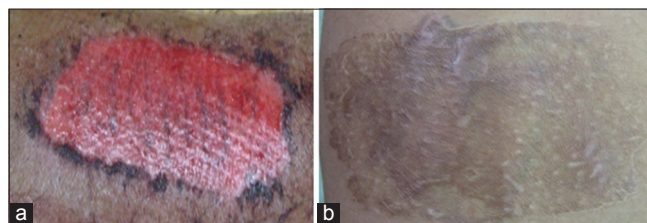


Figure 7: Tangential excision and dermal over grafting of a self-attempted tattoo removal by shaving leading to incomplete removal and raw area showing tattoo impressions. (a) Pre-operative, (b) post-operative



Figure 8: Excision and grafting in a tattoo where chemical application led to ulceration and infection. (a) pre-operative and (b) post-operative

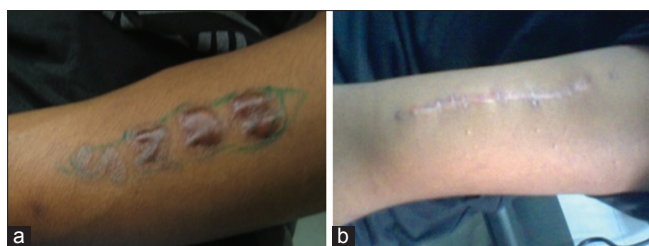


Figure 9: Excision and primary closure achieved in a tattoo where attempt of tattoo removal was done by some chemical. (a) Pre-operative and (b) post-operative

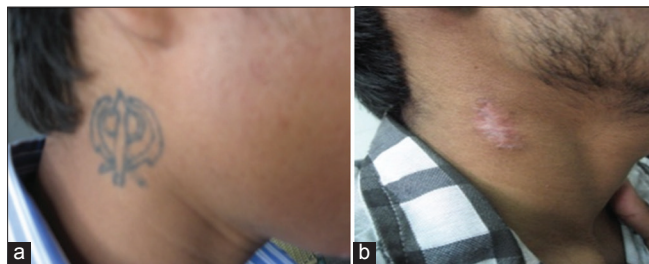


Figure 10: Serial excision of tattoo: (a) Pre-operative and (b) post-operative marked scar stretching is seen

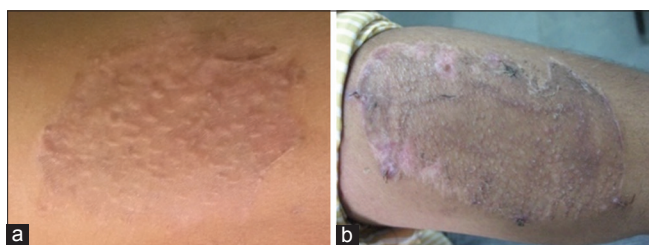


Figure 11: (a and b) Marginal hypertrophy hyperpigmentation, after tangential excision and grafting

improved with time and by avoidance of sun exposure. Operative site was healed in 10–15 days in all cases.

Donor area in all patients healed very well without any complication with 14–21 days.

In all the patients, complete pigment removal could be achieved. At the end of the follow-up of 3 months, the score of VSS ranged from 1 to 4 [Figure 13]. 172 (49%) patients were very satisfied, 150 (43%) were satisfied, and 28 (8%) were neutral [Figure 14].

DISCUSSION

No method of tattoo removal is perfect. Even the laser, though the latest in the armamentarium of tattoo removal and claim of having good results,^[8,9] is itself associated with complications such as pain, pigment changes in the skin, allergic reactions, and incomplete removal of tattoo.^[3]

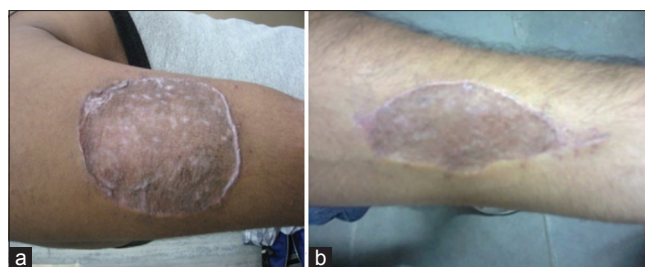


Figure 12: (a and b) Marginal hypertrophy and hyperpigmentation, after excision and grafting

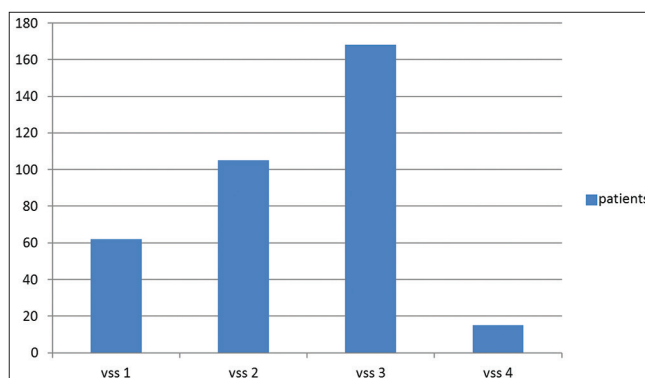


Figure 13: Vancouver scar scale score chart

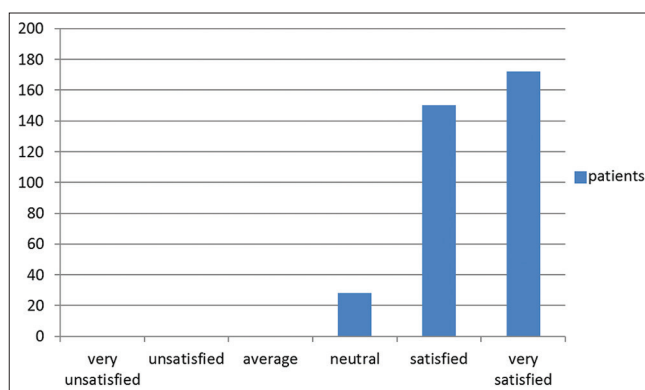


Figure 14: Patient satisfaction level chart

Of all five surgical techniques used for tattoo removal in the present study, none can be labeled as better or superior to the other, and each has its own applicability and drawbacks. Tattoos come in all sizes and shapes. There are many variables, and therefore, every method has different indication and what is important is to select a method which is the best for a particular tattoo. It is not possible to compare one method with the other.

Excision and primary closure are the best, are easy to do, and give minimal scar, but it has its limitations. The closure has to be tension free and no fix parameters can be laid for this. Tattoo of a particular size may be fit for primary closure at one site where skin is lax but may not be so at another site where the skin is not so lax.

Serial excision obviates the need for skin graft. The procedure is staged but definitely has its role where some skin laxity is present, for example, on neck and dorsum of the hand where the patchy look of skin graft is esthetically less acceptable than scar stretching which is unavoidable with this procedure (all cases had some sort of scar stretching).

Tangential excision of tattoo without skin grafting has found the least application in the present study, in two patients only. To avoid creation of a donor area of graft harvesting, some authors suggested a quick method of tangential split-thickness excision for tattoo removal, believing that it will heal like a graft donor area and some leftover pigment will come out with crust.^[4,15] If tattoo pigment is penetrating into deep dermis, the skin graft has to be applied after tangential excision otherwise healing will be delayed resulting in bad scar formation.

Tangential excision of tattoo with dermal over grafting and excision of tattoo with skin grafting had to be done in most of tattoos because size and skin laxity were not limiting factors for these two procedures. All patients who underwent tangential excision with dermal over grafting could be treated with excision and grafting also.

The marginal hypertrophy seen after tangential excision with dermal over grafting was 62% as compared to 75% seen after excision and grafting. It might be due to preservation of some elements of deep dermis in the former method. The latter method was best indicated for the patients not suitable for the former method, i.e., those who presented with complications of tattooing and self-attempted tattoo removals, tattoos over web spaces where tangential excision is difficult to perform, along with scattered irregular shaped and subcutaneous tissue deep tattoos. The higher incidence of marginal hypertrophy in this group might be due to inclusion of tattoos which had already undergone interventions in the form of application of chemicals or cauterization. Further controlled studies comparing the results of these two procedures in similar tattoos may be required to label the superiority of one method over the other.

The hypertrophy responded very well to coconut oil massage, silicone gel application, and wearing of pressure garment as shown by studies in the past.^[16] Avoidance of sun exposure was advised for hyperpigmentation.

Initially, we tried to follow each patient for 6 months, but we found follow-up very erratic. It was found that most of recruitment aspirants got busy in their trainings and those who got tattoos removed as a result of breakups

either got new partners or were just not interested in long follow-ups; therefore, we decreased follow-up to 3 months. We assessed the final outcome of our study using VSS score and patients' satisfaction survey.^[14] VSS has been accepted as a valid scale for post-surgery scar or burn scar assessment.^[13] VSS ranged from 1 to 4. The patients were simply asked to select an option out of very unsatisfied, unsatisfied, neutral, satisfied, and very satisfied at the last follow-up. The aim of complete tattoo removal was achieved in all patients along with good patient satisfaction levels as 49% of patients were satisfied and 43% of patients were very satisfied.

While conducting this study, we came across five patients who were found to be hepatitis c positive (4 patients) and HIV positive (1 patient). Although we were not sure of the cause of viral infection in them, they are known complications of tattooing along with various allergic reactions, therefore, "think before you ink."^[3] The trend of big tattoos is on rise, and the controlled studies comparing surgical techniques with other methods such as lasers may be required to search for an ideal method.

CONCLUSION

Each surgical technique of tattoo removal has its applications as well as limitations. One surgical method may be suitable for one type of tattoo and not so for the other; therefore, selective application is required. In the armamentarium of surgical methods of tattoo removal, all techniques are serving the purpose well and are acceptable. Surgical methods are a valid option for tattoo removal.

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Comparison of Visual Inspection with Acetic Acid and Pap Smear in Detecting Premalignant Lesions of Cervix

Nikita P. Naidu¹, Purushottam B. Jaju²

¹Post Graduate, Department of Obstetrics and Gynecology, Shri. B. M. Patil Medical College and Research Center, Vijayapura, Karnataka, India,

²Professor, Department of Obstetrics and Gynecology, Shri. B. M. Patil Medical College and Research Center, Vijayapura, Karnataka, India

Abstract

Background: Worldwide cervical cancer comprises approximately 12% of all cancers in women with 122,844 new cases reported annually in India. Cervical cancer progresses slowly for a decade as it is preceded by intraepithelial histological changes, visual inspection aided by acetic acid test (VIA), Pap smear, and colposcopy can be utilized as a tool for cytological analysis of cervix, early identification of risk factors and preinvasive lesions of cervix and hence early diagnosis and treatment of cervical cancer even in rural areas.

Objectives: The objectives are as follows: (1) To compare VIA with Pap smear in detecting premalignant lesions of cervix, (2) to correlate VIA and Pap smear findings with colposcopic findings, and (3) to localize the lesion by colposcopy and obtain biopsy wherever necessary.

Materials and Methods: A prospective study of 200 women attending the Gynecology Outpatient Department at BLDE (deemed to be university) Shri B. M. Patil Medical College Hospital and Research Center, Vijayapura, between October 2016 and August 2018 was included in the study.

Results: The incidence of premalignant and malignant lesions of the cervix was 7%. Cervical cytology was normal in 16%, inflammatory in 77.5%, ASCUS in 4%, LSIL in 1.5%, HSIL in 0.5%, and squamous cell carcinoma in 0.5%. Maximum number of patients with ASCUS and LSIL was in the age group of 35–39 years and 40–44 years and HSIL and squamous cell carcinoma occurred in the age group of 25–29 years and 30–34 years, respectively. ASCUS, LSIL, and HSIL were seen in parity 3–5 and malignancy in parity >3 observed mostly in low socioeconomic status. All abnormal Pap smears mainly presented with white discharge PV, pain abdomen and with irregular PV bleeding as the second most common and erosion and cervicitis as the most common clinical picture. Cervical biopsy confirmed HSIL and invasive carcinoma cytology.

Conclusion: In India, cytology, a low cost and easily accessible test, is the most logical screening modality although it has very low sensitivity, detection rates could be further improved using liquid-based cytology and the use of endocervical cytobrush.

Key words: Biopsy Screening XIII, Cervix, Colposcopy, Pap smear, Visual inspection aided by acetic acid test

INTRODUCTION

Worldwide cervical cancer comprises approximately 12% of all cancers in women with an incidence of 5 lakh new cases reported each year of which almost one-fourth of it

occurs in India.^[1] About 122,844 new cervical cancer cases are diagnosed annually in India, and 67,477 cervical cancer deaths have been reported annually in India.^[2] It is the second most common cancer in women worldwide but the most common in developing countries like India. It accounts for 80% of cervical cancer deaths in developing countries like India.^[3]

The dramatic reduction in the incidence of cervical cancer in developed countries is due to the widespread use of an effective cytological screening test, i.e., Papanicolaou Smear, which can identify the premalignant and malignant lesions of the uterine cervix, which cannot be detected or even suspected by history and clinical examination.^[4-6]

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Corresponding Author: Dr. Nikita P. Naidu, Department Of Obstetrics and Gynecology, B. L. D. E, Deemed to be University, Shri. B. M. Patil Medical College and Research Center, Solapur Road, Vijayapura, Karnataka, India. Phone: +91-9008893742. E-mail: nikitapnaidu@gmail.com

Various screening methods are available such as cytology by Pap smear, visual inspection of cervix with acetic acid and/or Lugol's iodine, HPV-DNA test, and liquid-based cytology.

1. Screening by Papanicolaou test (Pap) should not be used for women aged <21 years, regardless of initiation of sexual activity.
2. A screening interval of 3 years should be maintained by Pap smear for women aged 21–30 years. HPV test is not recommended.
3. Women aged 30–65 years should have a Pap test and a HPV test (cotesting) every 5 years or are even acceptable to have a Pap test alone every 3 years.

MATERIALS AND METHODS

Methods of Collection of Data

Source of data

A prospective study of 200 women attending the Gynecology Outpatient Department at BLDE (deemed to be university), Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapura was included in the study.

Period of the study

The period of the study was from October 2016 to August 2018.

Sample size calculation

Using the formula:

$$n = z^2 p(1-p)$$

$$d_2$$

Where

Z = z statistic at 5% level of significance

d is margin of error

p is anticipated prevalence rate

A sample size of 185 (~200) was allowed for the comparison of visual inspection with acetic acid and pap smear as screening methods for premalignant lesions of the cervix with a 95% confidence level and margin of error of $\pm 7\%$ with finite population correction.

Statistical Analysis

Data were represented using Mean \pm SD and analyzed by Chi-square test for association, comparison of means using *t*-test, ANOVA for comparison, sensitivity, specificity, positive predictive value, and negative predictive values.

Methods of Collection of Data

Informed consent was taken from each woman. Relevant obstetrics and gynecology history were taken and recorded.

Inclusion Criteria

The following criteria were included in the study:

1. Age between 25 and 65 years
2. Chronic cervicitis
3. Symptoms such as vaginal discharge, postcoital bleeding, postmenopausal bleeding, intermenstrual bleeding, and persistent leukorrhea not responding to antibiotics
4. Normal looking cervix but symptomatic.

Exclusion Criteria

The following criteria were excluded from the study:

1. Menstrual bleeding at the time of examination
2. Cancer cervix
3. Clinical evidence of acute pelvic infection
4. Pregnancy.

Methodology in Brief

Method

A total of 200 patients as per the inclusion and exclusion criteria attending the Gynecology Outpatient Department, BLDE (deemed to be university), Shri. B. M. Patil Medical College and Hospital were considered for the study and patients were subjected to visual inspection aided by acetic acid test (VIA) and PAP smear and colposcopy and colposcopy assisted biopsy if necessary after taking informed consent.

RESULTS

The study was performed on 200 women who attended the Department of Obstetrics and Gynaecology at Shri B. M. Patil Medical College and Research Hospital, Vijayapura. The objectives of the study were to correlate the findings in women using, PAP smear, VIA, colposcopy, and colposcopic directed biopsies wherever necessary, in detecting the premalignant lesions of the cervix and to find the efficacy of individual tests. The detailed analysis of the study conducted, and the results are computed together after all the tests were employed to arrive at a conclusion [Tables 1-9].

Association of the Type of Smears and VIA Findings

Patients who had VIA positive, among them, 7 patients had ASCUS, 1 patient had HSIL, 70 patients had inflammatory, 1 patient had invasive carcinoma, and 3 patients had LSIL.

Association of Colposcopic Findings and Pap Smear

Among the patients who had PAP smear positive, 92.3% showed positive colposcopic findings.

Association of the Type of Smears and Cervical Biopsy

On the persistence of unhealthy cervix and inflammatory smear even after a course of antibiotics direct cervical punch

Table 1: Association of the type of smears and VIA findings

VIA	Types of smears						P value
	ASCUS	HSIL	Inflammatory	Invasive carcinoma	LSIL	Normal	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Positive	7 (87.5)	1 (100.0)	70 (45.2)	1 (100.0)	3 (100.0)	0 (0.0)	<0.001*
Negative	1 (12.5)	0 (0.0)	85 (54.8)	0 (0.0)	0 (0.0)	32 (100.0)	
Total	8 (100.0)	1 (100.0)	155 (100.0)	1 (100.0)	3 (100.0)	32 (100.0)	

*Significant at 5% level of significance (p<0.05)

Table 2: Association of colposcopic findings and pap smear

Colposcopic findings	Pap smear		P value
	Positive	Negative	
	n (%)	n (%)	
Positive	12 (92.3)	2 (1.1)	<0.001*
Negative	1 (7.7)	185 (98.9)	
Total	13 (100.0)	187 (100.0)	

*Significant at 5% level of significance (P<0.05)

biopsy was taken. Most of patients with inflammatory smear who underwent cervical biopsy had cervicitis 28.3% and 1.8% showed CIN; this stresses the importance of further screening inflammatory smear patients. Most of patients with ASCUS smear who underwent cervical biopsy had mild dysplasia and LSIL had mild dysplasia in biopsy. HSIL and invasive carcinoma showed moderate dysplasia and CIN (severe) as their biopsy finding, respectively.

Association of the Type of Colposcopic and VIA Findings

A total of 82 cases out of 200 women were positive on VIA. 14 out of 200 women were positive on colposcopy. 14 cases of VIA positive cases were also the 14 colposcopy proven positive cases. 69 cases of VIA were false positive which were cases of inflammation/erosion/metaplasia. There was one false-negative case.

Association of Cervical Biopsy versus Pap Smear

Out of 15 biopsy positive cases, 12 were positive for PAP smear and 3 were negative.

Association of Cervical Biopsy versus VIA

Out of 15 biopsy positive cases, 14 cases were positive for VIA and only 1 case was negative.

Association of Cervical Biopsy versus Colposcopic Findings

Out of 15 biopsy positive cases, 14 were colposcopically positive and only 1 was negative.

DISCUSSION

This is a prospective study, in which 200 women of reproductive age group who attended the Gynaecology

Outpatient Department at Shri B. M. Patil Medical College and Hospital, Vijayapura, from October 2016 to August 2018 were studied to know the “comparison of visual inspection with acetic acid and Pap smear in detecting premalignant lesions of cervix” pattern of cervical cytology by Papanicolaou smear and its incidence and correlation with various parameters [Figures 1-6].

The results are discussed as follows.

Association of the Type of Smears and VIA Findings

Patients who had VIA positive, among them, 7 patients had ASCUS, 1 patient had HSIL, 70 patients had inflammatory, 1 patient had invasive carcinoma, and 3 patients had LSIL.

Association of Colposcopic Findings and Pap Smear

Among the patients who had Pap smear positive, 92.3% showed positive colposcopic findings.

Association of the Type of Smears and Cervical Biopsy

On persistence of unhealthy cervix and inflammatory smear even after a course of antibiotics direct cervical punch biopsy was taken. Most of the patients with inflammatory smear who underwent cervical biopsy had cervicitis 28.3% and 1.8% showed CIN; this stresses the importance of further screening inflammatory smear patients. Most of the patients with ASCUS smear who underwent cervical biopsy had mild dysplasia and LSIL had mild dysplasia in biopsy. HSIL and invasive carcinoma showed moderate dysplasia and CIN (severe) as their biopsy finding, respectively.

Association of the Type of Colposcopic and VIA Findings

A total of 82 cases out of 200 women were positive on VIA. 14 out of 200 women were positive on colposcopy. 14 cases of VIA positive cases were also the 14 colposcopy proven positive cases. 69 cases of VIA were false positive which were cases of inflammation/erosion/metaplasia. There was a one false-negative case.

Association of Cervical Biopsy versus Pap Smear

Out of 15 biopsy positive cases, 12 were positive for PAP smear and 3 were negative.

Table 3: Association of the type of smears and cervical biopsy

Cervical biopsy	Types of smears						P value
	ASCUS	HSIL	Inflammatory	Invasive carcinoma	LSIL	Normal	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Cervicitis	0 (0.0)	0 (0.0)	31 (31.3)	0 (0.0)	1 (33.3)	0 (0.0)	<0.001*
CIN	0 (0.0)	0 (0.0)	1 (1.0)	1 (100.0)	0 (0.0)	0 (0.0)	
Mild dysplasia	5 (62.5)	0 (0.0)	1 (1.0)	0 (0.0)	2 (66.7)	0 (0.0)	
Moderate dysplasia	3 (37.5)	1 (100.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Normal	0 (0.0)	0 (0.0)	65 (65.7)	0 (0.0)	0 (0.0)	1 (100.0)	
Total	8 (100.0)	1 (100.0)	99 (100.0)	1 (100.0)	3 (100.0)	1 (100.0)	

*Significant at 5% level of significance ($P < 0.05$)

Table 4: Association of types colposcopic findings and VIA findings

VIA	Colposcopic findings					P value
	Cervicitis	Dense acetowhite areas	Erosion	Hazy	Normal	
	n (%)	n (%)	n (%)	n (%)	n (%)	
Positive	56 (73.7)	6 (100.0)	6 (35.3)	7 (87.5)	7 (7.5)	<0.001*
Negative	20 (26.3)	0 (0.0)	11 (64.7)	1 (12.5)	86 (92.5)	
Total	76 (100.0)	6 (100.0)	17 (100.0)	8 (100.0)	93 (100.0)	

*Significant at 5% level of significance ($P < 0.05$)

Table 5: Association of colposcopic findings and VIA

Colposcopic findings	VIA		P value
	Positive	Negative	
	n (%)	n (%)	
Positive	13 (15.9)	1 (0.8)	<0.001*
Negative	69 (84.1)	117 (99.2)	
Total	82 (100.0)	118 (100.0)	

*Significant at 5% level of significance ($P < 0.05$)

Table 6: Cervical biopsy versus pap smear

Cervical biopsy	Pap smear		P value
	Positive	Negative	
	n (%)	n (%)	
Positive	12 (92.3)	3 (3.0)	0.029*
Negative	1 (7.7)	97 (97.0)	
Total	13 (100.0)	100 (100.0)	

*Significant at 5% level of significance ($P < 0.05$)

Table 7: Cervical biopsy versus VIA

Cervical biopsy	VIA		P value
	Positive	Negative	
	n (%)	n (%)	
Positive	14 (17.9)	1 (2.9)	<0.001*
Negative	64 (82.1)	34 (97.1)	
Total	78 (100.0)	35 (100.0)	

*Significant at 5% level of significance ($P < 0.05$)

Association of Cervical Biopsy versus VIA

Out of 15 biopsy positive cases, 14 cases were positive for VIA and only 1 case was negative.

Table 8: Cervical biopsy versus colposcopic findings

Cervical biopsy	Colposcopic findings		P value
	Positive	Negative	
	n (%)	n (%)	
Positive	14 (100.0)	1 (1.0)	<0.001*
Negative	0 (0.0)	98 (99.0)	
Total	14 (100.0)	99 (100.0)	

*Significant at 5% level of significance ($P < 0.05$)

Table 9: Comparison of diagnostic efficacy of biopsy, VIA, and pap smear compared to colposcopic findings

	Pap smear	VIA	Cervical biopsy
Sensitivity (%)	85.7	92.9	100.00
Specificity (%)	99.5	62.9	98.99
PPV (%)	92.3	15.9	93.33
NPV (%)	98.9	99.2	100.00
Accuracy (%)	98.5	65.0	99.12
TP	12	13	14
FN	2	1	0
FP	1	69	1
TN	185	117	98
False-negative rate (%)	14.3	7.1	0.0
False-positive rate (%)	0.5	37.1	1.1

TP: True positive, FN: False negative, FP: False positive, TN: True negative

Association of Cervical Biopsy versus Colposcopic Findings

Out of 15 biopsy positive cases, 14 were colposcopically positive and only 1 was negative. The sensitivity of VIA was 95%, specificity was 55%, and PPV was 61%.

The sensitivity of Pap smear was 43%, specificity was 97%, and PPV of Pap smear was 90%. The overall accuracy of



Figure 1: Abnormal colposcopic images

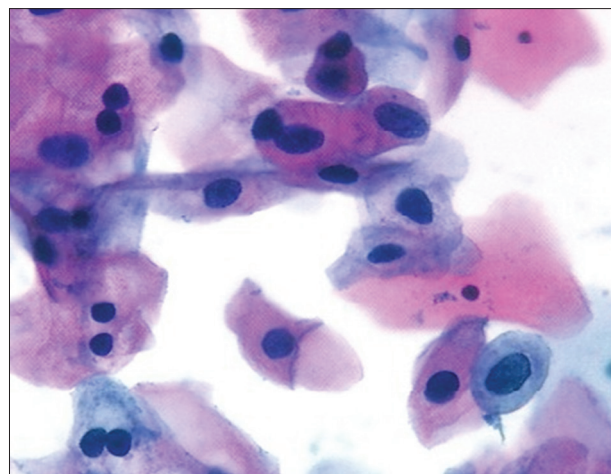


Figure 4: Pap smear showing LSIL

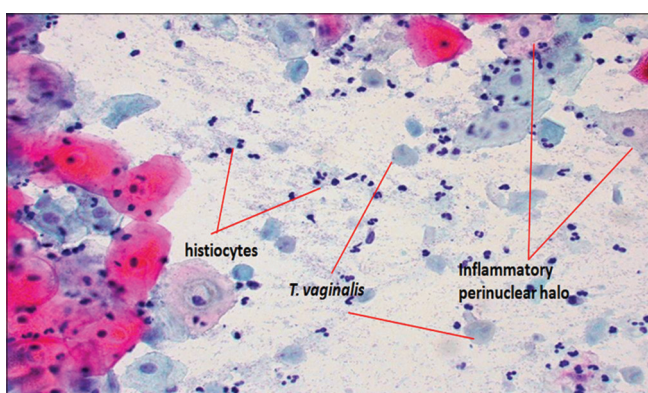


Figure 2: Pap smear showing inflammatory changes

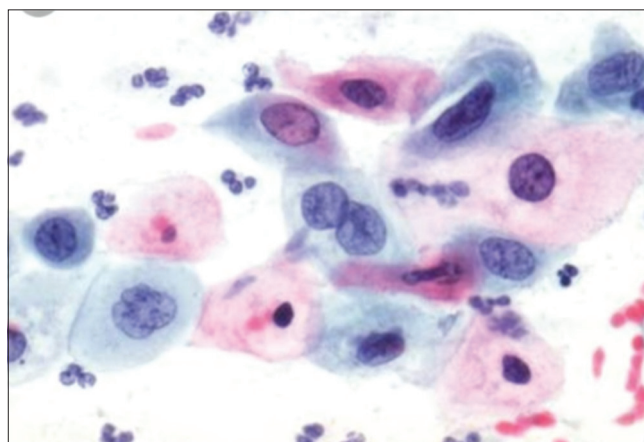


Figure 5: Pap smear showing HSIL

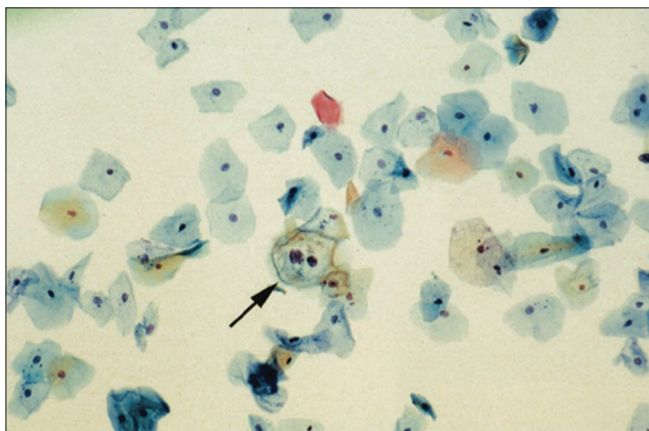


Figure 3: Pap smear showing ASCUS changes

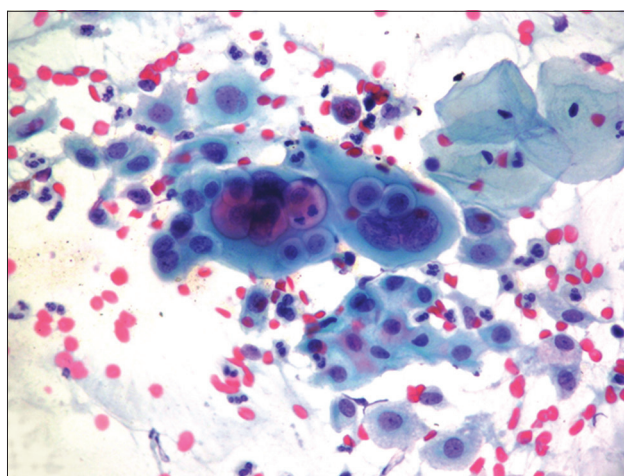


Figure 6: Pap smear showing squamous cell carcinoma

VIA was 72% and cervical cytology was 74%. Positive cases were subjected to biopsy and majority was reported as either normal or chronic cervicitis.^[7]

Most of the patients with inflammatory smear who underwent cervical biopsy had cervicitis 28.3% and 1.8% showed CIN; this stresses the importance of further screening inflammatory smear patients. Most of patients with ASCUS smear who underwent cervical

biopsy had mild dysplasia and LSIL had mild dysplasia in biopsy. HSIL and invasive carcinoma showed moderate dysplasia and CIN (severe) as their biopsy finding, respectively. Massad *et al.*^[8] found 77% of ASCUS cases to be nonmalignant.

In another study by Divya Hegde, out of 225 patients, VIA was positive in 27(12%) patients and Pap smear was abnormal in 26(11.7%). Pap smear had a sensitivity of 83%, specificity of 98%, PPV of 80%, and NPV of 97.9%. VIA had a sensitivity of 70.8%, specificity of 95%, PPV of 62.9%, and NPV of 96.5%.^[8]

The incidence of cervical cancer can be reduced by as much as 80% if the quality, coverage, and follow-up of screening methods are of high standard.^[9] Frequently repeated cytology screening programs have led to a large decline in cervical cancer incidence and mortality in developed countries.

Cytology-based screening programs have achieved very limited success in developing countries such as India due to lack of trained personnel, laboratory facilities, equipment's, high cost of services, and poor follow-up. It has become necessary to find out alternative screening procedure to cytology which has high sensitivity and specificity.^[10]

In a multicentric study by Sankaranarayanan *et al.* showed sensitivity of Pap smear ranging from 36.6% to 72.3% and specificity ranging from 87.2% to 98.6%.^[11] In a study conducted by Goel *et al.*,^[12] the sensitivity of Pap smear was found to be 50% and specificity was 97%.

Wahi *et al.* found 65.5% patients with dysplasia having cervical erosion. Purandare *et al.* found most dysplasia's in women with cervicitis and erosion. Padmanabhan *et al.*^[13] found 31.25% patients with SIL having erosion and Sunanda Rao *et al.* showed cervical erosion and infection accounted for 40–50% of abnormalities.

CONCLUSION

The VIA and Papanicolaou procedures are the most simple, safe, practical, and cost-effective method for early detection of cervical cancer and its precursors to prevent invasive cancer.

Although screening with colposcopy and biopsy tend to over-diagnose the immature squamous metaplasia with optimal magnification. The technique has a high false-positive rate, not cost effective, and therefore, offers little in a screening program.

The Papanicolaou procedure is considered as a screening test, not a diagnostic test; therefore, abnormalities of the smear should be confirmed histologically by biopsy. Screening with PAP smear should be done yearly or every 2 years to reduce the chance of missing an early lesion. As the progression from pre-invasive to invasive carcinoma is slow, more frequent screening appears the gold standard for screening programs.

In developing countries like India, cytology, a low cost and easily accessible test, is the most logical screening modality although it has a very low sensitivity but has got good specificity rate and detection rates could be further improved using liquid-based cytology and the use of endocervical cytobrush and later can be referred to a higher center for biopsy which has got high sensitivity and specificity.

Hence, efforts must be directed toward education of women regarding cervical cancer to promote awareness of malignancy and to motivate them for cytological screening in the future.

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A Comparative Study of Pulmonary Function Tests between Normal Male Sedentary and Tennis Players

B. Baby Sai Rani¹, Y. Indira²

¹Assistant Professor, Department of Physiology, Government Medical College, Anantapur, Andhra Pradesh, India, ²Associate Professor, Department of Physiology, Rajiv Gandhi Institute of Medical Sciences, Kadapa, Andhra Pradesh, India

Abstract

Background: In the assessment of the respiratory system, pulmonary function tests (PFTs) have achieved a lot of importance nowadays due to an increase in the cardiorespiratory disease and to a steep rise in air pollution. These functional tests and their parameters tend to have a relationship with lifestyle such as regular exercise and non-exercise. Hence, the present study was undertaken to assess the effects of exercise in tennis players on the respiratory system which are compared with normal healthy sedentary individuals.

Aim of the Study: The aim of this study was to determine and compare the differences between the pulmonary functions of healthy individuals playing regular tennis for 2 h daily and normal sedentary individuals.

The Objective of the Study: The study included 39 tennis players playing regular tennis for 2 h and 37 normal sedentary individuals who are not interested in any sports or games actively.

Materials and Methods: PFTs such as forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), VC, and maximum voluntary ventilation (MVV) of the study group were included in the study. The results were analyzed with standard spirometer. The arithmetic means and standard deviations of data have been obtained in the statistical evaluation. As a result of the findings obtained, independent sample *t*-test has been applied.

Observations and Results: No significant difference has been found among the age, height, body weight, body mass index, FEV1, and PEF values of the groups at the end of the test ($P > 0.05$); however, a significant difference has been found among MVV, FVC, and VC values.

Conclusions: Final analysis of the study showed that no difference is present between the FEV1 and PEF values of tennis players who have long-term and regular exercises and sedentary individuals. However, there is a significant difference among MVV, FVC, and VC values between the two groups. Therefore, it has been found that the pulmonary capacities (MVV, FVC, and VC) of individuals having regular exercises have higher values than that of sedentary individuals.

Key words: Athletes, Exercise, Maximum voluntary ventilation and vital capacity, Pulmonary function tests

INTRODUCTION

During exercise, it is evident that both respiratory and circulatory systems work in close interaction.^[1] For

healthy growth and maintenance of the body, regular and systematic physical exercises is important.^[2] The increased demand of oxygen by the working muscles has to be met by the respiratory system which should adapt to the said status to satisfy the required oxygen. However, this increased level is limited, and the limits of the enlargement capacity of breathing muscles and chest wall and elasticity levels of bronchi lead to changes in that particular status.^[3] The amount of oxygen used by the muscles is directly proportional to the amount of energy they generate.^[4] The oxygen and carbon dioxide values are maintained at an appropriate level without increasing the load on the

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Corresponding Author: Dr. Y. Indira, Department of Physiology, Rajiv Gandhi Institute of Medical Sciences, Kadapa - 516 002, Andhra Pradesh, India.

breathing muscles during the exercise.^[5] Heart rate increases to meet increasing oxygen demand,^[6] the energy used by the breathing muscles is decreased, and the signals that will increase the pulmonary functions tend to be minimized. Due to these chain events, the exhaustion that is bound to occur otherwise in the breathing muscles is decreased; however, exercise performance is increased.^[5] During the exercises, there would be increase in the consumption rate of O_2 in the metabolism, which is also called $MaxVO_2$, is experienced. It is indicated that said increase is above 10%. Therefore, it is important to increase the availability of oxygen, in other words, $MaxVO_2$, during the exercises.^[7] It is accepted that the exercise is effective extremely on the circulatory and respiratory systems. The pulmonary capacity and functions of an individual are related to his body structure as well as the oxygen need of the sport or exercise performed by him. The respiratory systems of the athletes who are trained adequately adapt to the increasing oxygen need during the exercise rapidly.^[8] Elite endurance athletes have parallel increases of left atrial pressure and right atrial pressure (Pra) at high levels of exercise, whereas less well-trained or sedentary subjects have smaller increases in Pra than pulmonary wedge pressure with exercise, which suggests that pericardial constraint is acting in the elite athletes at very high levels of exercise. Further confirmation of this theory is provided by studies with athletic animals, in which removal of the pericardium resulted in increased peak end-diastolic volume, stroke volume, and maximal oxygen uptake.^[6] The pulmonary volumes and capacities of the people differ (age, sex, body surface, exercise condition, athlete, and sedentary individuals). Therefore, it is better to evaluate the pulmonary functions of the athletes in accordance with maximum voluntary ventilation (MVV) results. Apart from MVV, the rate of FEV/forced vital capacity (FVC), which is below 80%, is accepted as a problem.^[9] The effects of physical activity on the pulmonary functions are tried to be classified as early age, adolescence, and adulthood stage. While making the classifications, the effects of the exercises performed in accordance with the branches, on the pulmonary functions, must be taken into consideration. Certain lifestyle parameters such as smoking, lack of habitual physical activity, low physical fitness, high dietary intake, and consumption of alcohol can alter the lung function.^[10] Smoking tends to have a deleterious effect on lung function. Alternately, having a physical fitness and good physical activity is said to have positive effect on lung function.^[11] The parameters of lung functions are considered as important indicators of health in clinical research.^[12] Pulmonary function test (PFT) is considered as one of the important tools for the assessment of respiratory function.^[13] PFTs determine the objective and quantifiable measures of the lung function. They are used to evaluate and diagnose diseases that affect

lung function and heart function, to determine the effects of environmental, occupational, and drug exposures.^[14] PFT aids in information about the small and large airways, the lung parenchyma, and the integrity, and size of the pulmonary capillaries.^[14] The objective of this study is to determine the differences between the pulmonary functions of the individuals who are regular long-term players of tennis and sedentary individuals in accordance with new literature data.

Type of the Study

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

Duration of the Study

The study duration was from December 2017 to July 2018.

Institute of the Study

The study was conducted at the Government Medical College and Hospital, Anantapur, Andhra Pradesh.

MATERIALS AND METHODS

A total of 40 subjects were included in these studies who were divided into two groups. Group A consisted of 20 tennis players and Group B consisted of normal healthy individuals. A long-term healthy tennis player was defined as one who is playing tennis for >10 years regularly and has not suffered from any acute cardiovascular or respiratory illnesses during this period, with at least 2 h of active power tennis game daily (minimum 14 h/week). Healthy sedentary controls were adult males who have not suffered from any acute cardiovascular or respiratory illnesses during 10 years' period and conditioned to not being connected with any particular sport activity and with no regular exercise program. Data concerning age and social habits such as smoking, alcohol, dietary intake, and type of work were observed and tabulated.

Inclusion Criteria

1. Adult males who are regular tennis players for >10 years were included.
2. Adult healthy sedentary males were included.
3. Males aged between 35 and 65 years were included.
4. Males who consented to participate in the study were included in the study.

Exclusion Criteria

1. Males who were suffering from any kind of pulmonary disease were excluded.
2. Males who have suffered from recent acute attacks of cardiorespiratory illnesses were excluded.
3. Males who have undergone any type of surgical procedures on the chest or abdomen were excluded from the study.

Table 1: The mean values of demographic data of the subjects (n=40)

Groups	Age	Height	Weight	BMI	Smoking (%)	Alcohol (%)	Working (%)
A - Tennis players - 20	48.5±3.75	5.7±0.4	73.50	28.40	10	67	82
B - Control group - 20	49.10±2.60	5.8±0.6	71.25	29.15	12	78	85

BMI: Body mass index

Table 2: The PFT parameters in the subjects (n=40)

Pulmonary function parameters	Groups	Mean and standard deviation	P value
FEC (L)	Group A	5.43±0.37	0.041
	Group B	5.10±0.76	
FEV1 (L)	Group A	4.35±0.28	0.376
	Group B	4.12±0.41	
PEF (L/s)	Group A	8.55±1.46	0.710
	Group B	8.51±2.10	
MVV (L/min)	Group A	116.54±38.24	0.023
	Group B	152.37±45.18	
VC (L)	Group A	5.79±1.11	0.034
	Group B	4.65±0.97	

FEC: Forced Expiratory Capacity, FEV1: Forced expiratory volume in 1 s, PEF: Peak expiratory flow, MVV: Maximum voluntary ventilation, VC: Vital capacity, PFT: Pulmonary function test

All tests were performed in laboratory settings with the same instruments and techniques.

Measurement

Standard spirometry was performed using the same instrument for all the subjects. Subjects underwent the test in a sitting position, wearing a nose clip. After a maximal inhalation, they sealed their lips around the mouthpiece and exhaled as hard and fast as possible. They were encouraged to continue exhaling for at least 6 s so that forced expiratory volume for 1 s (FEV1) and FVC could be measured. Tests were repeated 3–5 times until the two highest were recorded; FVC and FEV1 varied by <3%. Direct measurements included FVC (L), FEV1 (L), and PEF (L/s). The forced expiratory ratio (FEV1/FVC × 100) was also calculated (%). All of the above measurements were carried out under standard environmental conditions, by continuously measuring the temperature, humidity, and atmospheric pressure which enabled comfort temperature (between 18°C and 22°C), the atmospheric pressure of 760 mmHg, and a relative atmospheric humidity of 30–60%. Body mass (kg) and body height (m) were measured using standardized anthropometric techniques. Body mass index was calculated for all participants as the ratio of body mass (kg) divided by the body height (m) squared. An ethical approval was obtained from the institutional ethical committee. All the data were analyzed using standard statistical methods [Table 1].

OBSERVATIONS AND RESULTS

When the findings of the study have been evaluated, no significant difference was found between FEV1 and PEF values ($P > 0.05$); however, a significant difference was

found among MVV, FVC, and VC values ($P < 0.05$ which was taken as statistically significant) [Table 2].

DISCUSSION

The principle function of the respiratory system is to maintain the blood gas levels within fixed limits and to provide gas exchange between blood and air.^[9] In the present study, no significant difference has been found between FEV1 and PEF values ($P > 0.05$); however, a significant difference was found among MVV, FVC, and VC values ($P < 0.05$). The study results showed that the FVC, FEV1, and MVV ratios were higher in tennis players than in the normal sedentary control individuals, similar to the studies conducted by other authors.^[15–18] FVC and MVV findings of these authors support the present study and could be considered as an important correlation. Similar observations were made by Prakash *et al.*^[16] with reference to FVC. A study by Stuart and Collings^[19] also reported higher mean FVC scores in athletes as compared to non-athletes. In relation to the FEV1 values in this study, there was no statistical significant difference, but few authors showed, When Sedentary and Athlete groups were compared; they showed higher FEV1 in Athletes when compared to sedentary individuals,^[16,20] while Khanam *et al.*^[21] did not observe any significant change in FEV1 similar to the present study. Due to an increase in pulse volume, a less cardiac pulse is required. The increase in pulse volume helps O₂, which is required during maximal exercises, to be transferred to the muscles. In the meantime, the increase in pulmonary volume and capacity increases the passing movement of O₂ from the lungs to the blood.^[22] Such an increase may arise from the positive effect of exercise on dynamic pulmonary capacity together with strengthening in the breathing muscles. It is indicated that exercises cause increase in pulmonary functions,^[23] while aerobic exercises lead to a higher level of increase in FVC values when compared to anaerobic exercises.^[24]

CONCLUSIONS

Final analysis of the study showed that no difference is present between the FEV1 and PEF values of tennis players who have long-term and regular exercises and sedentary individuals. However, there is a significant difference among MVV, FVC, and VC value between

the two groups. Therefore, it has been found that the pulmonary capacities (MVV, FVC, and VC) of individuals having regular exercises have higher values than that of sedentary individuals.

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Microbiological Efficacy of Meropenem–ethylenediaminetetraacetic Acid Combination as Compared to Meropenem in a Tertiary Care Intensive Care Unit

Charu Dutt Arora¹, Ajay Yadav², Mehak Batra³, Maggie Ann Johnson⁴

¹Clinical Associate, Department of Critical Care, W. Pratiksha Hospital, Gurgaon, Haryana, India, ²Head, Department of Anesthesia, W. Pratiksha Hospital, Gurgaon, Haryana, India, ³Research Volunteer, Department of Critical Care, W. Pratiksha Hospital, Gurgaon, Haryana, India, ⁴Student RN, Department of Nursing Education, University of North Carolina, Charlotte, USA

Abstract

Background: With the global epidemic of sepsis on the rising trend and gram negative sepsis being one of the most common cause of increasing morbidity and mortality in developing nations like India, it becomes imperative to understand the role of combination antibiotics in controlling this burden. **Aim and Methodology:** In this study, we recognized the potential therapeutic role of Meropenem combined with EDTA against a clinical endemic isolate of multi-drug resistant extended spectrum beta-lactamases (ESBLs) producing pathogens was investigated. The E-test strips studied the antimicrobial susceptibility of the pathogens and were applied to check for in-vitro sensitivity to Meropenem and combination of Meropenem and Ca-EDTA. **Result:** The MIC value of Meropenem-EDTA (0.25) was less than 50% of that of Meropenem (2.45) in sensitive isolates. **Conclusion:** Meropenem in unification with EDTA can exhibit more potent antimicrobial activity against ESBL producing pathogens than just Meropenem or EDTA alone.

Key words: Antimicrobial resistance, Combination therapy, Gram-negative pathogens, *In vitro* study, Sepsis, Synergy

INTRODUCTION

Sepsis is a serious infection and remains a common cause of mortality and morbidity in developing, scantily-resourced countries such as India. It occurs in 2% of all hospitalizations in developed countries with 6–30% of those affected belonging to intensive care unit (ICU patients) and places a huge burden physically and financially worldwide.^[1] The global estimates approximate around 25000 USD and 50000 USD. With over 8.7% increase in sepsis patients per year in the US, the problem is now a global epidemic.

In developing countries such as India, which holds one of the highest disease burdens in the world, reflective studies claim that 12% of adults (1–51%) of those diagnosed with acute febrile illness will have bacteremia. The most affected being the younger individuals and the liable organisms likely to be Gram-negative and atypical pathogens.^[1,2]

Delays in providing effective antimicrobial therapy, in cases of severing septic shock, increase the risk of dying by approximately 10% for every hour of delay - making it crucial to initiate antimicrobial therapy at an appropriate time depending on the location of the patient and the suitability of the antimicrobial treatment. This criticality poses a significant challenge as antimicrobial resistance (AMR) is on the rise and poses a significant threat toward achieving favorable outcomes.^[1]

AMR and Emergence of Extended-spectrum Beta-lactamases (ESBLs)

Many studies have suggested that almost 2 million cases of infection with resistant bacteria are reported in the

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Corresponding Author: Dr. Charu Dutt Arora, Department of Critical Care Medicine, W. Pratiksha Hospital, Gurgaon, Haryana, India.
E-mail: charu.dutt@w-hospital.in

US every year leading to \$20 billion incremental direct health-care costs. Recently, the European Medicine Agency and European Centre for Disease Prevention and Control reported a toll of 25,000 deaths per year as a direct consequence of a multidrug-resistant infection with total costs of EUR 1.5 billion.^[3,4]

The studies by the Indian Network for Surveillance of AMR group reported a prevalence of 41% with methicillin-resistant *Staphylococcus aureus* (MRSA). High prevalence of Gram-negative bacterial resistance has also been reported and India is being one of the largest consumers of antibiotics; the effectiveness of several antibiotics is threatened by the emergence of resistant microbial pathogens.^[4]

The path to antibiotic development is challenged at every step by the emerging AMR. The emergence of MRSA-resistant *Pseudomonas aeruginosa* has already compromised the most effective treatments. Urgent threats with *Clostridium difficile*, Carbapenem-resistant *Enterobacteriaceae*, and drug-resistant *Neisseria gonorrhoeae* have also been reported by the U.S. CDC.^[4]

A disquieting example is the spread of New Delhi metallo-beta-lactamase 1, a transmissible genetic element encoding resistance genes against most known beta-lactam antibiotics, from its emergence in New Delhi, India, in 2008.^[3]

β -lactamase production by several Gram-negative and Gram-positive organisms is possibly one of the most significant single mechanisms of resistance to penicillins and cephalosporins. It was earlier believed that cephalosporin was immune to attack by β -lactamases, but it was surprising to find that cephalosporin-resistant *Klebsiella* spp., as among the clinical isolates - the mechanism of this resistance was the production of ESBLs.^[5,6]

ESBLs are plasmid mediated, which have the ability to hydrolyze β -lactam antibiotics. ESBL-producing organisms exhibit coresistance to many classes of antibiotics, resulting in the limitation of therapeutic options.^[5]

Minimum Inhibitory Concentration (MIC) and Combination Antibiotics to Fight AMR

The MIC is the lowest concentration ($\mu\text{g/mL}$) of an antibiotic that inhibits the growth of a given strain of bacteria.^[7] A quantitative method of susceptibility testing and MIC helps determine which class of antibiotic is most effective. This information can lead to an appropriate choice of an antibiotic that will increase the chances of treatment success and help in the fight to slow antibiotic resistance.^[8]

Infections caused by ESBL-producing pathogens are problematic because, when coresistance to other antimicrobial class is present, limited antibiotic options

are available. At present, imipenem or meropenem is considered as a drug of choice for infections caused by ESBL-producing pathogens. However, the selective pressure from increasing use of carbapenems will lead to the development of carbapenem-resistant microbes.^[9]

The objectives of this study were to understand the outcomes of patient with various agents in the treatment of ESBL-producing bacteremia and to evaluate the efficacy of meropenem and ethylenediaminetetraacetic acid (EDTA) combination against ESBLs.

MEROPENEM-EDTA IN FIGHTING ESBL PRODUCTION

Materials and Methods

Hospital Setting

This observational and prospective study was conducted for a period of 3 months, from February 15, 2018, to May 15, 2018. 94 patients in the ICU of W. Pratiksha Hospital, Gurgaon, India, were listed to be a part of the inquiry aging from 18 to 80 years.

Medical and surgical patients in the ICU were included in the study, and for the purposes of this study, patients who were immunocompromised, pregnant, HIV positive, and bone marrow transplantation were excluded from the study.

Study Design

Two groups of patients were created:

1. Who were admitted for the 1st time in the past 1 year ($n = 56$) and
2. Who have been admitted before, in the past 1 year ($n = 34$).

During these 3 months, blood, urine, and sputum (including endotracheal and tracheostomy tube) samples were collected and sent to microbiology laboratory for routine and culture-sensitivity pattern [Figure 1].

Microbiological Efficacy of Meropenem-EDTA Combination

Blood cultures were tested positive for 15 patients, the most common being *Escherichia coli* ($n = 7$) followed by *Klebsiella pneumoniae* ($n = 5$), followed by *P. aeruginosa* ($n = 3$), *Candida albicans* ($n = 2$), *Acinetobacter baumannii* ($n = 1$), and *Ralstonia pickettii* ($n = 1$) [Figure 2].

Urine cultures were tested positive for 27 patients, the most common being *K. pneumoniae* ($n = 12$), followed by *E. coli* ($n = 9$), and *C. albicans* ($n = 6$) [Figure 3].

Sputum cultures were tested positive for 15 patients, the most common being *E. coli* ($n = 9$), followed by *P.*

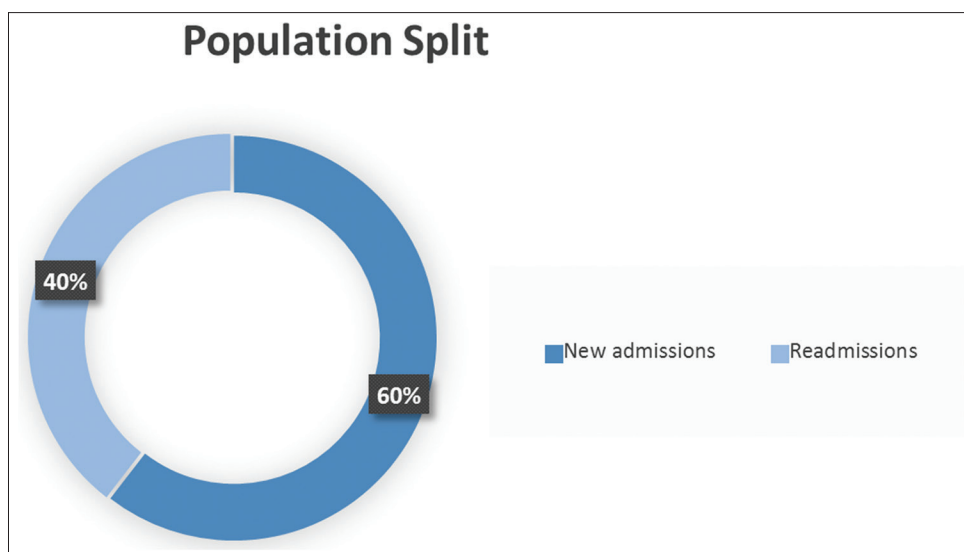


Figure 1: Percentage of population as new and re-admissions in the ICU

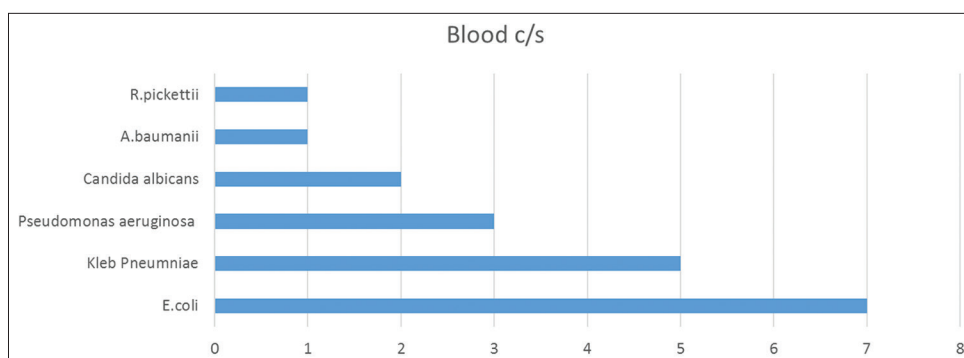


Figure 2: Common organisms which tested positive in the blood cultures of the patients

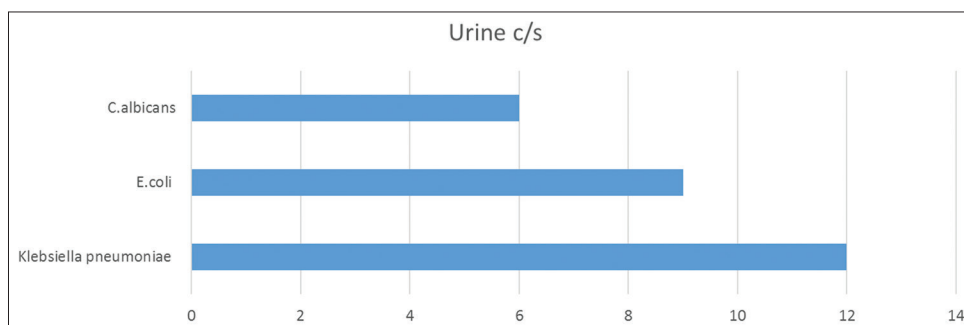


Figure 3: Common organisms which tested positive in the urine cultures of the patients

aeruginosa ($n = 2$), *S. aureus* ($n = 2$), and *Candida tropicalis* ($n = 2$) [Figure 4].

MIC Values for Meropenem–EDTA Combinations

Cultures showed 51 isolates in total, which were ESBL-producing bacteria. Further, E-strips were applied to check for *in vitro* sensitivity to meropenem and combination of meropenem and Ca-EDTA, of which, 14

were meropenem-resistant isolates and showed sensitivity to meropenem–EDTA [Figure 5].

The MIC value of combination for meropenem–EDTA was reported to be 50% less than that of meropenem in sensitive isolates ($n = 29$) and intermediate sensitive ($n = 8$) isolates, $P < 0.005$. The mean MIC value of meropenem in such patients ($n = 37$) was 2.45 MIC and that of combination was 0.25 [Figure 6].

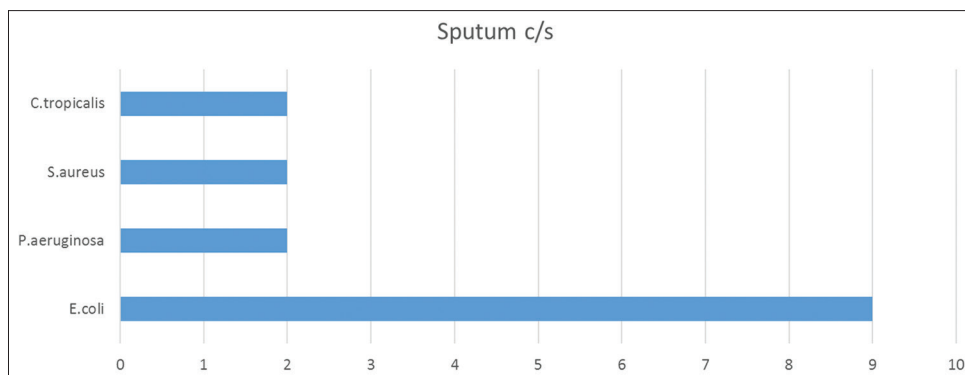


Figure 4: Common organisms which tested positive in the sputum culture of the patients

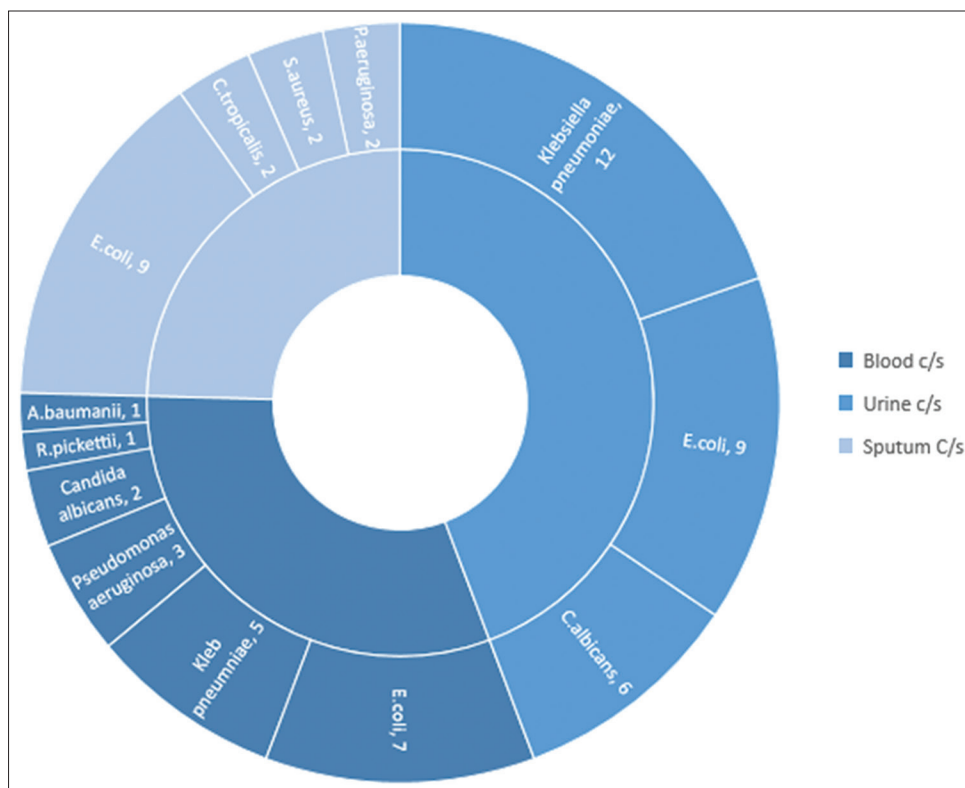


Figure 5: Most common pathogenic organisms isolated from the admitted patients

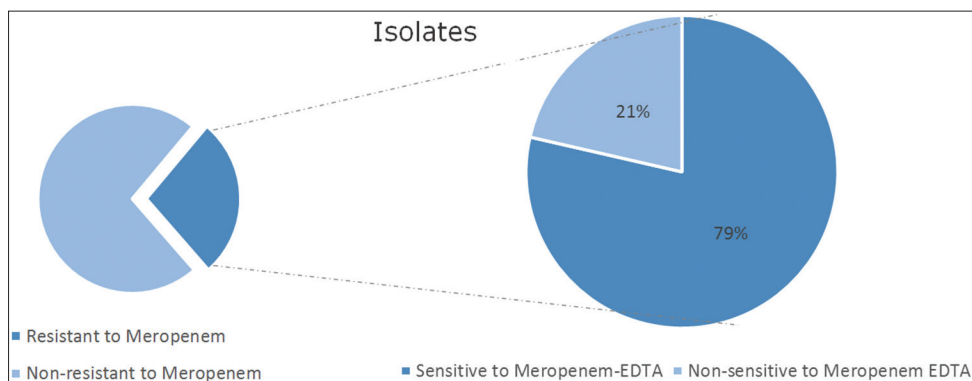


Figure 6: Division of pathogens sensitive to Meropenem and Meropenem-EDTA combination

DISCUSSION

ESBLs are well known for their resistance to many commonly used antimicrobial agents and pose a major problem for clinical therapeutics. Initially restricted to hospital-acquired infections, they have also been isolated from infections in outpatients. Major outbreaks involving ESBL strains have been reported from all over the world, thus making them emerging pathogens.^[11,12,13]

Of all the available beta-lactams, carbapenems are the most effective and reliable as they are highly resistant to the hydrolytic activity of all ESBL enzymes, due to the trans-6 hydroxyethyl group.^[14,15]

In the retrospective study, the combination of meropenem and EDTA resulted in a sustained synergistic bactericidal effect lasting for at least 12 h. However, we found that the meropenem–EDTA combination regimen significantly improved the survival rate of those infected with ESBLs, compared with those treated with either drug alone. Meropenem plus EDTA was effective against our multiresistant isolate of ESBLs. Given the limitations of small size and being a retrospective study, our report may lack the power to discriminate real difference in the outcome. Further study is warranted to establish the therapeutic roles of meropenem and EDTA combination in the treatment of infections caused by ESBL-producing pathogens.

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A Prospective Study of the Hearing Loss in Global Developmental Delay Children

Meena Maruti Ohal¹, Mary John²

¹Pediatric ENT Fellow, Senior Resident, Department of ENT, Christian Medical College General Hospital, Vellore, Tamil Nadu, India,

²Professor, Department of ENT, Unit-2, Christian Medical College, Vellore, Tamil Nadu, India

Abstract

Background: Developmental disabilities are a group of related chronic disorders of early onset estimated to affect 5–10% of children. Global developmental delay is a subset of developmental disabilities defined as a significant delay in two or more of the following developmental domains: Gross/fine motor, speech/language, cognition, social/personal, and activities of daily living.

Aim of the Study: The aim of this study was to describe the clinical profile and audiological profile in children with global developmental delay presenting to the pediatric ENT unit.

Materials and Methods: The study sample size was a total of 121 children with global developmental delay. Children with complaints of global developmental delay underwent a detailed ENT examination including examination under microscope of ear which is the standard of care. Hearing loss was assessed by audiological tests such as behavioral observation audiometry (BOA), otoacoustic emission, brain stem evoked response audiometry (BERA), and tympanometry (Tymps). The degree of hearing loss was classified using the American Speech-Language-Hearing Association classification.

Observations and Results: Among 121 children with global developmental delay, there were 72 (59.5%) males. The mean age of the study group was 3.2 years. The youngest child in the study was 6 months old and the oldest child being 14 years old. 25 (20.6%) children participating in the study had syndromic association. Of 121 children, only 36 (29%) presented with speech delay and suspected hearing loss. BOA done in 242 ears showed 56 (23%) ears with normal hearing, 68 (28%) with hearing loss, and inconsistent report in 38 (15.5%) ears. In the 80 remaining ears (33%), test could not be done.

Conclusions: The mean age of referral was 3.2 years in global developmental delay children who were referred for the evaluation of speech delay. Among the 121 global developmental delay children included in the study, 36 (29%) had hearing loss with speech delay. Our study detected a higher incidence of undetected hearing loss of 144 ears (59.5%) in children with global developmental delay.

Key words: Behavioral observation audiometry, Brain stem evoked response audiometry, Global developmental delay, Hearing loss, Tympanometry

INTRODUCTION

Developmental disabilities are a group of related chronic disorders of early onset estimated to affect 5–10% of children.^[1-3] Global developmental delay is a subset of developmental disabilities defined as significant delay in

two or more of the following developmental domains: Gross/fine motor, speech/language, cognition, social/personal, and activities of daily living.^[4-6] Children with global developmental delay require complex, individualized therapy to maximize their long-term quality of life. One subset of children with special needs includes those with both developmental delays and deafness. One of the major causes of global developmental delay is cerebral palsy (CP). CP was first described in 1862 by an orthopedic surgeon named William James Little.^[7] CP is a condition caused by damage to the brain, usually occurring before, during, or shortly after birth. “Cerebral” refers to the brain and “palsy” refers to a disorder of movement or posture. CP is a central nervous system (CNS) disorder of movement,

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Corresponding Author: Dr. Meena Maruti Ohal, Pediatric ENT Fellow, Department of ENT, Christian Medical College General Hospital, Vellore, Tamil Nadu, India. E-mail: feb15lov@yahoo.com

coordination, and posture, reflecting a non-progressive abnormality or insult to the immature brain.^[8,9] CP is neither progressive nor communicable. It is also not curable, although education, therapy, and applied technology can help people with CP to lead productive lives. Children with CP have an organic complication in the peripheral and CNS.^[10] Therefore, CP is often accompanied by other disorders and problems of cerebral function, in particular speech and language impairment, intellectual impairment, disorders of vision and hearing, attention, vigilance, and behavior.^[11,12] Consequently, the majority of the affected individuals cannot participate and find their place in normal society.^[13-15] Advances in the treatment of prenatal infections and improved medical facilities for neonatal care have resulted in more surviving infants but with complications that may include hearing impairment. In particular, reduced mortality rates of premature babies with very low birth weight are responsible for more infants with complications including hearing impairment. Hearing impairment estimates as high as one-third population of CP; a study done by Susan *et al.* shows 4–13% hearing loss in children with CP.^[16,17] Hearing impairment is the most common in children with very low birth weight or severe hypoxic-ischemic insults.^[18-20] The existence of hearing problems with unique motor problem in CP presents a range of special educational and psychological needs, to an even greater degree than for children with single disability. Untreated reduced hearing acuity during infancy and early childhood compounded with additional disability may have a more deleterious effect on communication abilities, speech and language, and cognitive development that can severely interfere with their parent-child and peer-child interactions, low self-esteem, and linguistic, auditory perceptual, and educational development.^[21,22] However, the effects of hearing impairment are amenable to the treatment and rehabilitation strategies if identified at an early age and effective intervention program is initiated. Thus, overall future and success of a child can be improved by reducing the complications of hidden disability of hearing impairment.^[23-25] However, there are no data available in the Indian context, with regard to the degree and type of hearing impairment in children with global developmental delay. Hence, we propose to study the presence of hearing impairment in children with global developmental delay. The aim is to increase the awareness of possible correctable audiological impairment that hinders development and learning in children with global developmental delay children.

Aim of the Study

The aim of this study was to describe the clinical profile and audiological profile in children with global developmental delay presenting to pediatric ENT unit and to determine the type and severity of hearing impairment in children with global developmental delay.

MATERIALS AND METHODS

This prospective study was done on children with global developmental delay who presented to the ENT 2 outpatient care (OPD) between October 2017 and April 2018. Patients were selected as per the inclusion and exclusion criteria. The study was explained to every patient in detail and they were included in the study after obtaining informed written consent. The sample size was calculated from the statistical input taken from the reference article by Susan *et al.* in 2011. Taking $P = 81.8\%$ and precision as 6, the sample size was calculated using Master software version 2.0. The study sample size was a total of 121 children with global developmental delay.

$$n = \frac{Z_{1-\alpha}^2 p(1-p)}{d^2}$$

Where,

- p : Expected proportion
- d : Absolute precision
- $1-\alpha/2$: Desired confidence level.

Inclusion Criteria

(1) All children with global developmental delay from 6 months to 16 years attending ENT-2 OPD and (2) parent giving consent to be part of the study were included in the study.

Exclusion criteria

(1) Children less than 6 months of age and (2) parents not giving consent to be part of the study were excluded from the study.

Clinical evaluation

Children presenting to ENT 2 OPD with the complaints of global developmental delay underwent a detailed ENT examination including examination under microscope of ear which is the standard of care. Hearing loss was assessed by audiological tests which included behavioral observation audiometry (BOA), otoacoustic emission (OAE), brain stem evoked response audiometry (BERA), and tympanometry (tymps). BERA was done using intelligent hearing screening machine to assess hearing loss. In BERA, click stimulus of 60–90 dB above hearing threshold in the frequency of 2–4 KHz and tone burst both are used. The stimulus rate used was 30.1 clicks/s. Active electrode (red) was placed over the forehead, reference electrode (black) was placed over ipsilateral mastoid or ear lobe, and ground electrode was placed over contralateral mastoid. Tympanometry was done in all children to use Grason Stadler 61 tympanometer. The degree of hearing loss was classified using the American Speech-Language-Hearing Association (ASHA) classification [Table 1].

The numbers are representative of the patient's hearing loss range in decibels (dB HL).

Outcomes measured were as follows: (1) Otomicroscopy findings of tympanic membrane, (2) the degree of hearing loss in global developmental delay children using the ASHA classification, (3) OAE–distortion product OAE, and (4) type of curve in tympanogram curve.

- Type A - Normal curve having a single peak of admittance between 150 and 100 daPa and a volume of 0.2–1.8 mL.
- Type B or flat curve - Flat curve with no admittance peak.
- Type C - Admittance peak shifted to negative pressures.

All the patients were assessed, and findings were noted down.

Appropriate statistical tests were used to analyze the data. For categorical data, the number of patients and percentage were presented. Chi-square or Fisher's exact test was applied to the data. All tests were two-sided at $\alpha = 0.05$ level of significance. All analyses will be done using Statistical Package for the Social Services software Version 21.0 (Armonk, NY: IBM Corp).

OBSERVATIONS AND RESULTS

A total of 121 children meeting the inclusion criteria were recruited in the study after parental consent. All the

children underwent detailed ENT examination including examination under microscope of ear and audiological assessment.

Gender and Age Distribution

Majority of the participants was male, 72 (59.5%) [Figure 1].

The mean age of the study group was 3.2 years. The youngest child in the study was 6 months old and the oldest child being 14 years old. Nearly three-fourth (76%) of the participants were under the age of 5 years [Figure 2].

Syndromic and Autism Spectrum Disorder Association

About 25 (20.6%) children participating in the study had syndromic association [Figure 3].

Of 25 syndromic children, two children had congenital rubella syndrome, 12 children had Down's syndrome, three children with mucopolysaccharidosis-associated syndromes, two children with West syndrome, one child each with fragile syndrome, opercular syndrome, Cornelia de Lange syndrome, orofacial digital syndrome, opercular syndrome, oculo-auriculo-vertebral spectrum syndrome, and Schinzel syndrome, and 10 children (8.2%) had autistic features [Figure 4].

CP: More than half of the children in the study had CP (55.6%). Of the 67 children with CP, 14 (20%) had hypotonic CP, 33 (49.25) had spastic CP, 13 (19.4%) had dystonic CP, and 7 (10%) had mixed variety [Figure 5].

Table 1: The ASHA classification

Degree of hearing loss	Hearing loss range (dB HL)
Normal	–10–15
Minimal	16–25
Mild	26–40
Moderate	41–55
Moderately severe	56–70
Severe	71–90
Profound	91+

ASHA: American Speech-Language-Hearing Association

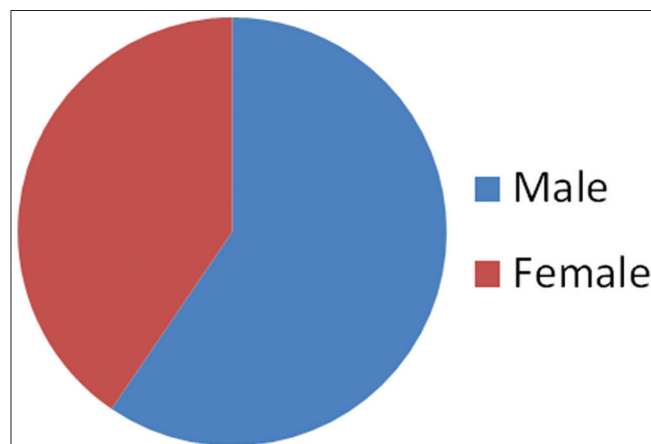


Figure 1: Gender distribution

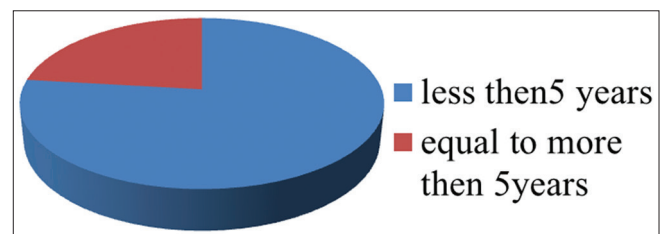


Figure 2: Age distribution

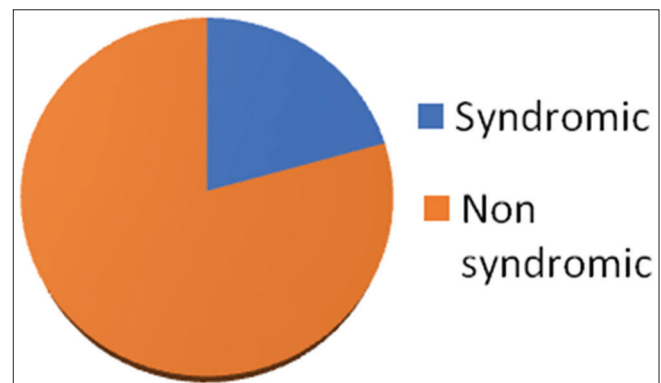


Figure 3: Syndromic and non-syndromic distribution

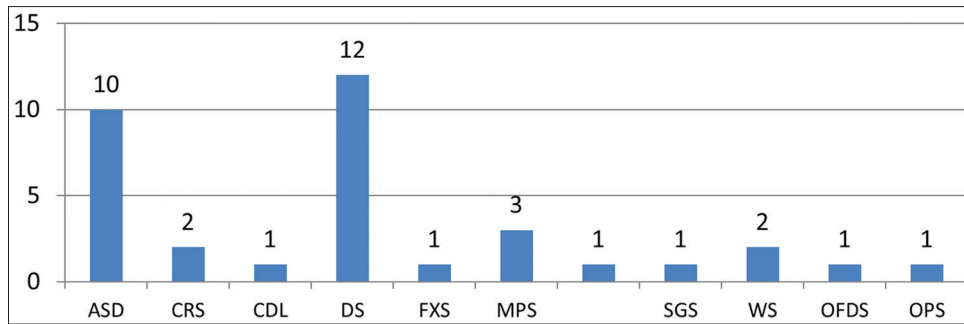


Figure 4: Various syndrome and autism spectrum disorder distribution

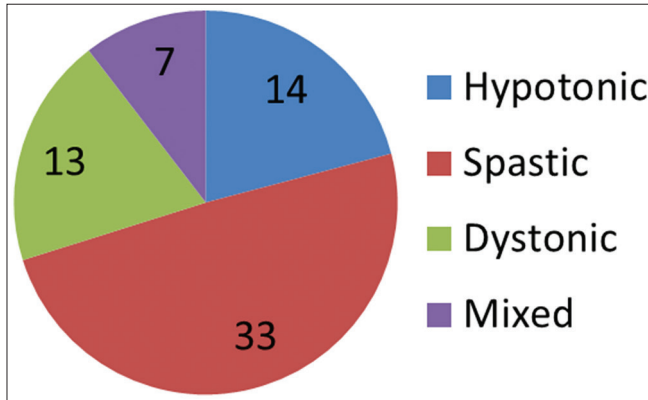


Figure 5: Types of cerebral palsy

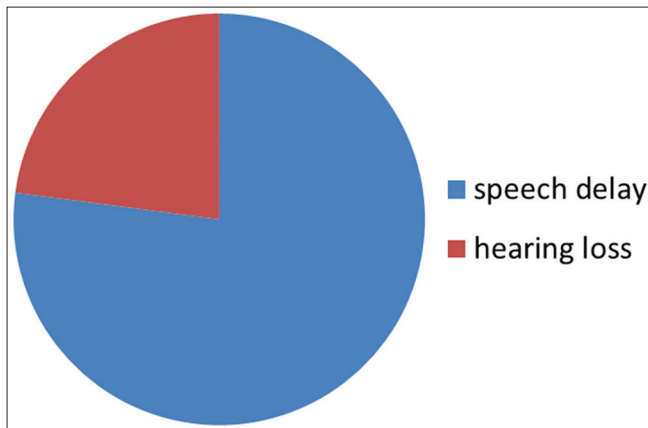


Figure 6: Presenting complaints

Presenting Complaint

Of 121 global developmental delay children all presented with speech delay, only 36 (29%) presented with suspected hearing loss with speech delay [Figure 6].

Otomicroscopy findings

In this study, a total of 242 ears were examined. Otomicroscopy revealed an intact and normal tympanic membrane in majority of the subjects, 233 (96.2%), 7 (2.8%) had a dull tympanic membrane, and one (0.4%) ear had otitis media with effusion. One child in the study had unilateral grade 3 microtia [Figure 7].

Hearing Assessment

(1) BOA: Of 242 ears assessed with BOA, 56 (23%) ears had normal hearing, 68 (28%) had hearing loss, and 38 (15.5%) ears had inconsistent report. In the eighty remaining ears (33%), test could not be done as the children were either uncooperative for the test or an auditory brain evoked response audiometry was done instead [Figure 8].

Of 68 ears examined for hearing loss, the severity was found to be profound in (29%), severe in (27%) and mild in (22%) [Figure 9].

OAE

Of 242 ears evaluated, OAE were absent in 109 (45%) ears and present in 56 (23%) ears [Figure 10].

BERA

Of 242 ears examined for BERA, 78 (32.2%) had normal hearing, 20 (8.2%) had minimal loss, 23 (9.5%) had mild hearing loss, 26 (10.7%) ears had moderate hearing loss, 3 (1.2%) ears had moderately severe hearing loss, 20 (8.2%) ears had severe hearing loss, 52 (21.1%) ears had profound, and BERA was not done in 20 (8.2%) ears [Figure 11].

Tympanometry

Of 242 ears, 145 (59.9%) ears had A type curve, 27 (11.1%) ears had B type curve, and 37 (15.2%) ears have C type curve [Figure 12].

Hearing status of children with CP

Of 67 children with CP with global developmental delay, hearing assessment by BERA was done in 126 ears. Of 134 ears, 46 (34.3%) ears had normal hearing, 12 (8.9%) ears with mild hearing loss, 15 (11.4%) ears with moderate hearing loss, 7 (5.2%) ears with severe hearing loss, and 34 (25.3%) ears with profound hearing loss. BERA was not done in 8 (5.9%) ears, as their hearing was already assessed by previous methods and further evaluation by BERA was not indicated [Figure 13].

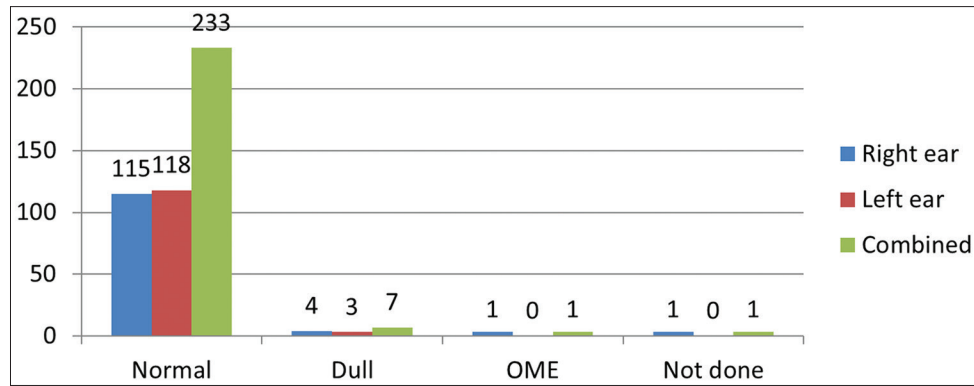


Figure 7: Otomicroscopy finding

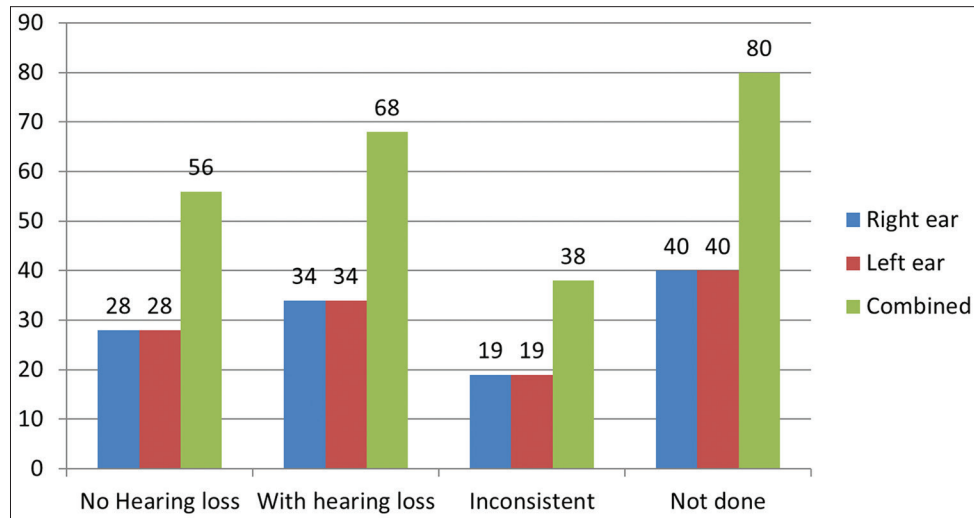


Figure 8: Behavioral observation audiometry hearing level distribution

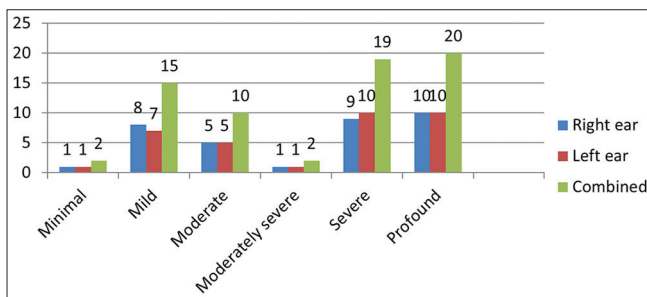


Figure 9: Degree of hearing loss distribution

DISCUSSION

The cross-sectional observational study was done in tertiary care center from October 2017 to April 2018 to find the clinical and audiological profile of children with global developmental delay attending to otorhinolaryngology OPD after obtaining informed consent. Children were recruited in this study according to the inclusion and exclusion criteria of the study. Various studies have attempted to understand the association between CP, delayed development, and hearing loss; mainly, the data

come from developed countries.^[16] Among those studies, a majority of the studies are retrospective studies. Moreover, the focus seems to be on CP a subset of global developmental delay but is limited with lack of detailed information regarding the audiological status of the children and the objective way of assessing hearing. The paucity of studies on hearing assessment in global developmental delay children probably reflects that the concept of audiological profile of children with global developmental delay has not yet been understood well. Our study addressed the hearing in children diagnosed with global developmental delay. Our aim was to determine the pattern and frequency of hearing loss in a cohort of children with confirmed diagnosis of global developmental delay. Children with global developmental delay require complex, individualized therapy to maximize their long-term quality of life. If hearing loss is undetected early in developmental stage, it affects the speech and language and adds on to delay. Moreover, speech delay sometimes is considered as part of developmental delay, ignoring the need for hearing assessment and rehabilitation. Children with global developmental delay usually report to

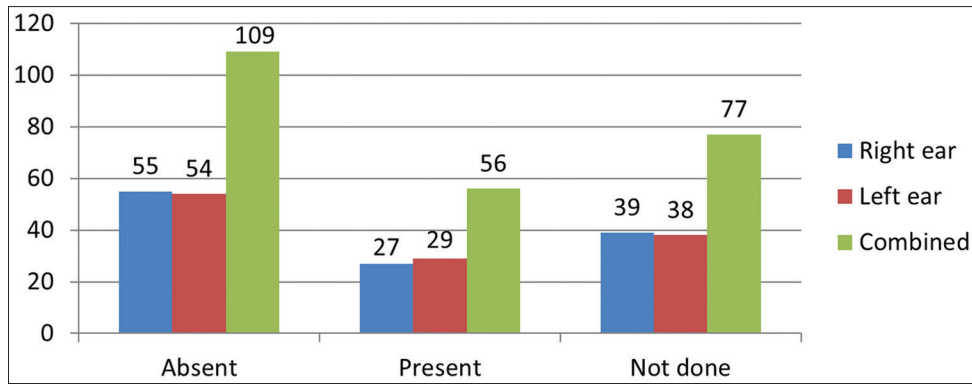


Figure 10: Otoacoustic emission

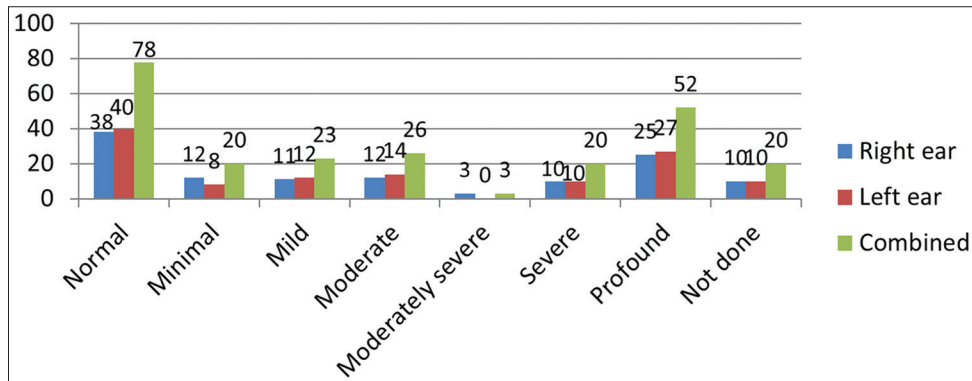


Figure 11: Brain stem evoked response audiometry degree of hearing loss

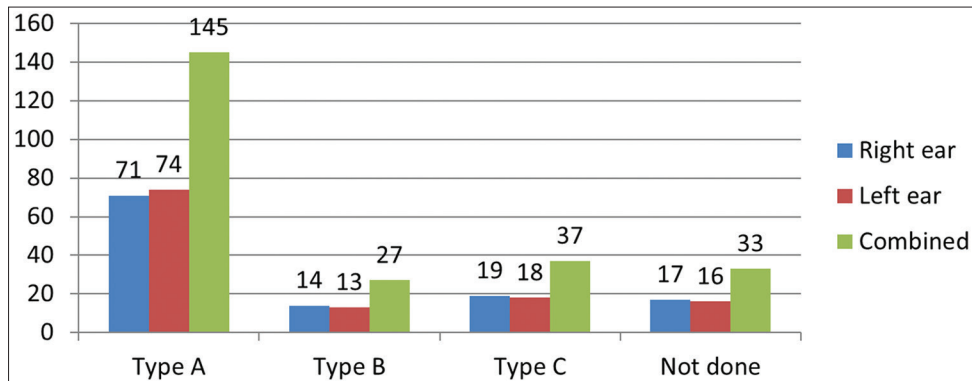


Figure 12: Tympanometry type distribution

developmental pediatrics outpatient clinic for intervention of delay in achieving developmental milestones, either in the motor domain or with problems in feeding. Speech delay is a common problem in these children which is often attributed to the intellectual delay and other oromotor problems. Hearing loss being a potential cause for speech delay is often overlooked in these groups of children as the parents misread the responses of the child to think that he has good hearing. When a general pediatrician consult is sort for speech delay, hearing tests are rarely suggested. Tests with very low sensitivity such as clap test are done by the general pediatrician who can rarely tell if the child is hearing or is the response due to visual or tactile stimuli.

Hence, it is very essential to educate the pediatrician looking after the child that hearing assessment is a vital tool in the diagnostic armament of evaluating the child, especially, with the suspected delay in development. For the young child, the term global developmental delay has emerged to describe a disturbance across a variety of developmental domains and such a child has limitations or delay in the acquisition of developmental and functional skills that are both observable and measurable within the context of the natural progression of infants and young children. The latest consensus definition used by the American Academy of Neurology practice parameter statement defines global developmental delay operationally, as a significant delay in

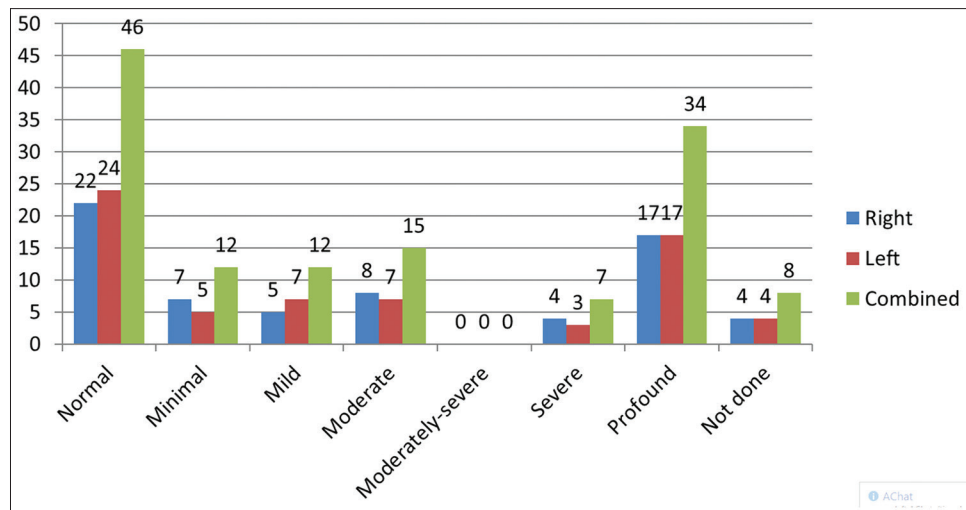


Figure 13: Brain stem evoked response audiometry results in cerebral palsy

two or more developmental domains (e.g., gross/fine motor, cognitive, speech/language, personal/social, and activities of daily living). Typically, if there is a delay in two domains, this implies a delay across all domains.^[26,27] In our study, we found that all the children with global developmental delay were referred from developmental pediatric clinic for speech delay and only 36 (29%) children were suspected to have hearing loss by the parents; the result is similar to the study done by Jane and Tipayno. According to this retrospective study, 1023 children were referred for BERA testing by various departments and when analyzed for the reason for the referral; it was found that speech delay was the most common cause for referral.^[28] There was a male preponderance in the study group with 72 (59%) males and 49 (40%) females. A study done by Coleen *et al.* also showed a male preponderance in their study group.^[29] In our study, the children were grouped into two categories according to the age, first group of children <5 years and the second group of children of 5 years of age or more. Majority (77%) of the study population were in the under-five age group. This can be attributed to the obvious delay in milestones of the child which compels the parents or caregivers to seek medical help early. The mean age of the study population was 3.2 years. The youngest child in the study was 6 months and the oldest child 14 years. The mean age of 3.2 years in our study was delayed compared to studies done in developed countries. Moeller in their study commented that the mean age of identification of hearing impairment and speech delay was 18 months of age.^[19] The studies from the developed countries show early diagnosis and rehabilitation probably due to the support offered by the health-care system. The youngest child in our study group was 6 months of age and was referred from developmental pediatrics after the request of principal investigator for audiological objective testing. The child showed an early

sign of motor delay by not attending neck holding at 6 months of age and hence included in the study. However, this is not a standard practice of referral to otorhinolaryngologist for global developmental delay at first visit, as usual practice is to identify hearing status by startle reflex and clapping test. In a study done by Coplan, it was pointed out that, in those children with mental retardation and developmental disabilities, hearing loss was diagnosed late as 11–17 years.^[30] Hearing loss was not considered during the initial assessment for speech delay similar to our study there was a child with global developmental delay and speech delay but underwent hearing tests for the first time at the age of 14 years. In our study, we found that, of 121 global developmental delay children studied, majority of them are with CP 67 (55%) and one-fourth had syndromic association; the most common is Down syndrome. 10 (8.2%) children had autistic spectrum disorder. These findings were similar to previous studies done elsewhere; the major cause of global developmental delay was CP and Down syndrome.^[31,32] The most common type of CP was spastic type in this study, which was similar to studies done by Sankar and Mundkur and Singhi and Saini.^[33,34] Otomicroscopy examination in our study revealed normal tympanic membrane in 233 examined ears (96.2%). Other findings included microtia with congenital aural atresia in one ear, dull tympanic membrane in seven ears, and OME in one ear which were confirmed by tympanometry. There were no features of cholesteatoma in any of the ears. Ho and Keller reported similar results in a retrospective series of 15 children with global developmental delay.^[35] In this study, children with global developmental delay underwent hearing assessment by BOA, OAE, BERA, and tympanometry. Behavioral observational audiometry was not conclusive in this cohort of children because many children had motor impairment, cognitive impairment, and instinctual and/or learning

disabilities. In this study BOA was done 124 ears (51%), others were inconsistent and could not be done in 118 (48%) ears. Of 242 ears, BOA shows that 56 (23%) had normal hearing and 68 (28%) ears had hearing loss. OAE were absent in 109 (45%) ears, present in 56 (23%), and could not be done in 77 (31%) ears. BERA could not be done in 20 examined ears (8%). BERA showed that 78 ears (32%) had normal hearing and 144 ears (59.5%) had hearing loss. In our study 67 children with global developmental delay were associated with CP and the majority were spastic type, BERA was done in 63 children (126) ears and could not be done in 4 children (8) ears. We studied the finding of BERA in this subset of CP children with global developmental delay. 46 (36%) ears had normal hearing, and 80 (63%) ears had hearing loss. Various studies have been reported 30–40% prevalence of hearing loss in CP children. Our study showed 63% prevalence of hearing loss in CP children.^[16] Among the children with CP with hearing loss, 34 (26%) ears had profound hearing loss, and the result was more than Dufresne *et al.* study which showed 12.7% sensorineural hearing impairment.^[36] In our study children who attended otorhinolaryngology OPD with global developmental delay and speech delay, only 36 (29%) children had a suspicion of hearing loss. On objective hearing testing, we identified that 144 (59.5%) ears had hearing loss. A long-term prospective study with comprehensive data would be more accurate and reliable for the recommendation for objective hearing test in global developmental delay so that early identification of hearing loss can be done before the children present with speech delay and developmental delay.

Limitations

The major limitation of this cross-sectional observational study was that it looked at a point estimate of hearing in children with global developmental delay. A cohort of children followed up for a short period would have given a better estimate of the problem. A second limitation of the study is that it is a hospital-based study and not a community-based study excluding children whose caregivers who did not seek medical advice for their children.

CONCLUSIONS

The mean age of referral was 3.2 years in global developmental delay children who were referred for the evaluation of speech delay. Among the 121 global developmental delay children included in the study, 36 (29%) had hearing loss with speech delay. Our study detected a higher incidence of undetected hearing loss (144 ears, 59.5%) in children with global developmental delay. On the basis of this finding, parents, family physician,

pediatrician, and otorhinolaryngology should work as a team. Our study recommends that every child of global developmental delay should have a detailed audiological workup to identify hearing loss and follow-up for the early identification of middle ear pathology so that timely intervention can be taken.

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Clinical Review of Juvenile Nasopharyngeal Angiofibroma in Urban Tertiary Care Centre: A Retrospective Analysis

T Indra¹, R Muthu Kumar², G Sundar Krishnan³

¹Associate Professor, Department of ENT, Kilpauk Medical College, Chennai, Tamil Nadu, India, ²Director and Professor, Department of ENT, Upgraded Institute of Otorhinolaryngology Madras Medical College and Government General Hospital, Chennai, Tamil Nadu, India, ³Professor, Department of ENT, Upgraded Institute of Otorhinolaryngology Madras Medical College and Government General Hospital, Chennai, Tamil Nadu, India

Abstract

Introduction: The aim of this study was to review management, surgical approaches used, blood loss, complications, and recurrence rate of juvenile nasopharyngeal angiofibroma (JNA) in our institution during 2002–2005 period.

Materials and Methods: All patients referred for a JNA were included in the study. Medical files and imaging data were retrospectively analyzed. Surgical management was then evaluated consecutive patients operated on from April 2002 to June 2005. Case series with chart review. The study was conducted from data on patients operated from April 2002 to 2005 in Madras Medical College and Government General Hospital.

Results: A total of 42 patients were operated on, with a mean age of 16.8 years (range, 9–31 years). In the endoscopic approach blood loss was found to be <300 ml. With Weber Ferguson trans palatine extensive tumor with proptosis blood loss was >1000 ml embolization has reduced the intraoperative blood loss. Since they explored pterygopalatine fossa by removing posterior part of medial wall and posterior wall completely, recurrence was rare.

Conclusion: Progress in skull base anatomy, instrumentation, cameras, and surgical strategy allows for expansion of the indications for endoscopic removal of JNA. This approach may have a better outcome in terms of blood loss, hospital stay, and local sequelae. Still, an external approach should be considered only for selected cases due to a massive intracranial extension or optic nerve or internal carotid artery entrapment by the tumor.

Key words: Angiofibroma, Embolization maxillary swing, Endoscopic approach

INTRODUCTION

Juvenile nasopharyngeal angiofibroma (JNA) is a benign, locally aggressive tumor found commonly in young boys.^[1,2] The internal maxillary artery is the most common vascular source of JNAs followed by the ascending pharyngeal artery. Intracranial involvement has been reported to occur in 10–20% of all cases.^[3,4] Staging is based on anatomic tumor extension, and the Radkowski system of staging

is used most frequently. Over the years, surgical excision has remained standard treatment.^[5] Transnasal endoscopic resection is generally used in early stages, while advanced cases require craniofacial approaches.^[6] The available of pre-operative embolization has helped surgeons in reducing bleeding during surgery and improve outcomes of surgery.^[7] However, surgery alone in advanced stages has reported high recurrence rates especially if resection is not complete. The long-term morbidity associated with radiotherapy has remained a concern.^[8]

Aim

The aim of the study is as follows:

1. To study the age group presentations clinical features presentation in the study group.
2. To study the reference of computed tomography (CT)

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Corresponding Author: Dr. T Indra, Department of ENT, Kilpauk Medical College, Chennai 10, Tamil Nadu, India. Phone: +91-9444359191. E-mail: indraviniyagam@gmail.com

in JNA with regard to diagnosis extensions and bony involvement in the planning of surgical procedures.

3. To study the complications.

MATERIALS AND METHODS

The study was conducted at the Upgraded Institute of Otorhinolaryngology Madras Medical College and Government General Hospital. 2002–2005 series of 42 patients of JNA present in outpatient department with nasal bleed. Detailed history, clinical findings of each patient noted. All patients DNE and CT with contrast - axial/coronal cuts findings noted. Carotid angiography and embolization of vessels were done in selected cases. The following data were gathered: Gender, age at the time of diagnosis, signs, and symptoms, diagnostic nasal endoscopic examination, surgical approach, need for transfusion, pre-operative embolization, complications, follow-up exams, recurrences, and reoperation. The Fisch (Fisch, 1983) criteria were applied to classify the tumors. Case pro forma prepared for the study.

RESULTS

From May 2002 to January 2005, 42 male patients (100%) underwent treatment for angiofibromas. The ages ranged from 11 years to 31 years, with a mean 16.8 years. 10 patients were between the age group 11 to 15, 21 patients between the age group 16 to 20 years, 11 patients between the age group 21 to 31. The most frequent signs and or symptoms were epistaxis 70%, and nasal block (92%), followed by nasal discharge 21%, bulging of the face (20%), and palate bulge 60%. All patients underwent nasal endoscopy and CT. No biopsies were carried out in these patients. Based on the tomographic findings and the Fisch classification, 15 patients (36%) were Stage I, 14 patients (33%) were Stage II, 10 patients (24%) were Stage III, and 3 patients (7%) were Stage IV [Figure 1]. All patients underwent surgery as follows:

Trans palatine approach in 9 patients, nasal endoscopic approach in 7 patients, le fort osteotomy approach in 1 patient, modified le fort in 2 patients and facial translocation in 1 patient.

A total of 32 patients required intraoperative blood transfusions, of which 12 patients had 4 units of transfusions, 10 patients did not require intraoperative blood transfusions, nasal packing was done in all patients at the end of surgery and removed 48–72 h later.

The majority of the patients had O + blood group, 25 patients [Table 1].

Only 2 patients had post-operative complications, such as an oroantral leak following a transpalatine approach, and lower turbinate, and septal synechiae after nasal endoscopic method; both complications were corrected with no additional morbidity. Nasal crusting was seen in 16. The recurrence rate was associated with the absence of pre-operative embolization and advanced tumor stage at the time of diagnosis.

DISCUSSION

Out of transnasal endoscopic surgery offered six cases had undergone trans palatal approach in the past. Moreover, one case transnasal endoscopic Stages were I, II, or III; hence, a transnasal endoscopic approach offers a good salvage technique for complete excision of these tumors. In the endoscopic method- recurrence was due to failure to remove the posterior wall of the maxilla. Facial translocation approach was used in one of the cases and the same patient underwent transpalatal approach twice in the past. After the facial translocation approach, there was no recurrence of the tumor. Since the approach offered access to middle cranial fossa complete tumor excision was done. A modification of facial translocation approach instead of osteotomy of the maxilla done, a maxillary swing procedure was used; hence, the morbidity associated was less.

Mean age of presentation

Martin/Ehrlich/Abels 1948	29 cases	16 years
Figi/david1950	51 cases	15 years
Shaheen 1930	58 cases	20 years
In our present study	2002–2005	18 years

Minimum age of presentation was 12 years. Maximum age was 31 years.

This shows that number of cases decrease in the post-adolescence period.

Nasal obstruction was the most common symptom of presentation 92%. Nasal bleeding in 70 % of the study group, protrusion of eyeball was present in 20% of the study group [Table 2].

Preoperative CT evaluation was done in all the cases which enabled to clearly delineate [Table 3]. The bony landmarks surrounding the tumor, intracranial extension, and extension into adjoining structures.

Introduction of conformal radiotherapy has evolved as a promising treatment approach for locally advanced cohorts of JNA.^[9] Carotid angiography was done in 3 patients internal maxillary artery was found to be the most common feeding vessel for the angiofibroma. Embolization of

Table 1: CT extension of tumor mass

CT extension of tumor mass	Number of patients
Confined to nasopharynx	15
Extending onto nasal cavity/sphenoid sinus	14
Extending into one or more of the following antrum, ethmoid sinus, pterygomaxillary, infratemporal orbit, cheek	10
Extending into the cranial cavity	3

CT: Computed tomography

Table 2: Surgical approaches used

Surgical approaches used	Number of patients
Transnasal	5
Trans palatine	19
Lateral rhinotomy	2
Modified LeFort	2
Fascial translocation	1
Trans nasal endoscopic	12

Table 3: Blood group

Blood group	Number of patients
A+	11
B+	4
AB+	1
O+	25
O-	1

feeding vessel was done in three cases. Gel foam was used as an embolizing agent. In addition, external carotid artery ligation was done in 8 cases, and external carotid artery plication was done in 4 cases. Intraoperative blood loss was <500 ml [Table 4]. In the endoscopic approach blood loss was found to be <200 ml. With Weber Ferguson transpalatine extensive tumor with proptosis blood loss was >1000 ml embolization has reduced the intraoperative blood loss since we explored pterygopalatine fossa completely in transnasal endoscopic approach by removal of the posterior part of the medial wall of the maxillary antrum and posterior wall of the maxillary antrum [Table 5]. Radiotherapy needs to be used only when surgery is not possible or in recurrent and residual lesions.^[10] The chances of leaving behind the tumor in the pterygopalatine fossa are very minimal, and hence, the recurrence is very rare.

CONCLUSION

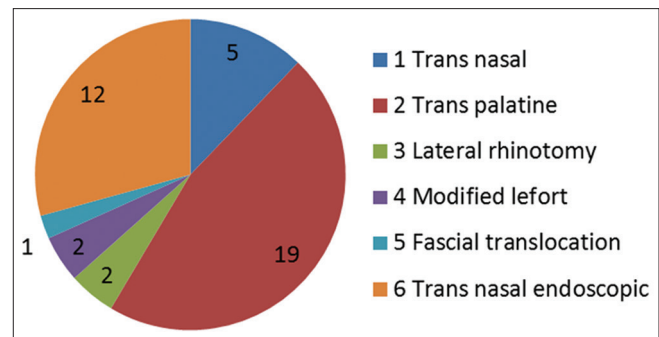
Pre-operative selective arterial embolization was the best treatment for angiofibromas among the cases we reviewed; the cure rate was about 94% follow-up using CT makes it possible to establish the presence and extension of tumor recurrences or the absence of tumors. Surgery is the gold standard for treatment of JNA. Data reveal that during the past 15 years, there has been a marked shift toward

Table 4: Blood loss

Blood loss	Units	Number of patients
ml	Not given	10
350	1	6
700	2	12
1050	3	1
1400	4	11
1750	5	1

Table 5: Complications

Palatal gap	Synechiae	Nasal crusting	Unightly scar	Deafness
2	8	16	3	6

**Figure 1: Number of patients**

endonasal procedures while the tumor stages of the patients treated remained the same.^[11,12] Modern imaging techniques allow accurate diagnosis and staging of JNA. Recurrence of juvenile angiofibroma after surgical removal is commonly ranging from 20% to 30%.^[13] Some studies have found encouraging results in reducing recurrence by meticulously drilling out the pterygoid base, the pterygoid canal, and the basisphenoid.^[14] When a tumor extends intracranially and remains medial or inferomedial to the cavernous sinus, it is more readily removed through the anterior approach.^[15] Our experience and a review of the literature show that the surgical approach should be selected according to tumor stage. Progress in skull base anatomy, instrumentation, cameras, and surgical strategy allows for expansion of the indications for endoscopic removal of JNA. This approach may have a better outcome in terms of blood loss, hospital stay, and local sequelae. Still, an external approach should be considered only for selected cases due to a massive intracranial extension or optic nerve or internal carotid artery entrapment by the tumor.

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Such contribution is extremely important, as it allows scientific research to advance, thereby improving the quality of life of patients.

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Psychosocial Perspective of Nipah Virus Outbreak in Kerala, India

Zacharias Lithin¹, U. Harikrishnan², C. Jayakumar³, K. Sekar⁴

¹PhD Scholar, Department of Psychiatric Social Work, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India, ²PhD Scholar, Department of Social Work, Mizoram University, Aizawl, Mizoram, India, ³Assistant Professor, Department of Psychiatric Social Work, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India, ⁴Professor, Department of Psychiatric Social Work, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Abstract

Nipah Virus (NiV) is a biological disaster and zoonotic pathogen which can be transmitted from animal to human beings. The NiV was first identified in Malaysia in 1998. In India it was traced at Siliguri in 2001, followed by second outbreak in Nadia district of West Bengal in 2007 and the present outbreak consumed more than 17 lives and affected many in Kerala, a southern Indian state which is globally known as “God’s own country”. The “all-time alert care” provided by the Kerala State Health Department have earned applause for early detection of Nipah outbreak. The prompt action ensured containing the spread of Nipah outbreak and halting a major catastrophe, in spite of the best efforts the anxiety and panic was commonly reported among the communities. The current review is to explore the psychosocial perspectives of NiV and its impact in Kerala. Studies on NiV were collected from different online search engines, journals and newspapers. The review points out that there is a need to address psychosocial aspects of NiV along with pharmacological intervention to reduce vulnerability by enhancing better coping and resilience of individual, family and community.

Key words: Biological Disaster, Nipah virus, Outbreak, Psychosocial

INTRODUCTION

Nipah virus (NiV) encephalitis is an emerging communicable disease which had history of sporadic outbreaks in South East Asian countries. The nature and impact of virus will be categorized under biological disaster and infectious disease of public health importance across the world. NiV is a formerly unfamiliar virus of the Paramyxoviridae family which causes illness and death in humans and animals. In the year 1998, there were news of the NiV outbreak in Malaysia where pigs were identified as the intermediate hosts as no other intermediate hosts were found. In the year 2004, there was another report in Bangladesh of NiV infection, where many locals who consumed date palm sap contaminated by infected fruit bats. Further, as

per the WHO report, human-to-human transmission in a hospital setting in India was also documented.^[1] NiV illness presents with 3-14 days of fever, head ache, drowsiness, disorientation, mental confusion, respiratory illness, neurological signs, pulmonary signs and can progress coma within 24-48 h.^[2] Table 1 depicts the number of death occurred due to NiV.^[3,1]

NiV is an emerging disease which has high fatality rate, >70% across the globe.^[4] The outbreak of NiV was limited to a geographical range and follows a strong seasonal pattern which has occurred during winter and spring (December–May). This could be associated with several factors such as the breeding season of the bats, increased shedding of virus by the bats, and the date palm sap harvesting season. NiV infection was first recognized in a large outbreak of suspected cases in peninsular Malaysia during September 1998–April 1999. Most patients had contact with sick pigs or had been in close physical contact with NiV-infected patients and the initial diagnosis made was Japanese encephalitis and later identified as NiV encephalitis.^[1] The most commonly reported psychosocial reactions were panic, fear, social disruptions, and economic

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Corresponding Author: Dr. C. Jayakumar, Assistant Professor, Department of Psychiatric Social Work, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India. Phone: +91-8026995929/+91-9910888173. E-mail: jaipsy@gmail.com

Table 1: Mortality rate of NiV

Place of occurrence	Month and year	Cases identified	Number of death
Malaysia and Singapore	September 1998–April 1999	276	206
Bangladesh	April 2001–February 2015	261	208
India	February 2001–May 2018	89	67

NiV: Nipah virus

loss across the region. In Bangladesh, the first identification of NiV reported in 2001 in Meherpur District. Almost every year the NiV reported in different district from 2003 to 2012.^[3]

Similarly, in India also, virus spread was recorded in humans without any involvement of pigs. The early recorded outbreaks were in Siliguri (2001) and Nadia (2007) in West Bengal^[5] and currently in Kerala (2018) resulting in death and affecting hundreds resulting in widespread panic and closure of business and educational establishments.

METHODOLOGY

Extensive search was done from following databases, PubMed, ScienceDirect, Google Scholar, Cochrane library, WHO reports, and PsychINFO. The search terms included “NiV,” “history of NiV,” “current scenario in Kerala,” and “psychosocial care on NiV.” Around 10 articles retrieved for finding various aspects of NiV from 1999 to 2018. An attempt was made to review the available resources to ascertain the mention objectives.

A study on antibodies to Nipah-like virus in bats (*Pteropus lylei*) in Cambodia identified antibodies cross-reactive to NiV by enzyme immunoassay in 11 of 96 Lyle's flying foxes.^[6] The findings of the study on fatal encephalitis due to NiV among pig farmers in Malaysia showed that three pig farmers presented with fever, headache, and myoclonus were identified in two patients. After 5 days, the virus caused syncytial formation of Vero cells. The virus stained positively with antibodies against Hendra virus.^[7] Another study found that NiV represents from the family Paramyxovirus and Hendra virus also from the same family.^[8] In a similar study, 324 bats from 14 species on peninsular Malaysia suggested widespread infection in bat populations.^[9]

NiV was transmitted from fruit bats (*Pteropus giganteus*) to person through drinking fresh date palm sap,^[10] the same was suspected in the recent outbreak. A case control study was conducted to identify the risk factors for human infection of Nipah Virus during the outbreak of encephalitis in Malaysia revealed that out of 265 patients the primary source of human Nipah infection was due to direct and close contact with pigs.^[11] Majority of the patients were

farmers and 8% of cases reported of no contact with pigs. The study found that close contact with pigs was the primary source of human Nipah infection. However, the studies were primarily focused on the public health mitigation and prevention focusing on pharmacological aspects of NiV; interestingly, the psychosocial care interventions were not focused or mentioned in the response. Therefore, under such scenario, there is a need to incorporate the psychosocial care in deadly outbreak like NiV is imperative.

NiV - THE KERALA SCENARIO

The situation in the state of Kerala was different when compared to the global scenario. One of the striking differences was the rapid spread of the NiV coupled with equally alarming speed of spread of rumors, misinformation, and fake news about the mystery disease, which was 1st time heard in this part of the land. The outbreak was reported in South India from Kozhikode district of Kerala, on May 19, 2018. As per the report till June 01, 2018, 17 deaths and 18 confirmed cases have been reported.^[1] All efforts of Kerala's health-care system were made to ensure that no more lives are lost. The government was prompt in handling the outbreak with utmost seriousness. The efficient action of the state was well appreciated. In spite of that, the professionals, community, and the government faced an unexpected challenge in the form of rumors which spiraled into a mass anxiety that crossed beyond the affected district to the entire state and even reached the neighboring states which had the potential to affect daily lives of the millions.

Social media plays a very important role in disseminating information about the emergencies like epidemic outbreaks whereas false news also spread through resulting in mass panic and anxiety of the people. The role of social media in creating false information on the fatality rate created panic among the population such as the reports like “60% of chickens from Tamil Nadu are carriers of the virus,” “NiV will spread to Goa in a week's time and to Mumbai in 8 days' time,” “People should not come in contact with those who return from Kozhikode in Kerala,” “Fruit bats are not the carriers of NiV and that the real reason for the spread of the virus is migrant workers,” and “Pesticides sprayed on food items could be the reason.”^[12] This misinformation can affect the emotional well-being of the people in the affected area.

The most affected were the common citizens of Kerala, interestingly people from faraway places also felt the impact. The “God’s own country” saw scores of tourists panicking to get out of the state resulting in equally anxious reactions in their home state. The inbound tourist session saw bulk cancellation ensuing enormous loss and hardship. The outbreak also resulted in business continuity as many countries banned the export of vegetables from Kerala, in turn, creating a ripple effect of even local population boycotting or refusing to buy the products resulting in huge monetary loss to the manufacturers. The people’s behavior saw a drastic change where the common food items such as meat and fruits were not consumed. The effect was felt on the education, where most of the competitive examinations had to be postponed, thus creating confusion and uncertainty among the students and parents. Finally, the flooding of news about traditional methods and fake spiritual therapies of cure for the outbreak made the population flocking to the quacks for an easy cure and prevention.

PSYCHOSOCIAL IMPACT OF NIV

The review of articles revealed that Nipah had widespread impact on human population not only biologically as well as psychosocially. Its rapid onset created panic situations among the population. Our search revealed that there is no literature found on psychosocial impact on Nipah, the authors collected and collated various reactions reported in newspapers, publications and reports during Nipah outbreak in Kerala.

Table 2 depicts the psychosocial impacts under three levels such as individual, familial, and community/ state level at large.

Although the outbreak overtly focused on the public health mitigation and prevention aspects, the above-mentioned psychosocial reactions warrant a multifaceted approach to address the psychosocial consequences of this epidemic at individual, family, and community/state levels. It is important to understand that any illness can bring physical, psychological, social, and economic impact among people. The underlying effect of this impact speaks that all these are interconnected and have a cyclic effect on each other. Therefore, intervention in one area will help to bring change in other areas and also in developing a holistic care model. For instance, if a person who is the breadwinner of family is hospitalized due to the virus infection, it is not only affecting the individual but also has an effect on his or her familial life. Thus, the focus needs to be shifted at looking an ill person from biomedical perspective of disease to a biopsychosocial (BPS) perspective of health. The emphasis of BPS approach is placed on achieving positive health and preventing dysfunctions across all the areas of person’s lives, in addition, to mitigate psychological distress and reducing symptomatology.^[13] The importance of providing authentic and adequate information, community engagement, sensitization of the community, psychosocial analysis of the situation, resource mobilization, preventive activities, and enhancing social supports is some of the strategies to improve the quality of life of the affected. Timely sensitization and awareness to health workers, administration, media, local health volunteers, Anganwadi

Table 2: Psychosocial Impact of NiV

Individual	Familial	Community/State
<ul style="list-style-type: none"> • Anxiety • Fear of death • Witnessing death • Hospitalization • Fear of transmission of illness • Social ostracization • Discrimination • Lack of understanding • Beliefs about misfortune • Loss of support system • Lack of treatment facilities • Myths about the illness • Lack of proper and inadequate information • Disruption in economic activity • Rumours • Stigma of health professional 	<ul style="list-style-type: none"> • Witnessing the traumatic course of the infection • Frustration • Fear of infection • Stigma of infected family member • Lack of care • Caregiver Stigma • Financial Burden • Feelings of loss and grief • Distress • Guilt • Helplessness • Role changes • Unable to comfort or care • Ethical concerns • Working long hours • Issues concerning to the bodies of the deceased 	<ul style="list-style-type: none"> • Social exclusion • Widespread fears • Lack of information • Spread of rumours • Stigmatization • Blame • Cultural belief of the illness • Threatened, attacked, evicted • Traditional mourning practices • Disruptions of community interactions • Affecting the economic status • Social restriction • Discrimination • Violence • Loss of economic investment, business, travel and tourism • Loss of support or coping resources

workers, auxiliary nurse midwifery, and accredited social health activist need to be given training to prevent the occurrence of such illness and its management.

CONCLUSION

The primary focus of any public health issue is the prevention and mitigation of the illness spreading to a larger population with the help of advanced holistic health care. The prompt intervention of the stakeholders limited the diseases spread and contained larger impact reflects proactive, systematic, and coordinated efforts can change the scenario. In response to the challenges such as Nipah outbreak, the stakeholders, government, professionals, and administration, first responders need to be aware of the psychosocial impact and care. The response and mitigation plans must include the psychosocial intervention. A proper capacity building and awareness to health first responders, those who are in charge of the management of the outbreak and public health would enhance their capacity to respond and face any eventuality in this age of misinformation and fake news.

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Fiber-reinforced Composite Resin Fixed Partial Denture to Restore Missing Anterior Teeth: A Case Report

Rohit Kumar Singh¹, Prakash Nidawani², Girish Galagali², Satyanarayana Naik², Srinivas Reddy²

¹Post Graduate Student, Department of Prosthodontics Crown and Bridge Including Implantology, Navodaya Dental College and Hospital, Raichur, Karnataka, India, ²Professor, Department of Prosthodontics Crown and Bridge Including Implantology, Navodaya Dental College and Hospital, Raichur, Karnataka, India

Abstract

Prosthetic dentistry constantly evolving as a result of innovative treatment solution based on new material, treatment technique, and technologies. The advent of fiber reinforced has further increased the potential uses of composite material within prosthetic dentistry. As we know that, missing anterior teeth are serious concern in the social life of a patient. To restore the missing anterior teeth, we are having several treatment options such as conventional fixed partial denture and implant-supported restoration all these are may the treatment of choice, but fiber-reinforced composite (FRC) resin offers a conservative, fast, and cost-effective alternative for single or multiple teeth replacement. In this paper, we are presenting how to use FRC technology to restore anterior edentulous area in terms of esthetic values and functionality.

Key word: Anterior prosthesis, Case Report, Fiber-reinforced composite

INTRODUCTION

Loss of anterior teeth is a common form of injury mainly in children and adolescents. As we know that, the patient with lost anterior teeth requires immediate attention for the restoration of esthetics and functional reason. The increased patient demand for tissue maintenance and esthetic as well as the desire to reduce treatment costs causes clinician to seek material and technique that enables minimally invasive and chair side (direct) or laboratory side (indirect) fabrication of teeth replacement with fixed partial denture (FPD).^[1]

Over the past few years, the development of fiber-reinforced composite has given the dental profession the possibility of fabricating adhesive, esthetic, and metal-free dental replacement even in case of posterior teeth.^[2] The

fiber-reinforced composite (FRC) bridges represent an interesting alternative to conventional metal bridge. They could be made directly or indirectly using an artificial plastic tooth or the avulsed tooth or by a direct buildup composite resin tooth with or without porcelain veneering.^[3,4]

The FRC restorations are resin-based restorations containing fiber aimed at enhancing their physical properties. This group of material is a very heterogeneous one depending on the nature of the fiber, the geometrical arrangement of the fiber, and the overlying resin used. The fibers within the composite matrix are ideally bonded to the resin through an adhesive interface. The role of the fiber is to increase the structural properties of the material by acting as crack stoppers. The resin matrices act to protect the fibers and fix their geometrical arrangement, holding them at predetermined position to provide optimal reinforcement. The interface between two components plays the key role of allowing loads to be transferred from the composite used to replace missing tooth structure to the fiber.^[5,6]

This clinical case report represents an indirectly made FRC resin FPD used to restore the missing anterior tooth according to the principle of the minimally invasive approach.

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Corresponding Author: Dr. Rohit Kumar Singh, Room no.5, Navodaya Dental College and Hospital, Navodaya Nagar, Raichur – 584103, Karnataka, India. Phone: +91-9742987218. E-mail: rks.prosthodontics@gmail.com

CLINICAL CASE REPORT

A 17-year-old boy reported with lost upper front teeth in the department of prosthodontics, crown, and bridge at Navodaya Dental College, Raichur, Karnataka [Figure 1]. The boy's medical history revealed no specific problem. His dental history indicated a traumatic accident few days back. In this case, traditional FPD was avoided due to patient's young age, intact neighboring teeth (incisors), and due to his financial condition. The plan is to replace the missing tooth with an implant-retained prosthesis later date. Indirectly made FRC FPD was selected to provide better esthetics, stress relief of bonding surface, and a conservative fixed solution to the patient. The case has been under observation from the past 10 months and the patient is problem free.

Clinical Procedure

Shade selection and preparation of abutment teeth

The shade of veneered composite resin was selected using vita classic A1-D4 shade guide (Vita, Germany). Before starting the treatment, we did occlusal analysis with articulating paper. A box shape cavity prepared on mesiopalatal side of central incisor (21) and lateral incisor (12). Dimension of prepared cavity is 1.5–2 mm depth and 2–3 mm width. As the retention of the prosthesis was due to adhesive luting and not to parallelism, the wall of the cavity was flared between 5 and 15°. All internal line angles were rounded [Figure 2].

Impression and temporization

After preparation of abutment, an impression of the prepared and opposing teeth were made using by an elastomeric impression material (Dentsply Aquasil Soft Putty and Light Body, Dentsply IH Ltd., United Kingdom) [Figure 3]. Then, the prepared cavity was provisionally restored by intermediate restorative material (Dentsply IH Ltd., United Kingdom).

FRC bridge fabrication

Impression poured with die stone [Figure 4] and casts were mounted in a semi-adjustable articulator. For this case, we were selected everStick C&B net fiber (GC Stick Tech Ltd., America). The fiber framework (i.e., substructure) was then constructed with high-volume design placed in pontic region on the patient cast [Figures 5 and 6].

Finally, the fiber framework was finished, wetted with sticky resin, and veneered with Gradia laboratory composite (by GC India) [Figure 7].

The FRC framework and veneered resin composite resin were polymerized with hand light curing unit (Optilux-501, Kerr, USA) for 40 s per layer.



Figure 1: Pre-operative photograph



Figure 2: Tunnel preparation

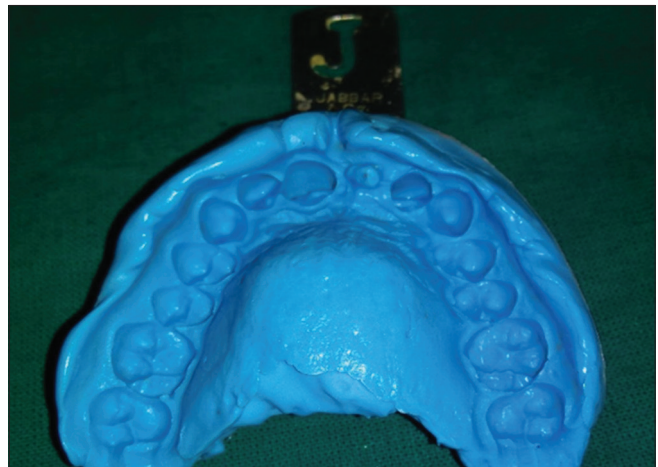


Figure 3: Elastomeric impression made

Try in and cementation of the FRC bridge

At the time of luting, the provisional restorations were removed with scaler and the preparation was cleaned with polishing paste. The prosthesis was evaluated intraorally to assess marginal fit, occlusion, and esthetics before definitive cementation.

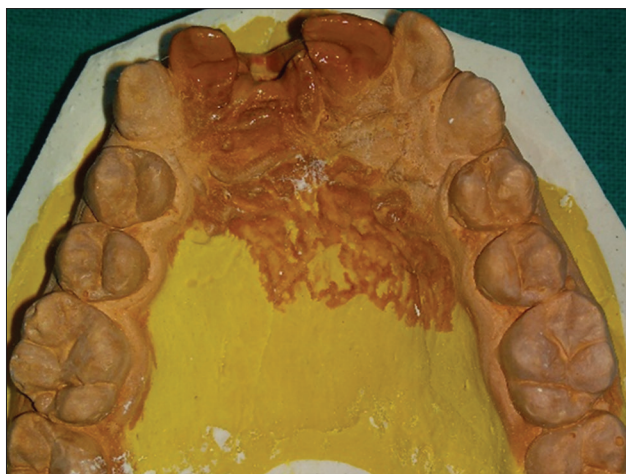


Figure 4: Cast poured with die stone



Figure 6: Fiber-reinforced composite framework



Figure 5: Fiber-reinforced composite framework facial view



Figure 7: Fiber-reinforced composite prosthesis

The adhesive cementation of the prosthesis followed the recommendations of the manufacturer. The area was isolated with a cotton role and the prepared cavity was ringed with an Ed primer, then gently dried with air. The inner surface of the retainers was etched (37% phosphoric acid) and then brushed with mega bond primer. Cementation was made using dual cure cement (GC G-Cem Linkage).

After removing the excess cement, and checking and adjusting the occlusion, then prosthesis was finished with diamond burs and polished with a polishing system (Shofu Composite Polishing Kit by Shofu Dental Corp, South America) [Figure 8].

DISCUSSION

The replacement of missing permanent anterior teeth could be performed through different prosthetic options. Fixed FRC bridges represent one of these options, with many advantages including bondability, reparability, ease

of fabrication, and relative longevity. This considered a noninvasive or minimally invasive procedure with very little or no tooth reduction. Compared to traditional prosthetic options, an FRC bridge is generally less costly and labor intensive.^[7-9]

Compared to direct technique, the indirect technique described in this article provides a better result in terms of adaptation, rate of polymerization, and final smoothness of the prosthesis. With direct technique, it is very difficult to control and avoid the composite excess in the embrasures and the undercuts. After curing, the composite can only be removed by rotary instruments. The use of burs is time consuming, imprecise, and possibly invasive. The lack of visibility and access could lead to fiber exposition during finishing and polishing procedures.^[10]

From clinical point of view, there is lack of long-term clinical research of FRC prosthesis. However, the longitudinal studies reported general failure rates between 5% and 16% over periods up to 4–5 years. These findings



Figure 8: Post-operative photograph

were demonstrated for prosthesis with both extracoronal and intracoronal retainer designs, but only for patients who did not exhibit severe parafunctional habits. Van Heumen *et al.* showed a survival rate of 64% after 5 years follow-up of three units anterior FRC prosthesis made with the material and techniques used in the late 1990s.^[10-12] One study reported much higher failure rate of 40% over a 3-year period. The recent clinical data, on the semi-IPN resin matrix FRC FPDs made directly in patient mouth, suggest high survival rate (more than 96% at 5 years), which reflects material development and learning of fabricating FRC FPDs. The most common failures in FRC FPDs reported in the earlier studies were delamination of veneering composite at pontic area, which are normally easy to repair in patient mouth. The current designing principles enable to fabricate FRC FPD to eliminate known risks for technique failure.^[13-15]

CONCLUSION

Over recent years, the desire expressed by many patients for cosmetic and metal-free restorations has led to the development of better performance and truly esthetic composite resins. The use of fibers as reinforcement has also provided appropriate mechanical behavior of materials used to replace missing teeth. When we are using FRCs as a direct technique for a bridge construction, it requires a high

level of skill in the composite buildup and knowledge of the esthetic aspect of teeth. To provide longer lasting FRCs bridges, the indirect technique would be recommended.^[16,17]

Based on current studies and clinical results, it is reasonable to expect FRC FPDs reach longevity of 5–10 years. However, it needs to be emphasized the importance of many high quality and proven material.

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Congenital Right Lung Agenesis with Dysplastic Sternum - A Constellation of Two Rare Cases

Sanjeev Kumar¹, Bhagyashree Rathore², Lovely Kaushal³

¹Senior Resident, Department of Radiodiagnosis and Imaging, Gandhi Medical College and Hamidia Hospital, Bhopal, Madhya Pradesh, India, ²Post Graduate Student, Department of Radiodiagnosis and Imaging, Gandhi Medical College and Hamidia Hospital, Bhopal, Madhya Pradesh, India, ³Professor and Head, Department of Radiodiagnosis and Imaging, Gandhi Medical College and Hamidia Hospital, Bhopal, Madhya Pradesh, India

Abstract

Congenital lung agenesis is a rare disease spectrum which includes complete agenesis, lung aplasia (with rudimentary bronchus) and partial agenesis. It is embryological anomaly arising from failure of unilateral lung bud to develop. Sternal dysplasias are very rare entities with only few reported cases^[1]. We present case report of a 1 year old female with complete right lung agenesis associated with dysplastic sternum and vertebral segmentation anomaly.

Key words: Lung agenesis, sternal dysplasia, opacified hemithorax

INTRODUCTION

Congenital lung agenesis is a rare disease spectrum which includes complete agenesis, lung aplasia (with rudimentary bronchus), and partial agenesis. Sternal dysplasias are very rare entities with only few reported cases.^[1] We present the case report of a 1-year-old female with complete right lung agenesis associated with dysplastic sternum and vertebral segmentation anomaly.

A 1-year-old female infant with clinical complaints of recurrent pneumonia was referred to the department of radiodiagnosis for chest evaluation. On examination, the patient had apex beat on the right side. The breath sounds were absent on the right side and the right chest wall motion was reduced.

Scout computed tomography (CT) film showed completely opacified right hemithorax with mediastinal shift toward the right side. Cardiac silhouette and cardiac apex were absent from the left side. The left lung was

hyperinflated and herniated across anterior junctional line [Figure 1].

CT chest lung window showed no lung tissue on the right side. The right main bronchus was absent. Trachea continued into the left main bronchus which further divided into two lobar bronchi. The left lung was hyperinflated and herniated toward the right side across anterior and posterior junctional lines [Figure 2].



Figure 1: Scout computed tomography film showing completely opacified right hemithorax with mediastinal shift toward the right side. Cardiac silhouette and cardiac apex were absent from the left side. The left lung was hyperinflated

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Corresponding Author: Dr. Bhagyashree Rathore, Department of Radiodiagnosis and Imaging, Gandhi Medical College, Bhopal, Madhya Pradesh, India. Phone: +91-9669731069. E-mail: drbhagyashree.rathore@gmail.com

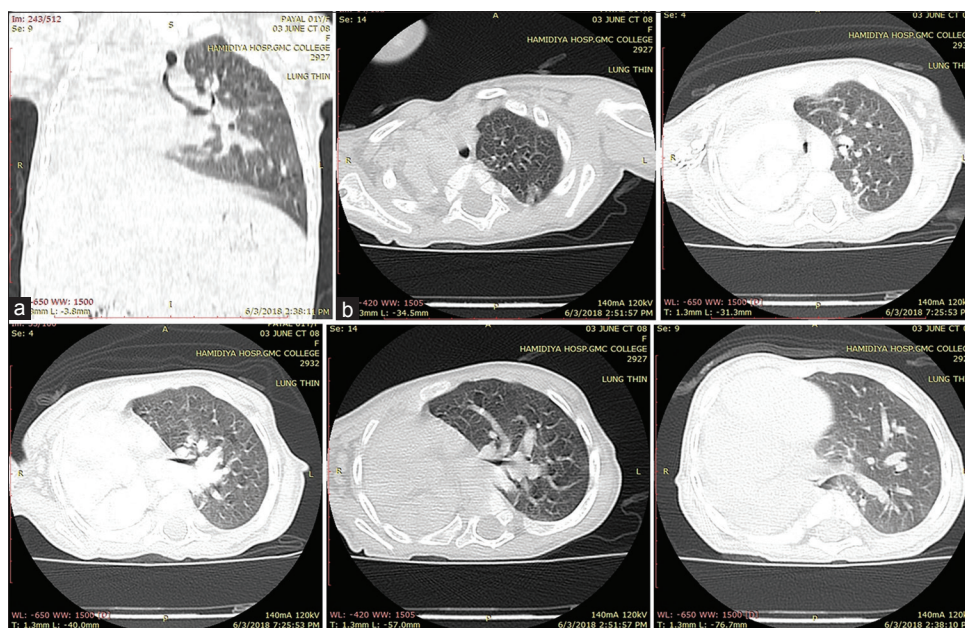


Figure 2: (a): Coronal reformatted computed tomography chest image in lung window showing absent right main bronchus, (b): Absent right lung parenchyma with herniation of the left lung across anterior and posterior junctional lines

Contrast-enhanced CT chest mediastinal window showed heart occupying the right hemithorax with cardiac apex pointing toward the right side; however, aortic arch was the left sided. The right pulmonary artery was not visualized. Few prominent superficial veins were noted over the right hemithorax which drained into the right brachiocephalic vein; however, no venous thrombosis was seen [Figure 3].

CT chest bone window depicted dysplastic sternum with abnormal development of the manubrium, the presence of a hypoplastic body, and the absence of the xiphoid process. There is also an alteration of the sternoclavicular joint [Figure 4].

Body and spinous process of D8 vertebra were unfused in midline [Figure 5]. The left lung parenchyma was normal.

POINTS TO PONDER

- Congenital lung agenesis can be diagnosed antenatally by target scan.
- It should be considered in differentials of patients presenting with absent or reduced breath sounds, completely opacified hemithorax, and ipsilateral mediastinal shift in any age group. Case report of congenital lung agenesis diagnosed in 24-year-old patient does exist!^[2]
- Although it appears to be very morbid condition scientifically, case reports of asymptomatic patients

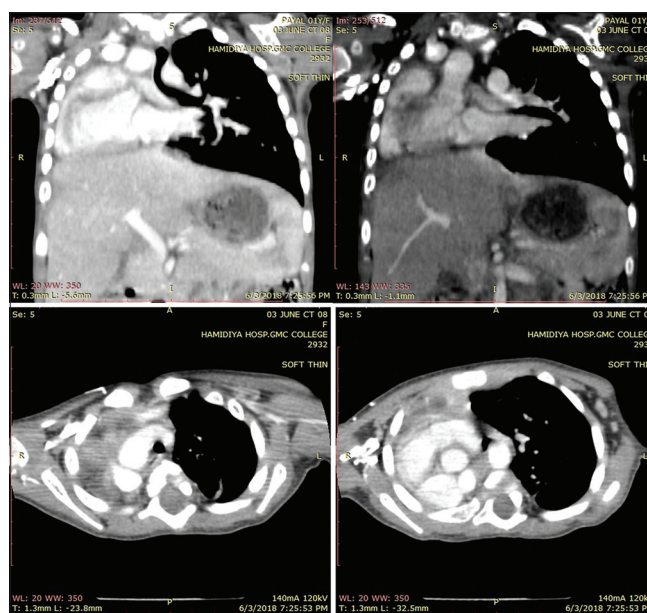


Figure 3: Contrast-enhanced computed tomography chest mediastinal window showing shifting of mediastinum toward the right side with heart occupying the right hemithorax. Cardiac apex is toward right; however, aortic arch is toward left

have been published. Oldest patient of lung agenesis reported at autopsy was 72 years old.

- In literature, the right lung agenesis is considered to have a poorer prognosis and is often associated with cardiac anomalies. It can be attributed to the fact that both lung bud development and cardiac migration occur around 4–5 weeks.^[3]

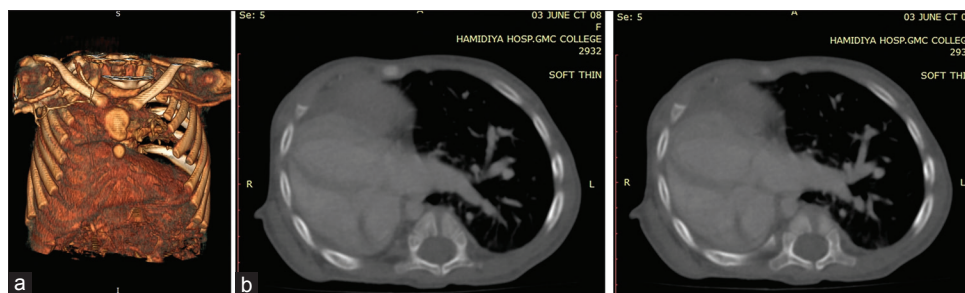


Figure 4: (a): Dysplastic sternum with abnormal development of the manubrium, the presence of a hypoplastic body, and the absence of the xiphoid process, (b): Unfused D8 vertebral body and spinous process

- In almost half of the cases, lung agenesis is associated with some other systems anomaly; like in this patient, it is associated with skeletal system anomaly. So be on lookout for other anomalies to catch!
- Difference between lung agenesis and aplasia is that rudimentary bronchus is found in lung aplasia, while it is completely absent in lung agenesis.^[4]
- Dysplastic sternum is a very rare anomaly and is usually associated with other chest wall abnormalities.

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Colonic Perforation Following Percutaneous Nephrolithotomy: Retrorenal Colon - A Case Report

Peerzada Mohd Irfan¹, Amit Suri²

¹Post Graduate Student, Department of General Surgery, Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, Jammu And Kashmir, India, ²Mch Urology and Professor, Department of Urology, Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, Jammu And Kashmir, India

Abstract

Colonic perforation is an unusual and serious complication of percutaneous nephrolithotomy. It can result in more complicated open exploration of the abdomen, involving colostomy construction. The necessity of a second operation for the closure of the colostomy causes financial and emotional burden on the patients and surgeons.

Key words: Computed tomography scan, Nephrostomy, Percutaneous, Retrorenal colon

INTRODUCTION

Fernstrom and Johansson (1976) first reported the technique of creating a percutaneous tract specifically to remove a stone. Subsequent reports have established percutaneous nephrolithotomy (PCNL) as a routinely used technique to treat patients with large or otherwise complex calculi. PCNL is the gold standard for the elimination of large renal calculi^[1,2] providing maximal stone-free rates with minimal trauma to the kidney and the surrounding tissues. PCNL offers a 78%–95% success rate in the treatment of kidney stones. However, the rate of major and minor complications related to the procedure is as high as 83%.^[3] The major complication rate for PCNL varies between 1.1% and 7%,^[4] despite improvements in endourologic equipment and the development of new treatment modalities such as mini-micro PCNL, supine PCNL, and laparoscopically assisted PCNL. Nonetheless, significant risks remain, including those of bowel perforation, pleural injury, and bleeding. Although injury to the retroperitoneal colon is rare, occurring in fewer than 1% of cases^[5,6] classified as a Stage IVa complication on

Clavien-Dindo classification of surgical complications, the potential severity of this complication is such that a high index of suspicion and alertness for its signs and symptoms is essential during the post-operative period.

CASE REPORT

An average built 65-year-old female patient reported to us with a complaint of the left flank pain on and off from 4 months, with surgical history of open pyelolithotomy 10 years back for the left renal calculus. On ultrasound, 25-mm calculus in the left renal pelvis with Grade 1 hydronephrosis was found. Intravenous pyelography was also done. All the laboratory investigations were within normal limits. After her symptoms were controlled with medications, she was planned for PCNL.

The patient was administered prophylactic antibiotics, and the left-sided PCNL was done in the prone position. Percutaneous access to the middle calyx was obtained under fluoroscopic vision. The left-sided subcostal puncture was done just lateral to the paraspinal muscles. The tract was dilated to 26 Fr in routine fashion without any suspicion of bowel injury. The stone was fragmented with lithotripter and removed with tricep forceps. A double J stent was placed antegrade and after hemostatic matrix was placed in the tract 24 Fr nephrostomy tube was placed in the tract. No leakage of feces through the tract or on the access sheath was seen. Postoperatively, all the blood investigations were within normal limits with no total leukocyte count (TLC)

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Corresponding Author: Dr. Peerzada Mohd Irfan, Hostel Block E-4, Acharya Shri Chander College of Medical Sciences and Hospital, Jammu, Jammu and Kashmir – 180017, India. Phone: +91-7051288359. E-mail: irfanpeer19711@gmail.com

or differential leukocyte count (DLC) change observed from the pre-operative baseline. On post-operative day 1, the patient was started on orals, and on day 2, nephrostomy tube was removed and antiseptic dressing was done at the site. On post-operative day 3, the patient was planned to be discharged, but we found feculent smell coming from the patient, the dressing at nephrostomy was opened, and we found it soaked with fecal matter and saw feces coming out through nephrostomy site.

The patient was kept NPO and we placed a central venous catheter and started total parenteral nutrition (TPN). Broad-spectrum antibiotic coverage was provided (piperacillin-tazobactam + metronidazole + amikacin). Daily dressing was done both in morning and evening to quantify the output through nephrostomy site by a number of dressing pads soaked. Anal dilation was also done to give bowel rest. Contrast-enhanced computed tomography - abdomen was done which showed the left-sided retrorenal colon as shown in Figures 1 and 2 and an incidental finding of circumferential thickening involving cecum and part of the ascending colon. The patient was kept NPO for 7 days till there was no soakage from the nephrostomy site. Ultrasound of the abdomen was also done on post-operative day 7 to rule out any intra-abdominal collection. During the time, our patient did not develop fever nor there was rise in TLC or DLC. On day 8, the patient was started on orals and TPN was stopped. There was no leakage of fecal matter from the site, and subsequently, the patient also passed stools later. The patient was discharged; thereafter, double J stent was removed at 3 weeks from the date of surgery.

Established risk factors for the colonic injury during PCNL were as follows:

1. Slim body habitus.
2. Female sex.
3. Prior colonic or renal surgery.
4. Too lateral incision and access to lower pole.
5. Elderly patients with chronic constipation or other causes of colonic distension.
6. Anatomical anomalies such as horseshoe kidney.
7. Retrorenal colon.

Risk factors associated with our case were female sex with a previous history of left-sided open pyelolithotomy and retrorenal colon.

Recent reports describing bowel perforation during PCNL have emphasized the opportunity for conservative management for the bowel injury with replacing nephrostomy tube into the bowel lumen to act as a drain. However, in our case, we detected the injury after removal of the nephrostomy tube and managed

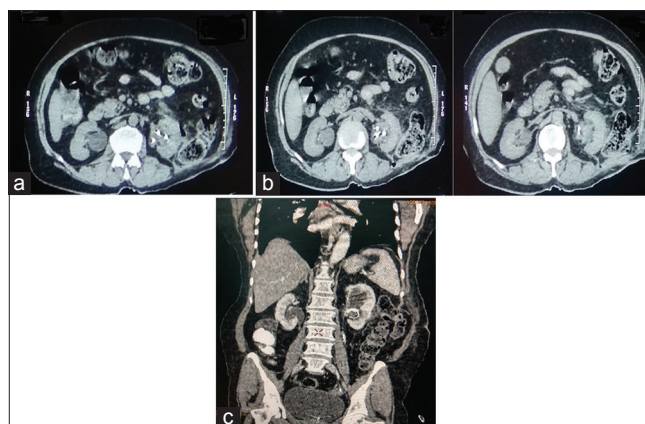


Figure 1: (a-c) Left renal retrorenal colon with double J stent *in situ* in the left kidney and small fistulous tract communicating with the descending colon with air foci along the operative site

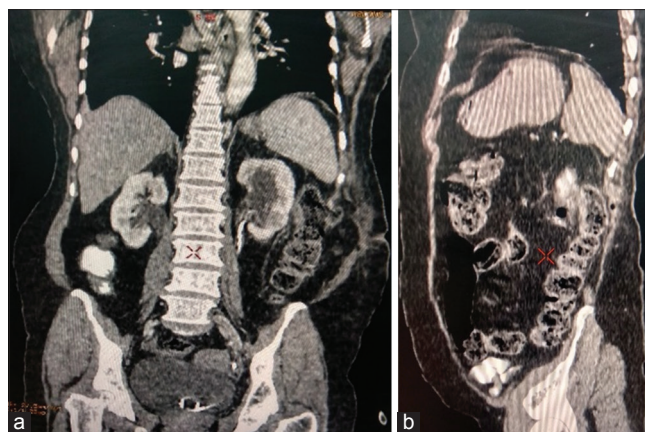


Figure 2: (a and b) Relation of the descending colon with the left kidney

it conservatively. Prompt recognition of a colonic perforation is critical to limiting the serious infectious sequelae. Colonic perforation should be suspected if the patient develops unexplained fever or has intraoperative or immediate post-operative diarrhea, signs of peritonitis, gas, or feces through the nephrostomy tract. Unrecognized colonic injury can result in abscess formation, nephrocolic or colocutaneous fistulae, peritonitis, or sepsis.

CONCLUSION

Retrorenal colon is more frequently found on the left side; therefore, accessing the left kidney risk of colonic injury should be considered during PCNL. We recommend that pre-operative CT scan should be obtained in high-risk patients to identify retrorenal colon to prevent unnecessary cost, morbidity, and mortality of the patients.

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Primary Malignant Jejuno-colic Fistula: A Rare Presentation

B R Sathyakrishna¹, V Yatheendra²

¹Senior Surgeon and Chief Unit-3, Department of General Surgery, St. Martha's Hospital, Bangalore, Karnataka, India, ²Post Graduate Student, Department of General Surgery, St. Martha's Hospital, Bangalore, Karnataka, India

Abstract

Primary malignant fistulas of the gastro-intestinal tract are very rare. Usually they are secondary to diverticular disease, crohn's gastric ulcer, lymphoma, post surgery etc. Here we have reported a very rare case of primary malignant fistula with primary located at recto-sigmoid junction, leading to a fistulous tract between the jejunum and sigmoid colon. We have briefed on the course of the disease, investigations done and management of the same.

Key words: Primary malignant, Fistula, Jejuno-colic, Rare, Management

INTRODUCTION

Malignant fistula of the gastrointestinal tract was first described by Haldane, in 1862.^[1] Gastrointestinal fistula usually occurs due to many reasons. Diverticular disease has been the major cause.^[2] Others include Crohn's disease, gastric ulcer, lymphoma,^[3] and carcinoid tumor.^[4] Carcinoma is a rare cause of gastrointestinal fistula. (0.3–0.4%).^[5,6] Fistula formation in malignancy can be explained in two ways.

- Contiguous growth to the other organ from the primary source.
- Primary tumor causing deep ulceration with or without peritoneal reaction or an organization of exudates which leads to adherence to adjacent structures. This perforates into the lumen of the other organs forming a fistulous tract.

Patient Details

A 55-year-old male patient presented with complaints of loose stools for 1 week, 10–12 episodes per day, watery, non-foul smelling, not bloody associated with vomiting non-bilious, not blood tinged, and containing ingested food. He also had a history of increased frequency of

the micturition, not associated with dysuria, incomplete voiding, poor stream, or dribbling of urine. He has lost around 10 kgs in the past 1 month and complains of decreased appetite, no comorbidities, no history of any surgery in the past, insignificant family history.

On examination, he was pale. Per abdomen examination revealed a non-tender, hard 15 × 10 cms, irregular, fixed mass in the suprapubic region.

Blood investigations showed hemoglobin of 10 g. CEA level of 4. Contrast-enhanced computed tomography (CT) abdomen and pelvis showed a mass involving the distal jejunum and sigmoid colon with fistulization between the two structures [Figure 1 (a and b)]. Colonoscopy was done which showed a growth at rectum 10 cms from anal verge from which biopsy taken - which was suggestive of malignant lesion [Figure 1a]. Positron emission tomography-CT (PET-CT) showed hypermetabolic density at jejunal loop and sigmoid with surrounding lymph nodes, mesenteric lymph nodes, and external iliac lymph nodes involvement.

Management

- The patient was taken up for laparotomy, adhesion between the distal jejunum and sigmoid was noted with fistula formation between the two [Figure 2 (a and b)]. Fistula forming segments were resected and anastomosis was done. Anterior resection was done as rectum was involved. Retroperitoneal lymph node clearance and left pelvic lymph node dissection were carried

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Corresponding Author: B R Sathyakrishna, Department of General Surgery, St. Martha's Hospital, Bangalore-560 001, Karnataka, India.
E-mail: dr.brsk@gmail.com

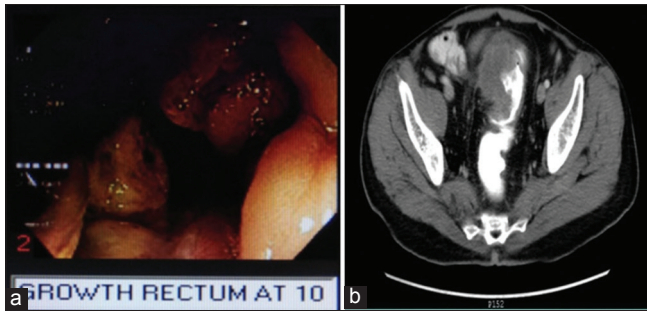


Figure 1: (a-b) Colonoscopic picture and fistulous tract on contrast-enhanced computed tomography

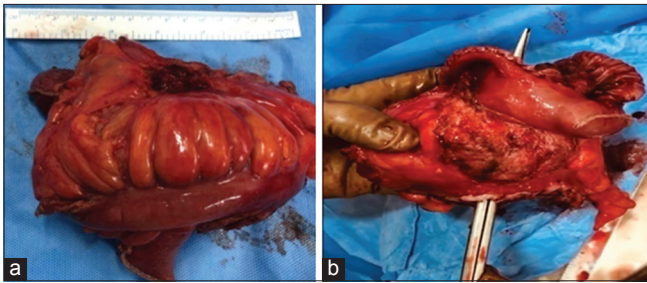


Figure 2: (a-b) Resected specimen showing fistulous tract between the sigmoid and the jejunum

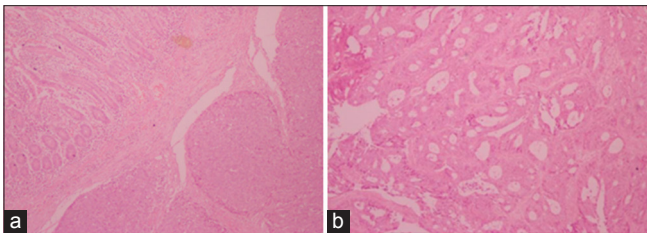


Figure 3: (a-b) Histopathology showing poorly differentiated adenocarcinoma of sigmoid invading the jejuna wall

out. Histopathology showed poorly differentiated adenocarcinoma of sigmoid invading the jejunal wall [Figure 3 (a and b)].

- Post-operative staging was $pT_{4b}N_{1c}M_0$. The patient was started on 6 cycles of FOLFOX 6 followed by radiotherapy again followed by 6 cycles of FOLFOX 6.

DISCUSSION

The exact incidence of internal fistula in large bowel carcinoma is approximately 0.3–0.4%. Malignant

enteroenteric fistulas are usually from ileum or jejunum to colon and primary is frequently in sigmoid colon. However, in malignancy obstruction and perforation are more common than fistulization. Bacterial overgrowth, mechanical bypass, and choleretic effects of conjugated bile acids entering colon, all contribute to diarrhea. Poor intake, impaired absorption due to informed bypass, and catabolic sepsis lead to weight loss. Symptomatic patients will require surgery. Short life expectancy and high operative risk will preclude operative treatment for malignant fistula. Few advocate prompt attention to malignant fistula even if palliative, as underlying obstructive carcinoma must be resected. In the absence of nodal metastasis, radical local surgical clearance may be associated with reasonable prognosis. Colorectal cancer forming a fistula is characteristic in that it scarcely occurs in patients having liver metastasis, peritoneal dissemination, or lymph node metastasis.^[5-7] Therefore, it is thought that a curative operation is possible by performing extended tumor resection with fistula-forming organs and that a good prognosis is expected.

CONCLUSION

Primary malignant gastrointestinal fistulas are very rare; hence, they need a thorough pre-operative workup and staging. Resection if properly planned can give a very good prognosis to the patient.

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Tumor-induced Osteomalacia: A Case Study of a Nasal Tumor

T Santhi¹, A P Abdunnazar², U M Archana³

¹Associate Professor (ENT), Department of ENT, Government Tirumala Devaswom Medical College, Vandanam, Alappuzha, Kerala, ²Assistant Professor (ENT), Department of ENT, Government Tirumala Devaswom Medical College, Vandanam, Alappuzha, Kerala, ³Junior Resident (ENT), Department of ENT, Government Tirumala Devaswom Medical College, Vandanam, Alappuzha, Kerala

Abstract

Oncogenous osteomalacia, which is also known as tumor-induced osteomalacia, is a condition where a neoplasm is associated with systemic bone demineralization and renal phosphaturia. We report a case who presented with a bleeding nasal mass, generalized fatigue, and cramps in her leg. Excision was done, and histopathologically, it was diagnosed to be a phosphaturic mesenchymal tumor. The cramps disappeared soon after surgery and she is on regular follow-up for the past 2 years.

Key words: Oncogenic osteomalacia, Mesenchymal tumor, Hyperphosphaturia, Hypophosphatemia

INTRODUCTION

Oncogenous osteomalacia (OOM) is a rare condition of a paraneoplastic syndrome^[1] characterized by the association of a neoplasm with systemic bone demineralization due to renal phosphate wasting. In 1947, McCance published the first case of a patient who presented with phosphaturia which did not resolve until the tumor involving the femur was removed.^[2,3] Andrea Prader, in 1959, treated an 11-year-old girl who presented with hypophosphatemia and rickets. She was operated later for a rib tumor which turned out to be a giant cell granuloma and her rickets got cured thereafter.^[2]

In 1987, the term phosphaturic mesenchymal tumor (PMT) was introduced by Weidner and Santa Cruz,^[3] and they described four morphological patterns, among which the most common one was a mixed connective tissue tumor variant (PMT), the others being an osteoblastoma-like tumor, a non-ossifying fibroma-like tumor, and an ossifying fibroma-like tumor.^[2] PMTs can involve both bone and

soft tissue.^[3] 95% of these tumors involve the extremities and appendicular skeleton, with 5% involving the head and neck region.^[4]

Around 50% of the PMT tumors of head and neck involve the sinonasal tract.^[3] The remaining 50% are located in the mandible, floor of mouth pharynx, temporal bone, and thyroid.^[4] Due to its rare presentation, PMTs are often mistaken in diagnosis for other tumors such as glomangiopericytoma and low-grade osteosarcoma,^[3] chondrosarcoma, and chondroblastoma.^[1]

We are reporting a case of PMT involving the nose and paranasal sinus presenting with epistaxis and bone pain. The clinical features, the pathology, and the management are described.

CASE REPORT

A 55-year-old lady limped into the ENT OP with a 6-month history of intermittent, profuse epistaxis, and a right-sided nasal block. She also had generalized fatigue with cramps and pain in her right leg below the knee for the past 8 months. She was treated symptomatically at a local hospital and once blood had to be transfused, due to the severity of the bleed from the nose. She was found to be hypertensive and was on medication for the same. There was no remarkable family history.

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Corresponding Author: Dr. T Santhi, Department of ENT, Government Tirumala Devaswom Medical College, Vandanam, Alappuzha – 688 009, Kerala. Phone: +91-9446300271. E-mail: sttpillai@gmail.com

On anterior rhinoscopic and nasal endoscopic examination, a reddish, smooth, firm polypoidal mass was seen filling the right middle meatus extending anteriorly up to the middle half of the inferior turbinate [Figure 1]. Nasal septum was deviated to the left side.

Contrast-enhanced computed tomography (CT) scan revealed a well-enhancing soft tissue mass of 3 cm × 2 cm × 2 cm in the right middle meatus with extension to the right maxillary antrum [Figure 2a and b]. No bony erosion was noted on the orbital walls and skull base. On T1- and T2-weighted magnetic resonance imaging (MRI) images, the soft tissue mass was heterogeneously enhancing [Figure 3a and 3b]. Blood routine and thyroid function and renal function tests were within normal limits.

Under local anesthesia, biopsy was taken and the brisk bleeding was controlled by nasal packing. The diagnosis was hemangiopericytoma-like tumor.

Following the advice of the pathologist, a battery of tests was performed, among which elevated levels of serum alkaline phosphatase (998 IU; normal < 275IU),^[5] reduced levels of inorganic phosphorus (1.43 mg/dl; normal 3–4.5),^[5]

and 1, 25-dihydroxyvitamin D₃ (12.6 pg/ml; normal 25–45 pg/ml)^[5] were recorded. Serum ionized calcium was 4.9 mg/dl (normal 4.3–5.6).^[5]

High level of 24 h urine phosphate (1640 mg/24 h; normal 400–1300)^[5] confirmed a low tubular reabsorption of phosphate.

The conclusions of the above biochemical tests were hypophosphatemia, normocalcemia, high alkaline phosphatase levels, and phosphaturia.

Radiological investigation revealed a severe osteopenia of the right femur and tibia.

Under general anesthesia, complete endoscopic excision of the mass was done [Figure 4]. The bleeding was controlled using bipolar cautery and nasal packing. The post-operative period was uneventful. The histopathology report came as a PMT. On high power microscopic view, there were small stellate cells with prominent vascular stroma in a myxoid matrix. The cells were negative for CD 34, CD 99, and S-100 and positive for vimentin. Further, analysis of fibroblast growth factor 23 (FGF23) expression by

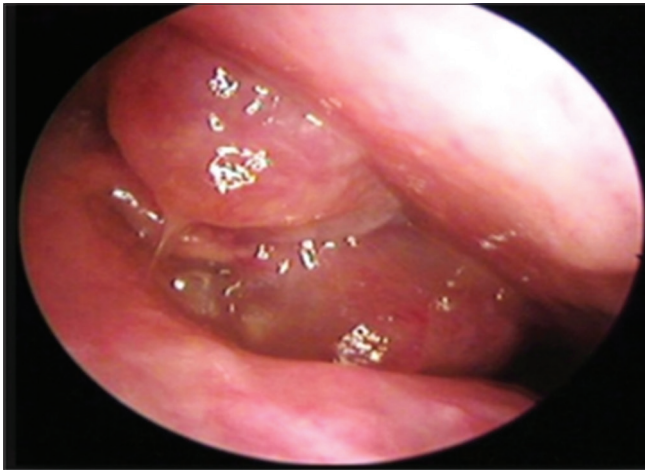


Figure 1: 0 degree nasal endoscopy showing smooth, polypoidal mass in middle meatus

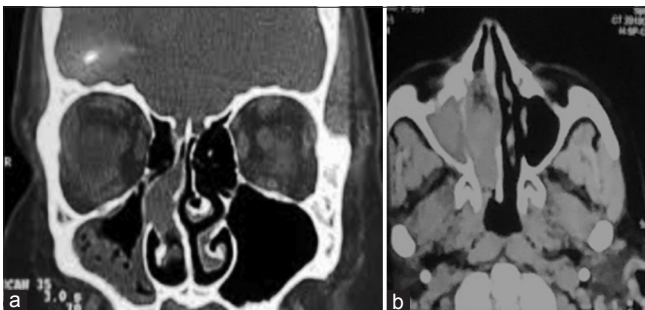


Figure 2: (a and b) Computed tomography scan, coronal and axial views showing a moderately enhancing mass in the right nasal cavity with extension to maxillary antrum

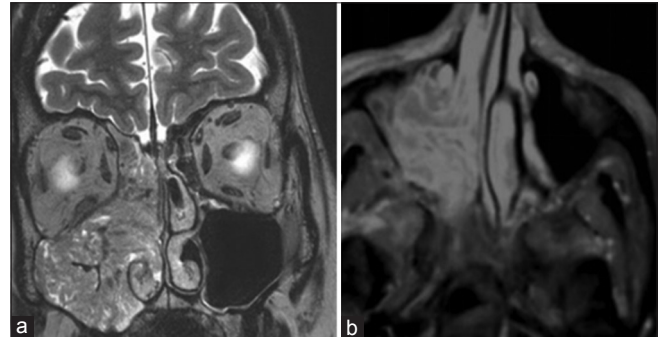


Figure 3: (a and b) Magnetic resonance imaging scan: Soft tissue mass in the right middle meatus extending to the right maxillary sinus shows heterogeneous enhancement on T1- and T2-weighted images

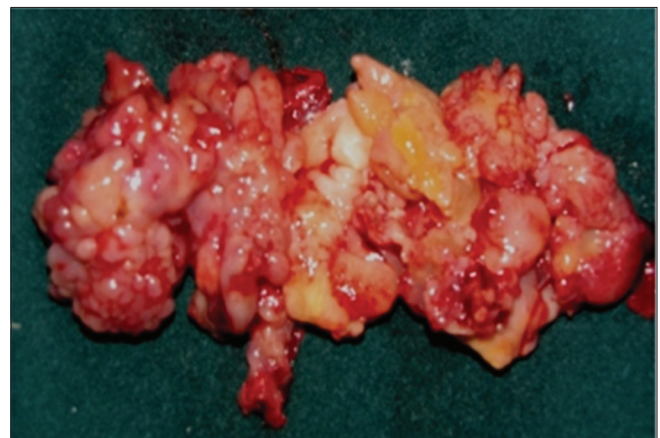


Figure 4: Gross specimen after resection

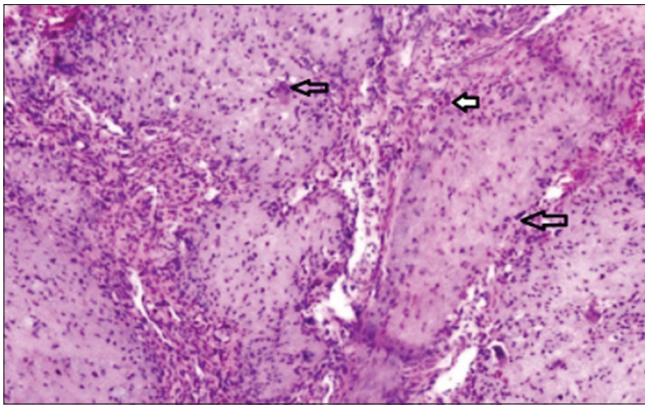


Figure 5: Immunohistochemistry for fibroblast growth factor 23 protein staining positive under high power

immunohistochemistry showed distinct, punctate staining in the cytoplasm of the cells [Figure 5].

The patient was given oral supplements of phosphate and Vitamin D. Within the next 2 months, her bone pain got reduced and her limp disappeared. Her serum phosphate and alkaline phosphatase levels got back to normal. Her general health improved and she is still on regular follow-up for the past 2 years. Thus, the diagnosis of osteogenic OOM was made.

DISCUSSION

Osteomalacia means soft bones. It is a disorder in which there is demineralization resulting in weak bones and this condition occurs in adults.^[6]

OOM or tumor-induced osteomalacia (TIO) is characterized by phosphaturia, hypophosphatemia, and osteomalacia with regression once these tumors are completely resected.^[7]

PMTs occur commonly in extremities and paranasal sinus involvement is seen only in 6.2% of the cases.^[6] As these tumors are generally small and asymptomatic, localization becomes difficult and challenging which results in delayed diagnosis, sometimes even as long as 15 years.^[2,7]

PMTs are found equally in both sexes with an average age of onset at 40 years. Patients usually present with generalized musculoskeletal pain, weakness, and recurring fractures of the long bones and vertebrae.^[5]

Relationship between PMT and osteomalacia was established in 1959 by Prader *et al.* PMTs secrete excess of FGF23. This physiological phosphate regulator peptide is also known as phosphatonin. FGF23 binds to the FGF receptor on the renal proximal tubules and reduces reabsorption of phosphates by inactivating

the sodium-potassium pump.^[5] It also inhibits 1-alpha-hydroxylase enzyme which brings down the levels of 1-alpha, 25-dihydroxyvitamin D3.^[2] Thus, it is a regulatory hormone for 1-alpha, 25-dihydroxyvitamin D3. PMTs secrete FGF23 excessively leading to dysregulation of the FGF23 degradation pathway. FGF-23 in excess can lead to electrolyte imbalance with consequent damage to heart, kidneys, and brain.^[1]

Serum FGF23 can be measured using C-terminal enzyme-linked immunosorbent assay, the normal range being 21 ± 11 SDRU/ml.^[5] Tumor expression of FGF23 can be detected by reverse transcription polymerase chain reaction on mRNA and FGF23 protein by western blotting and immunohistochemistry using FGF23 antibody.^[1,8]

On histopathology, PMTs are composed of spindle-shaped or stellate cells, myxoid or myxochondroid calcified matrix with abundant microvascular supply and flocculent calcification may be seen. The osteocytes in PMTs produce FGF23 resulting in bone demineralization.^[4,5] The rich microvascular stroma often misleads to a diagnosis of hemangiopericytoma.^[4]

The incidence of PMT in the head and neck is probably higher as tumors in this region is frequently misdiagnosed.^[3] Tumors such as osteosarcoma, mesenchymal chondrosarcoma, chondroblastoma, atypical enchondroma, spindle cell lipoma, angiolipoma, sclerosing hemangioma, hemangiopericytoma with osteoclast-like giant cells, tenosynovial giant cell tumors, and benign mesenchymal tumor are some of the differential diagnoses.^[1]

Although PMTs are considered benign, histologic evidence of malignancy with multifocal or metastatic disease has been reported.^[2,3]

CT scan shows a moderately enhancing soft tissue lesion, while it is isointense to diffuse enhancement to gadolinium in T1-weighted MRI and low intensity in T2-weighted MRI. MRI with short tau inversion recovery sequence, F-18 FDG-PET, whole body ^{99m}Tc sestamibi scintigraphy, and octreotide scintigraphy is the investigations of choice in locating these lesions.^[5,7] Ga-DOTANOC PET/CT is the other newer investigation modalities.^[7]

Osteomalacia is not seen in all PMTs, but TIO should always be considered in patients who are being treated for musculoskeletal pain, pathological fractures, and non-familial adult-onset osteomalacia.^[3]

Sinonasal PMT is a rare variant and closely resembles hemangiopericytoma histologically.^[5] The positive molecular studies for FGF23 and the negative expression

of the neuronal markers such as synaptophysin and neurofilaments for PMTs are helpful in distinguishing the two.^[1] Similarly, the grungy calcification noted on histopathology is seen only in PMTs.^[1]

Monitoring levels of serum FGF23, 1, 25-dihydroxy D3, and phosphate levels are useful in the detection and the response to surgical outcome of TIO.^[2]

Wide resection of the tumor is necessary to prevent recurrence. If the tumor is unresectable or not located, alternative medical therapy is given. Phosphate supplements such as calcitriol or alfacalcidol can be used, but complications such as hypercalcemia, renal failure, and hyperparathyroidism may result.^[2]

In our case, nasal endoscopic evaluation and serum levels of inorganic phosphate and 1, 25-dihydroxyvitamin D3 are being monitored every 6 months. She has been asymptomatic ever since the surgery and has been asked to report for any further untoward symptom.

CONCLUSION

A diagnosis of phosphaturic tumor should be kept in mind while assessing a case of osteomalacia with hypophosphatemia and imaging of the whole body can be a valuable diagnostic tool. Localization and resection of these tumors give a dramatic cure of the OOM. As

PMTs are rare in the ENT field, one needs to be aware of the possibility of such a cause in the nose for a patient presenting with cramps in the leg.

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An Unusual Presentation of Systemic Lupus Erythematosus with Vasculitic Polyneuropathy

Shruthi Muralidharan¹, K Arun², Subramaniyan Kumarasamy³, V Ruckmani⁴

¹Post Graduate, Department General Medicine, SRM Medical College Hospital and Research Institute, Kattankulathur - 603203, Kancheepuram, Tamil Nadu, India, ²Assistant Professor, Department of General Medicine, SRM Medical College Hospital and Research Institute, Kattankulathur - 603203, Kancheepuram, Tamil Nadu, India, ³Professor, Department of General Medicine, SRM Medical College Hospital and Research Institute, Kattankulathur - 603203, Kancheepuram, Tamil Nadu, India, ⁴HOD, Department of General Medicine, SRM Medical College Hospital and Research Institute, Kattankulathur - 603203, Kancheepuram, Tamil Nadu, India

Abstract

We report a case of systemic lupus erythematosus (SLE), in a 48-year-old woman, a known hypertensive and recently diagnosed diabetic, with a predominant complain of acute onset bilateral lower limb weakness and loss of sensation of the bilateral palm and soles with bowel incontinence and excessive hair loss. On evaluation, her vitals were stable, cardiovascular, respiratory, and abdominal systemic examination revealed no significant abnormality. Neurological examination revealed a normal tone with distal muscle weakness more in the lower limb than in the upper limb. She was thoroughly evaluated for the above-mentioned complaints and examination findings. Nerve conduction study was done - which revealed upper limb - severe asymmetric motor sensory neuropathy - axonal type and lower limb - axonal symmetrical severe polyradiculoneuropathy. Nerve biopsy revealed a vasculitic neuropathy. Autoimmune workup was positive for antinuclear antibodies, and low C3 levels, with direct Coombs test positive, increased UPCR ratio. According to the Systemic Lupus International Collaborating Clinic criteria, she was diagnosed with SLE. Hence, this is a case of SLE, with a primary presentation of a vasculitic neuropathy, an unusual occurrence.

Key words: Atypical presentation of systemic lupus erythematosus, Systemic lupus erythematosus, Vasculitic polyneuropathy

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder with a variety of manifestations. These manifestations are brought forth by immune complex deposition in various tissues such as skin, kidney, and vasculitis. This immune complex activation occurs through a variety of pathways, genetic, epigenetic, and environmental factors.

Clinical manifestations of SLE include a wide array of symptoms and signs, which can affect almost every part of the human body.

Approximately 10–20% of patients with SLE show an involvement of the peripheral nervous system.^[1,2]

Primary presentation of an axonal polyradiculopathy with a vasculitic neuropathy in a patient with SLE has rarely been reported.^[3]

Involvement of peripheral nervous system in patients with SLE includes non-specific axonal, microvascular changes, and vasculitis.^[2,4]

CASE DESCRIPTION AND RESULTS

A 48-year-old woman, hailing from Tambaram, Chennai, presented to us with complaints of acute onset lower limb weakness for 1 week, which was precipitated on exertion, and was bedridden and dependent for daily activities ever since. She also had a loss of sensation of the soles and feet for the past 1 week. She had no previous history of gait instability or lower limb weakness. She had no history of syncope, seizures, loss of consciousness, fever, headache, or vomiting.

She also complained of increased hair loss for 2 weeks and bowel incontinence for 4 days.

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Corresponding Author: Dr. Shruthi Muralidharan, Department of General Medicine, SRM Medical College and Research Institute, Kattankulathur - 603203, Kancheepuram, Tamil Nadu, India. Phone: +91-9884075591. E-mail: shruthi.muralidharan@gmail.com

Patient Name:	Mrs. USHA	Sample Collection Date:	19/06/2018 10:23 AM
Age :	48 years	Lab Reference No:	X-3076/18
Gender:	Female	Report Generated Date:	26/06/2018 01:11 PM
Ward Name/Collection Centre:	Biopsy Room	Lab Name:	Neuropathology
Sample Details : H-1806190004 (Nerve)			
NERVE BIOPSY			
Nature Of Specimen: Received a nerve segment measuring 1.8cm. All processed - A1A2.			
Histopathology Report: Section from the nerve segment shows dense perivascular lymphocytic infiltrate around medium sized epineurial vessels with transmural inflammation as well as an occasional small sized vessels. Acute axonal breakdown is present. K-pal myelin stain shows moderate to severe non - uniform loss of myelinated fibers with many regenerating clusters. Perl's stain for hemosiderin is negative.			
Final Impression: Vasculitic neuropathy; Left sural nerve.			
Drafted By: Dr. Anusha S PDF Resident		Reported By: Dr. T C Yasha Professor & Head	

Figure 1: Nerve biopsy report

SRM MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE SRM Nagar, Potheri, Kattankulathur - 603203, Kancheepuram Dist..			
DEPARTMENT OF SURGICAL GASTROENTEROLOGY UPPER GI ENDOSCOPY REPORT			
NAME :	Mrs. USHA	PATIENT ID :	1102921
REF BY :	FMW I	SEX :	FEMALE
		AGE :	48
		DATE :	09-Jun-18
Pharynx & Larynx :			
Oesophagus :	Mucosa appears normal.		
QG Junction :	Normal		
Stomach			
Fundus			
Body	Mucosa appears normal.		
Antrum			
Pylorus			
Duodenum Part - I	No abnormality seen.		
Part - II			
Impression	- No abnormality noted in this study.		
Dr. A RATHNASWAMI			

Figure 2: Upper gastrointestinal scopy report

She had no history of early morning stiffness of joints, rash, decreased urine output, no history of oral ulcers, headaches, memory loss, seizure episodes, photosensitivity, malar rash, chest pain, breathlessness, or sicca-like symptoms.

She is a known case of systemic hypertension on calcium channel blockers and a recently diagnosed diabetic, on biguanides. She had a history of a bulky uterus for which hysterectomy and bilateral oophorectomy were done 3 years ago, histopathological evidence of which suggested leiomyoma with no malignant etiology.

On examination, she was conscious, oriented, and afebrile, with no signs of neuropsychiatric manifestations. She was thin built and moderately nourished. Essential tremor of

SRM MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE SRM Nagar, Potheri, Kattankulathur - 603203, Kancheepuram Dist..			
DEPARTMENT OF SURGICAL GASTROENTEROLOGY COLONOSCOPY REPORT			
NAME :	Mrs. USHA	PATIENT ID :	1102921
REF BY :	FMW I	SEX :	FEMALE
		AGE :	48
		DATE :	25-Jun-18
Rectum			
Sigmoid Colon			
Ascending Colon			
Splenic Flexure			
Transverse Colon			
Hepatic Flexure			
Ascending Colon			
Caecum			
Ileum			
Impression	Scope passed upto caecum. Two nodular granular areas of 1cm size seen in the rectum, 10cms from the anal verge the opposite walls. Both biopsied. Rest of the rectum and colon upto caecum appear normal. Vascular pattern preserved. Biopsy (A) taken from Caecum, ascending colon and Biopsy (B) taken from sigmoid colon.		
	- Two 1cm nodular lesions in the rectum, 10cms proximal to anal verge. - ? Malignant. - ? Koch's.		
Dr. A RATHNASWAMI			

Figure 3: Lower gastrointestinal scopy report

the hands was present and had a left hand hypothenar muscle wasting (h/o trauma, surgical fixation done 5 years back). She was pale, with no signs of icterus, cyanosis, clubbing, pedal edema, or lymphadenopathy. Her pulse rate was 88 beats per minute, regular and normal volume. Blood pressure was 140/100 mm of mercury and she was saturating at 99% in room air.

Cardiovascular, respiratory, and abdominal examination revealed no significant abnormality.

Central nervous system examination revealed a normal higher motor function, with bilaterally equal and reactive pupils. Essential tremor of the hands was present. Cranial nerve examination was normal. Motor system examination revealed a normal tone, with a 5/5 power of the upper limb and lower limb power being bilaterally 4/5 proximally and 3/5 power distally. Deep tendon reflexes revealed a normal reflex of the biceps, triceps, supinator, and knee. Bilateral ankle jerk was absent with plantar reflex being flexion bilaterally. Sensation, joint position sense, and vibration sense were intact. Cerebellar signs on examination were negative, and Romberg's test could not be assessed.

She was thoroughly evaluated for the above-mentioned complaints and examination findings.

Her blood investigations showed hemoglobin of 8.0, mean corpuscular volume of 81, mean corpuscular

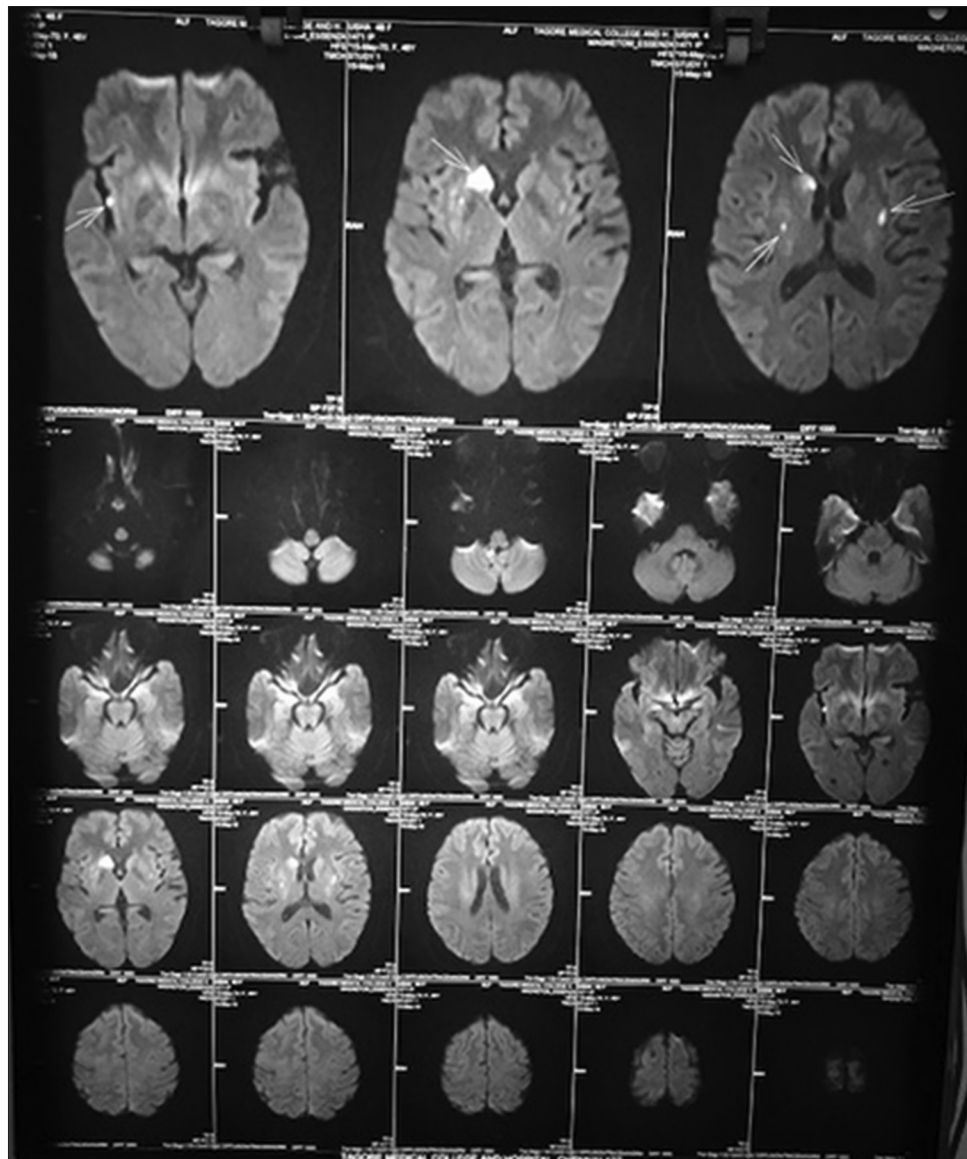


Figure 4: Magnetic resonance imaging brain

hemoglobin of 25, total counts of 14,300, neutrophils - 67, lymphocytes 26, eosinophils 01, prothrombin time 13, international normalized ratio 1.0, activated partial thromboplastin time 31, platelet counts of 290,000, HbA1c 6.5, urea 49, creatinine 0.9, sodium 137, potassium 4.5, chloride 100, HCO_3 30, calcium 8.1, phosphorus 3.5, uric acid 2.6, magnesium 1.9, total bilirubin 0.7, direct/indirect bilirubin - 0.2/0.5, alanine aminotransferase 27, aspartate aminotransferase 16, total protein 5.2, albumin 2.8, globulin 3.5, alkaline phosphate 103, thyroid-stimulating hormone 1.30, and free t4 2.05.

Urine analysis showed proteinuria with spot urine PCR of 1.21. Creatine kinase total was 08, lactate dehydrogenase 147, C-reactive protein positive (12), rheumatoid factor negative, HIV negative, HBsAg negative, iron 34, TIBC 175,

percentage transferrin saturation 19, cholesterol 61, TGL 75, HDL-c 21, LDL-c 29, and VLDL 15.

Antinuclear antibodies (ANAs) were 2+ with a positive direct Coombs test.

USG abdomen showed medical renal disease and left renal cortical cyst.

Echocardiogram showed Grade 1 diastolic dysfunction, normal left ventricular function, ejection fraction = 65%, and no regional wall motion abnormality.

Initial differentials thought of were a spinal pathology, causing a predominant lower limb weakness with bowel incontinence. Magnetic resonance imaging (MRI) spine was done which revealed a diffuse disc bulge at L3-L4,

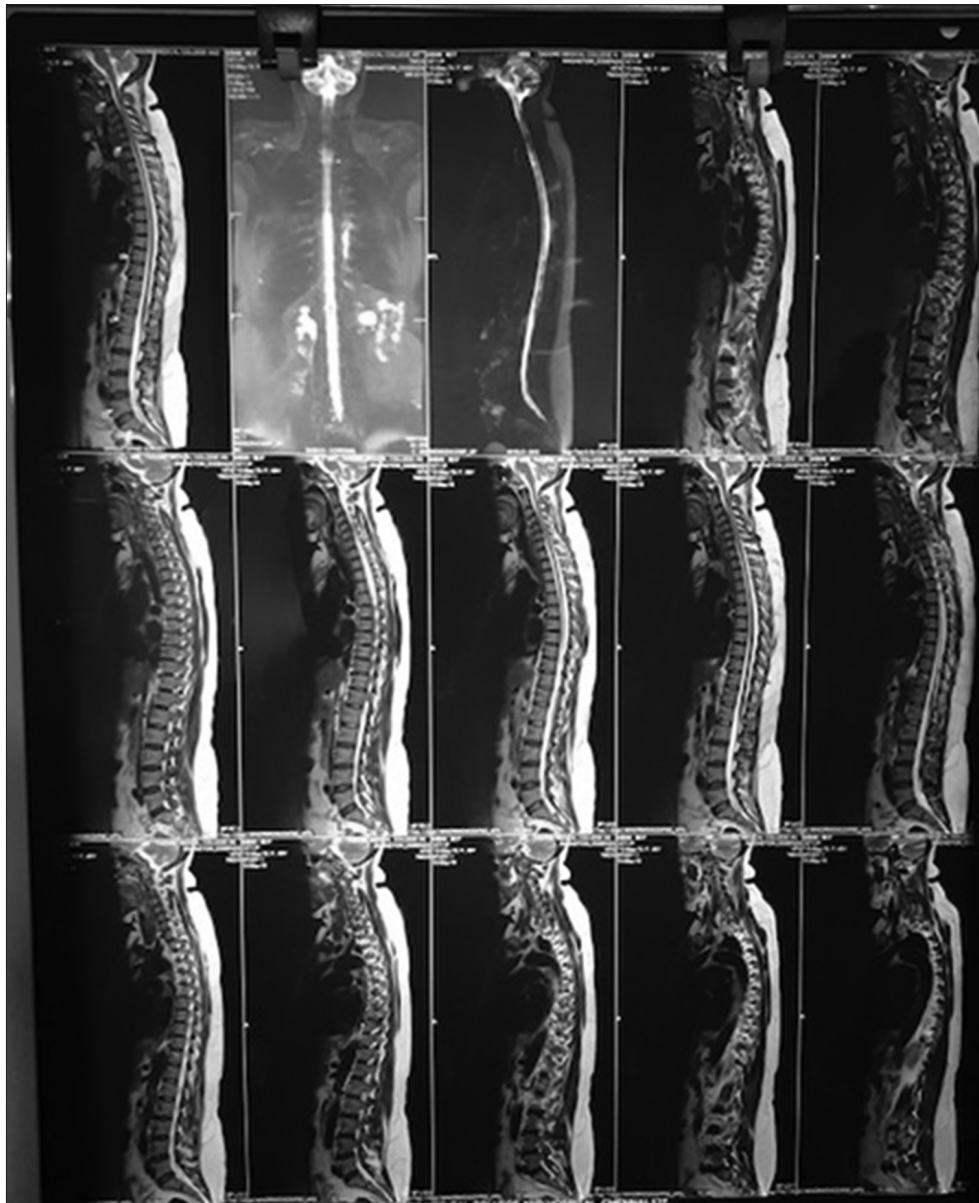


Figure 5: Magnetic resonance imaging spine

L5-S1, with nerve root compression of L3-L4. However, this did not explain the symptoms manifested. MRI brain was also done which showed - acute non-hemorrhagic infarcts involving head of right caudate nucleus, anterior limb of right internal capsule, and bilateral basal ganglia.

Hence, nerve conduction study was done - which revealed - upper limb - severe asymmetric motor sensory neuropathy - axonal type - lower limb - axonal symmetrical severe polyradiculoneuropathy. She was also evaluated for her bowel disturbance - contrast-enhanced computed tomography showed transverse colon and ileocecal region wall thickening - Crohn's etiology/malignancy. Hence, colonoscopy and biopsy were done which showed an

ulcer, biopsy of which showed non-specific granulation tissue.

Nerve biopsy was done from the sural nerve which showed a vasculitic neuropathy.

Hence, complete autoimmune workup was done which showed positive - ANA 3+, AB RO-52, SS-A AB, AB TO NUCLEOSOMES, and LOW C3 [Figures 1-5].

DISCUSSION

Thus, according to the Systemic Lupus International Collaborating Clinic criteria (1), she had clinical symptoms

Table 1: Systemic Lupus International Collaborating Clinic criteria for classification of systemic lupus erythematosus

Clinical manifestations	Immunologic manifestations
Skin	ANA > reference negative value
Acute, subacute cutaneous LE	Anti-dsDNA
Chronic cutaneous LE	Anti-Sm
Oral ulcers	Antiphospholipid
Alopecia	Low serum complement
Synovitis	Positive direct coombs test
Renal	
Prot/Cr ≥ 0.5	
RBC casts	
Biopsy ^a	
Neurologic	
Seizures, psychosis, mononeuritis, myelitis, peripheral or cranial neu-ropathies, acute confusional state	
Hemolytic anemia	
Leukopenia (<4000) or lymphopenia (<1000)	
Thrombocytopenia (<100,000)	

^aRenal biopsy read as systemic lupus qualifies for classification as SLE even if none of the other above features are present. Interpretation: Presence of any four criteria (must have at least one in each category) qualifies patient to be classified as having SLE with 93% specificity and 92% sensitivity. ANA: Antinuclear antibody, Cr: Creatinine, LE: Lupus erythematosus, Prot: Protein, SLE: Systemic lupus erythematosus

such as - neurologic manifestation involving peripheral neuropathy, renal involvement involving an elevated protein-creatinine ratio, immunological signs of a positive ANA, low serum complement, and positive direct Coombs test. Hence, having met the criteria, a diagnosis of SLE was made [Table 1].

CONCLUSION

Hence, a diagnosis of SLE was made, with an unusual presentation of a vasculitic neuropathy.

The patient was pulsed with steroid therapy, Solu-Medrol for 5 days after which she was started on maintenance doses of steroids and mycophenolate mofetil.

The patient symptomatically improved, regained power eventually with steroid therapy, and is currently ambulant for less than normal daily activities.

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