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# Fungal Diseases of Nose and Paranasal Sinuses in a Rural Tertiary Care Hospital

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## Abstract

**Introduction:** Fungi are ubiquitous in nature, and we are showered with their spores daily. In the recent past, the fungal infection has been increasing both as imported ills due to greatly enhanced international traffic and as opportunistic infection in consequence of the use of powerful cytotoxic drugs, steroids, and antibiotic therapy. Incidence of infection and death due to fungi has been grossly underestimated.

**Materials and Methods:** A total of 50 patients of Government Theni Medical College, Theni, who had clinical features suggestive of fungal infections of nose and paranasal sinuses were evaluated with standard pro forma-hematological investigations, radiological procedures, immunological procedures, and pathological diagnostics formed part of the armamentarium. Surgical management and follow-up were done.

**Results:** Out of 50 patients, 18 were male and 32 were female prominent age group being 21-40 all the patients had nasal symptoms and most of them headache. Nasal polyps and fungal mass were seen in all the patients. *Aspergillus flavus* constituted 40%, *Aspergillus fumigatus* and *Niger* accounted for 25%. Bilateral disease and involvement of ethmoidal sinus were noted in the majority of cases. Recurrence was observed in 6 of the cases, and orbital complications were observed in 8 of the cases.

**Conclusion:** About 100% of our series of 50 cases were histopathologically proven to be allergic *Aspergillus sinusitis*. CT was found to be highly effective for pre-operative evaluation and intraoperative guidance. Nasal polyposis was a concomitant feature in fungal sinusitis.

**Key words:** Allergic fungal rhinosinusitis, *Aspergillus*, Endoscopic sinus surgery, Fungal culture, Sinonasal polyposis

## INTRODUCTION

Fungi are ubiquitous in nature, and we are showered with their spores daily. Fungal infections of nose and paranasal sinus are not common in man in industrialized countries. However, in the recent past, the fungal infection has been increasing as imported ills due to greatly enhanced international traffic and as opportunistic infections in consequence of use of powerful cytotoxic drugs (as applied to the treatment of neoplasm) and also steroids and antibiotic therapy.<sup>1-3</sup>

The most common site of fungal infection in man is the lungs with or without hematogenous spread to other organs. However, the localized fungal infection can also occur in the upper respiratory tract and is more common than was previously suspected.<sup>4-6</sup>

Most fungal species which are pathogenic to human cause opportunistic infection and only dermatophytes are transmissible from host to host. The incidence of infections and death due to fungi has been grossly underestimated moreover the list of fungal species capable of producing disease in immune compromised person is increasing rapidly.

In an era with AIDS, broad spectrum of antibiotics, cytotoxic drugs and the organ transplantation, fungal infection which affect the nose and the sinus are candidiasis, rhinosporidiosis.

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*Aspergillus*, phycomycosis, actinomycosis, coccidioidomycosis, histoplasmosis, cryptococcosis, blastomycosis, sporotrichosis, and nocardiosis.

Martin and Berson noted a high incidence in South Africa which they attributed particularly to malnutrition the largest series of case involve.<sup>7-9</sup>

In our study, the fungal infections mainly presented with nasal polyps, nasal block, nasal discharge, headache, and proptosis mimicking benign or malignant tumors of the nose and paranasal sinuses.

The warm moist climate in Kerala, coastal regions of Tamil Nadu and Andhra Pradesh with its attendant high rate of allergic, hypertrophic, vasomotor rhinitis, and rhinosinusitis provide one of the prerequisites for fungal infection of upper respiratory tract. The agricultural economy of these three states also accounts for the high prevalence of the fungal infections.

Of the fungal infections of nose and paranasal sinuses, aspergillosis tops the list in terms of occurrence.

Here, the ENT Department, Government Theni Medical College Hospital with its advanced facilities serves as a referral center provides various possibilities for carrying out a study in fungal infections focusing mainly on opportunistic infections of the nose and paranasal sinuses. The lack of recognition of this disease and the scarcity of the reports prompted us to undertake the study.

## MATERIALS AND METHODS

The materials for this study were collected from patients who attended the outpatient Department of Government Theni Medical College Hospital between 2014 and 2016.

A total of 50 patients who had clinical features suggestive of fungal infection of nose and paranasal sinus were evaluated using a standard pro forma and underwent the following investigate procedures systematically as and when needed.

### Hematological Investigations

Complete hemogram, blood sugar level, serum electrolyte, serum protein, blood grouping, etc., were done as preliminary investigations to assess the general health condition as well as to rule out any underlying disorders.

### Radiological Procedure

Relevant X-ray of the nose and paranasal sinuses was taken for all patient and those who were provisionally diagnosed as fungal granulomas were subjected to CT scanning

of the nose, paranasal sinuses, and brain with contrast enhancement studies.

### Immunological Procedure

Cutaneous reactivity to *Aspergillus* species was tested by the prick test.

### Pathological Procedure

Biopsied material was placed in three sterile bottles as follow:

Bottle A containing sterile normal saline for staining with 10% potassium hydroxide bottle B with sterile normal saline for fungal culture.

Bottle A and B were transported to the microbiology lab within 1 h of the procedure.

Bottle C sent to the pathology department of histopathological examination.

Bottle A specimen was mounted with 10% potassium hydroxide. This dissolves or makes the tissue element translucent, and the fungi are easily observed when examined as wet preparation fungal elements stained black, easily visible.

Bottle B specimen was sent for fungal culture. It was cultured on potato - dextrose sugar. The best grade of white potatoes should be used. They should be washed and sliced, unpeeled at the rate 250 g/l of water and allowed to steam for 1 h in an autoclave with its exhaust open. The filtrate should be distinctly turbid. A clear filtrate is to be avoided agar and dextrose once added give serial concentration of 2% each and the whole was then tubed, autoclaved and stained for use. Properly made, each tube showed have a small button of sedimented material is its base. Potato-dextrose agar made in this manner in an excellent medium, this interval can sometimes be hastened by reducing the concentration of dextrose to 1%.

When growth was present, a bit of growth was removed from the colony, toasted apart in a drop of water and examined as a wet preparation.

Slide cultures show the structure and arrangement of the growth and true morphology and hence used.

These cultures were prepared by adding a bit of growth to a small portion of agar on a slide. A coverslip was placed on top and the slide was incubated in a moist Petri dish. After a week, when the spores had matured, the coverslip and medium were slowly removed. A drop of 10% KOH was added, and the coverslip replaced. Slide is heated gently and allowed to cool approximately 15 min. The preparation was then examined under microscope.



Some of the mycelium would have adhered to the slide and the spore head, conidiophores, etc., will be intact and seen in their characteristic arrangement. *Aspergillus* species was easily identified by the presence typical conidiophores.

Bottle C was used for routine histopathological examination of the specimen under low and high power magnification with a light microscope.

### Our Treatment Policy

The adequate management of fungal infections of the nose and sinuses at our institute revolves around five major principles.

- Timely diagnosis, usually dependent on a high index of suspicion.
- Control of local and systemic predisposing factors.
- Surgical debridement geared to level of invasiveness of the fungus.
- Antifungal treatment.
- Long-term follow-up.
- All the patients in this study underwent.

### Endoscopic Sinus Surgery

Postoperatively patients were advised to come for regular follow-up. The nasal douching was given to every patient for the 5<sup>th</sup> post-operative day after the first post-operative endoscopic examination and cleaning. Patient was treated by beclomethasone aqueous nasal spray, antihistamine, and vitamins.

The patients were requested to come for follow-up on the 15<sup>th</sup> post-operative day for endoscopic examination and cleaning and whenever possible thereafter (usually once in a month). The patient with allergic *Aspergillus sinusitis* did not require antifungal therapy. Antifungal therapy was given based on the type of fungal infection and its invasiveness (mucormycosis).

## RESULTS

All patients were evaluated as per the following parameter

- Age
- Sex
- Clinical symptoms
- Clinical sign
- Histopathological examination
- CT scan of nose and sinuses
- Surgical procedure
- Complications
- Follow-up and recurrence.

The majority of cases were in 2<sup>nd</sup> group, is between 21 and 40 years (Table 1).

Out of 50 patients study, 18 were male and 32 were female. All of them were racially Indians.

There were more female than male in this study (Table 2). Females in this study formed 64% of total number of cases.

All patients, in our study, have nasal symptoms (100%). They are nasal obstruction, nasal discharge, postnasal discharge, frequent sneezing, reduced sense of smell (hyposmia) or complete loss of smell (anosmia), and nasal bleeding.

Ocular symptoms such as proptosis, epiphora, diplopia blurring of vision in our study were 16%.

Fungal culture, in our study, showed out of 50 patients. 20 are *Aspergillus flavus*, 8 *Aspergillus fumigates*, 4 are *Aspergillus niger*, 2 are *Aspergillus terreus* (Table 8).

## DISCUSSION

The fungal diseases of the nose and paranasal sinuses encompass not one disease entity but a multitude of an entire spectrum of different diseases. We have studied different disease causes, namely allergic *A. sinusitis* (50 cases). Although the treatment of these diseases is vastly different, the presentation and clinical features are quite similar and thus they could be studied together. The authors have attempted to study these diseases under the common heading highlighting the important difference whenever required.<sup>10-12</sup>

AGE: The majority of cases in our study were between the age group of 21-40 years.

They constitute 68% of a total number of cases. This was followed by the age group between 41 and 60 years and <20 years who constitute 32% total number of cases.

This compares favorably with these studies.

Sex: In our study, there was a clear female preponderance numbering 32 out of 50 cases (64%) and male 18 out of 50 (36%) reported data by Waman *et al.* showed female preponderance with allergic *A. sinusitis* in our study was 64% female ratio (Table 3). This corresponds well with the previously mentioned study.

Symptoms: All patients in our study had nasal symptoms. The nasal symptoms included nasal obstructions, nasal discharge frequent sneezing, reduced smell (hyposmia) complete loss of smell (anosmia), and nasal bleeding. The next most common symptom was a headache was seen in 76% of our patient. The next most common symptoms

**Table 1: Age n=50**

Age	Number of patient (%)
<20	8 (16)
21-40	34 (68)
41-60	8 (16)
>60	-

**Table 2: Sex n=50**

Total number of cases	Males	Females
50	18	32

**Table 3: Age/sex/incidence n=50**

Age	Sex		Incidence		Total
	Male	Female	Male (%)	Female (%)	
<20	2	6	4	12	16
21-40	12	22	24	44	68
41-60	4	4	8	8	16
>60	-	-	-	-	-

**Table 4: Clinical symptoms n=50**

Symptoms	Number of patients (%)
1. Nasal	50 (100)
Nasal obstruction	
Nasal discharge	
Post nasal Discharge	
2. Headache	38 (76)
3. Ocular	8 (16)

**Table 5: Clinical signs n=50**

Sign	Number of patient (%)
1. Nasal polyp and fungalmass	50 (100)
2. Ocular manifestations	8 (16)
Proptosis	
Epiphora	
Diplopia	
Ophthalmoplegia	

were ocular symptoms such as epiphora, diplopia and blurring of vision comprising about 16% (Table 4).<sup>13,14</sup>

Various other studies showed that the common symptoms in allergic *A. sinusitis* are chronic nasal obstruction and postnasal discharge. These findings compare favorably with our studies.

Signs: In our study, out of 50 patients, all 50 patients presented with nasal polyps, fungal mass (100%). The ocular sign such as proptosis diplopia and ophthalmoplegia was seen 16% (Table 5).

**Table 6: Histopathology and fungal culture n=50**

Causative organism	Number of patient (%)
<i>Aspergillus flavus</i>	20 (40)
<i>Aspergillus fumigatus</i>	8 (16)
<i>Aspergillus niger</i>	4 (8)
<i>Aspergillus terreus</i>	2 (4)
No growth	16 (32)
Mucoromycosis	Nil

*A. flavus*: *Aspergillus flavus*, *A. fumigatus*: *Aspergillus fumigatus*, *A. niger*: *Aspergillus niger*, *A. terreus*: *Aspergillus terreus*, Histopathology showed all cases were *Aspergillus*

**Table 7: CT scan of nose and sinus n=50**

Sinus involvement	Number of patients (%)
Maxillary sinus	44 (88)
Ethmoidal sinus	38 (76)
Frontal sinus	24 (48)
Sphenoidal sinus	26 (52)
All sinuses	14 (28)
Orbital	10 (20)

**Table 8: Unilateral/bilateral comparison study n=50**

Sides of nose and sinuses	Number of patients (%)
Right	6 (12)
Left	8 (16)
Unilateral	14 (28)
Bilateral	36 (72)

**Table 9: Complications n=50**

BY A disease process	
Complication	Number of patient
1. Orbital complication	
Epiphora	6 (12)
Proptosis	2 (4)
2. Intracranial	Nil

**Table 10: Follow-up and recurrence**

Number of cases	Month of follow-up	Number of recurrence
16 cases	18 months	4
24 cases	12 months	2
10 cases	6 months	-

### Histopathological Examination

A total of 50 different fungal diseases have been reported in fungal sinusitis.

*Aspergillus*, ubiquitous fungus of the class ascomycetes is the most commonly encountered fungus in the environment and is the most common species encountered in fungal sinusitis generally and presumably in allergic fungal sinusitis. The latter is largely based on histopathological finding of fungi with morphologic features similar to *Aspergillus* and not on the basis of culture documentation. In our series,

100% of fungal sinusitis was histopathologically proven to be aspergillus.

In our study shows 100% allergic *A. sinusitis*. Klosssek *et al.* in his case series of 100 cases documented that 94% were histopathologically proven allergic *A. sinusitis* various other organisms have reported as pathogens in allergic *A. sinusitis* caused by different fungi. *Bipolaris specifera* B, Australians, *Aspergillus*, *Alternaria* and *Curvularia lunata*. The identification of these fungi may be related to the improved ability of microbiology laboratories to identify the diverse hyphae with variation in the conical pores (Table 6).<sup>15,16</sup>

In our study, all the cases of allergic *A. sinusitis* were sent for the fungal culture. In all the cases the material sent for culture were fungal mass taken from the infected sinus cavity. out of 50 cases 34 were culture positive for aspergillus and remaining 20 were *A. flavus*, 8 were *A. fumigates*, 4 were *A. niger*, and 2 were *A. terreus*. Rhinomucormycosis was no present in our study in histopathological examination.

In our studies, no other species of fungi was identified either on the HPE or cultural examination.

### CT Scan of Nose and Sinuses

All our patients in this series underwent CT scan preoperatively, magnetic resonance imaging (MRI) scan was not considered due to the high cost factor and relatively low amount of extra information in cases of fungal diseases of nose and paranasal sinus.

In one of the studies has reported that in t2 weighted MRI images, there is a signal void corresponding to surgically proven areas of thick inspissated allergic mucin.

The authors agree with above study with respect to the CT findings. All patients in our series with allergic *A. sinusitis* demonstrated areas of high alteration centrally within involved sinus by CT. These areas corresponded to surgical findings of thick allergic mucin. Some cases demonstrate a starry sky pattern of material, which appeared to be calcium densities on bone windows. CT scanning has been very useful in defining the full extent to the disease. *A. sinusitis* often has a mixture of high and low-density areas within the sinuses. Bone windows allow a very accurate assessment of possible invasion (Table 7).

In general, only one series in involved with *Aspergillus* most commonly the maxillary sinus. In our study, maxillary sinus (88%) is the common involvement. Next ethmoid 80%, frontal sinus 52%, sphenoid sinus 44%, and all sinuses involvement 24%.<sup>17</sup>

### Surgical Procedure

In our study, 50 cases were operated by endoscopic sinus surgery.

Endoscopic sinus surgery with less morbidity and mortality, clearance was total and recurrence rate is almost minimal in our study. Even though in our cases, we had no complication acquired in functional endoscopic sinus surgery. Only in 6 cases recurrence was noted. None of the patients developed complication and patient were discharged next day itself. This correlates well with the previous study.

We treated our patient with steroids both topically and systemically. The use of topical intranasal steroids is routine, and we restrict the use of systemic steroids. It is our experience that the topical intranasal steroids alone when taken regularly are effective in preventing recurrence of the disease. However, we feel that topical intranasal steroids and effectively only after a course of oral corticosteroids.

Antifungal agents were not used in any of our cases with allergic *A. sinusitis*. Similar reports have been published by many authors regarding the endoscopic approach is the sole approach in the treatment of allergic *A. sinusitis*. However, some author feels that external approach definitely has its place in the treatment of this condition especially in cases of orbital (or) intracranial extension of this disease.

### Complication

Complications of endoscopic sinus surgery have been as major and minor according to the degree of morbidity and treatment needed to prevent permanent serious sequelae.

Complications seen in our study includes intraoperative hemorrhage in 4 cases (8%) and no cerebrospinal leak (Table 9). Pneumocephalus and other reported major complication (Markmay *et al.*, 1994) includes orbital hematoma. Loss of vision, diplopia, epiphora, meningitis, brain abscess, and focal brain hemorrhage which were not seen in our study.

Intracranial complication can be prevented by not disturbing the mucosa lying against the roof of the ethmoid sinus. It is also worth remembering that the vertical bony wall of olfactory groove where the middle turbinate attaches to the roof of the ethmoid sinus may be extremely thin and should be avoided. The authors feel that two other guidelines may help to prevent cerebrospinal fluid leaks. (1) Instrumentations or suction cannulas should be placed into the nose or sinuses only under endoscopic guidance, (2) The basal lamella should be entered at a point farthest from the roof of the ethmoids posteriorly and inferiorly rather than anteriorly and superiorly.

Intraoperative hemorrhage severe enough to require blood transfusion is rare in our review none of them require blood transfusion. The authors agree with other reported studies that this kind of preoperative bleeding is mostly from the interruption of the sphenopalatine artery as it courses over the face of the sphenoid sinus, just above the arch of the posterior nasal choanae.

The most frequently encountered minor complication in our study 28% (14 cases) were synechiae. This adhesion was usually seen between the middle turbinate and septum or lateral wall of nose careful handling of the tissue during surgery minimizes the chance of contact between the two adjacent raw surfaces. Careful post-operative cleaning of the sinus cavity will also help in the prevention of adhesion of the 50 patient in our study, 14 had synechiae which were released in the outpatient department, and there was no recurrence.

Periorbital ecchymosis is the next minor complication and a total of 8%. These complications were seen after the endoscopic sinus surgery. This occurs usually due to violation of lamina papyracea. The authors agreed with other reported studies that the violation of the lamina papyracea occurs most commonly with uncinectomy during endoscopic sinus surgery.

### Follow-up and Recurrence

Post-treatment endoscopic surveillance is essential for long-term success since recurrent disease is common. Furthermore, the patient symptoms alone are not a satisfactory measure for persistent/recurrent disease.

In this series, 16 of our patient were followed up for a period of 18-month after surgery. 24 patients were followed up for a period of 12-month and another 10 patients followed up for 6 months. We have not lost any patient during the follow-up treatment and proper medication. 4 recurrences were noted within 12 months (Table 10).

The author feels that the complete and radical removal of fungal debris and careful regular follow up with intranasal steroids and if required systemic steroids when employed judiciously will result in the best long-term result after surgery.<sup>18-20</sup>

### CONCLUSION

This study on fungal diseases of the nose and paranasal sinuses was conducted at ENT Department Government Theni Medical College Hospital on 50 cases all are allergic *A. sinusitis*.

The most common age group with fungal disease of the nose and paranasal sinuses was between 21 and 40 years of age. There was a clear female preponderance with 64% and male cases constituted 36%.

All patients in this study had nasal symptoms. The most common symptoms was headache seen in 76% of our cases. 50 patients (100%) presented with nasal mass either polyps or fungal mass. The ocular sign was seen in 16% of cases.

In our series of 50 cases, 50 (100%) histopathologically proven to be allergic *A. sinusitis*. Fungal culture showed that *A. flavus* (40%), *Aspergillus fumigatus* (24%), *A. niger* (8%), and *A. terreus* (4%) were culture positive and no mucormycosis present.

CT scan was found to be highly valuable in pre-operative evaluation and intraoperative guidance.

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# Comparative Study of Laparoscopic Appendicectomy versus Open Appendicectomy

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## Abstract

**Introduction:** Acute appendicitis is a common indication for abdominal surgery with a life time incidence between 7% and 9% and appendicectomy is one of the most common surgical procedures.

**Aims and Objectives:** It is a stratified randomized comparative study. To study and compare laparoscopic (LA) and open appendicectomy (OA) with respect to duration of operation, post-operative pain, resumption of bowel sounds, post-operative complications, and duration of hospitalization.

**Materials and Methods:** This study is done in the Department of General surgery, Mahatma Gandhi Memorial Hospital, (Kakatiya Medical College), Warangal, Telangana, from January 2013 To September 2014. The total study sample consisted of 60 subjects. These subjects were randomly divided into two groups underwent OA and other group underwent LA. It was stratified randomized comparative study.

**Results:** In this study sample size is 60. (Lap - 30, open -30). All study samples had met inclusion criteria for acute appendicitis. The mean duration of surgery in OA is less when compared to LA. Wound infection was found to be more in OA than LA. Mean pain score was found to be more in OA than LA. Resumption of bowel sounds was earlier in LA than in OA. The mean duration of hospital stay in LA is less when compared to OA.

**Conclusion:** On analyzing the data, we find difference in outcome between laparoscopic and OA in selected patients. The LA was better than OA with regards to post-operative pain, resumption of bowel sounds, post-operative complications, and duration of hospital stay. Even though, the duration of surgery was more than the OA.

**Key words:** Appendicectomy, Appendicitis, Laparoscopy

## INTRODUCTION

Acute appendicitis is a common indication for abdominal surgery with a life time incidence between 7% and 9% and appendicectomy is one of the most common surgical procedures.<sup>1</sup>

Open appendicectomy (OA) performed through the right lower quadrant incision was first described by Charles McBurney in 1894 and has been safe and effective

operation for acute appendicitis for more than a century.<sup>2,3</sup> With the advent of new surgical techniques, the quest has been raised for minimally invasive techniques for treatment of various surgical ailments for minimum hospital stay, less surgical trauma, and a better quality of life.

In 1981, Semm, a German gynecologist performed the first laparoscopic appendicectomy.<sup>4</sup> Since, then, this procedure has been widely used. LA has emerged as safe procedure, and its potential advantages<sup>5,6</sup> are short hospital stay, early mobilization, early return of bowel function, less complication, and less post-operative pain. On the contrary, laparoscopic appendicectomy consume more operating time<sup>7,8</sup> and associated with increased costs.<sup>9</sup>

Few studies had found no such benefits<sup>10</sup> or even favored OA.

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Laparoscopic appendicectomy (LA) has gained popularity in recent years and has become one of the most performed procedures using the laparoscope globally. However, it has not become the universal gold standard for acute appendicitis as laparoscopic cholecystectomy has become for acute cholecystitis.

This study was done to compare the results of OA with laparoscopic appendicectomy in terms of duration of operation, post-operative pain, wound infection rate, and hospital stay.

## Aims and Objectives

- To study and compare laparoscopic and OA with respect to
  1. Duration of operation.
  2. Post-operative pain.
  3. Resumption of bowel sounds.
  4. Post-operative complications.
  5. Duration of hospitalization.

## MATERIALS AND METHODS

This study is done in the Department of General surgery, Mahatma Gandhi Memorial Hospital, (Kakatiya Medical College), Warangal, Telangana, from January 2013 to September 2014.

## Methodology

Written informed consent was taken from all patients of appendicitis. Complete history was taken, thorough general examination, physical examination with necessary investigations such as complete blood examination, ultrasound abdomen, and other routine investigations were done.

After confirmation of the diagnosis, the case was posted for open or laparoscopic.

Appendisectomy as per randomized allocation of two groups. Intraoperative parameters such as type of anesthesia, operative time, intraoperative complications, and reasons for conversion of LA to OA were noted.

Post-operative parameter such as post-operative pain and post-operative ileus, wound complications such as dehiscence, seroma formation, surgical site infections, and duration of hospital stay was checked. All the data were entered into pre-structured proforma and results were analyzed.

The total study sample consisted of 60 subjects. These subjects were randomly divided into two groups underwent OA and another group underwent LA. It was stratified randomized comparative study.

The study sample age was between 15 and 60 years and both the sexes were included in the study. The diagnosis of appendicitis was made on the following criteria:

- History of right lower quadrant pain or periumbilical pain migrating to the right lower quadrant with nausea and/or vomiting.
- Fever of more than 99°F
- Leukocytosis above 10,000 cells per mL.
- Right lower quadrant tenderness and guarding on examination.

The following patients were excluded from the study:

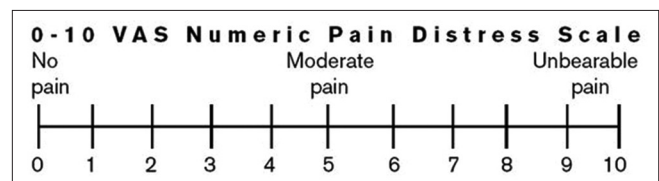
- Patients excluded if diagnosis of appendicitis was not clinically established.
- Appendicular mass.
- A palpable mass in the right lower quadrant, suggesting an appendiceal abscess treated with antibiotics and possible percutaneous drainage.
- Patients with Meckel's diverticulitis were excluded.
- Previous history of abdominal surgeries.
- Contraindication to general anesthesia (severe cardiac and/or pulmonary disease).
- Appendicitis in pregnant patients.

## Tools

- Self-structured intake proforma to collect necessary details.
- Pain scale - visual analog scale (VAS).

**VAS**

- A VAS<sup>10</sup> is a measuring instrument that subjectively measures the amount of pain that a patient feels.
- Scores range from 0 to 10 and are interpreted as “no pain” to “worst possible excruciating pain.”



- Resumption of bowel sounds was checked using stethoscope.

Post-operative complications - wound infection was recognized by erythema or purulent discharge from surgical site.

## RESULTS

In this study, 59% are males and 42% are females.

In this study, 73% inflamed appendix in LA group and all cases in OA group.

**Table 1: Age wise distribution n=60**

Age (in years)	n (%)		Total
	OA n=30	LA n=30	
15-20	8 (26.66)	6 (20.00)	14 (23.33)
21-30	14 (46.66)	20 (66.66)	34 (56.66)
31-40	4 (13.33)	4 (13.33)	8 (13.33)
41-50	3 (10.00)	0 (0)	3 (5.00)
51-60	1 (3.33)	0 (0)	1 (1.66)
	30 (100)	30 (100)	60 (100)

OA: Open appendicectomy, LA: Laproscopic appendicectomy

**Table 2: Gender wise distribution n=60**

Sex	n (%)		
	OA n=30	LA n=30	
Male	18 (60.00)	17 (56.66)	35 (58.33)
Female	12 (40.00)	13 (43.33)	25 (41.66)
	30 (100)	30 (100)	60 (100)

OA: Open appendicectomy, LA: Laproscopic appendicectomy

**Table 3: Ultrasound findings n=60**

Results	n (%)		Total
	OA n=30	LA n=30	
Normal	0 (0)	8 (26.66)	8 (13.33)
Abnormal (appendicular mass, abscess)	0 (0)	0 (0)	
Inflamed	30 (100)	22 (73.33)	52 (86.66)
	30 (100)	30 (100)	60 (100)

OA: Open appendicectomy, LA: Laproscopic appendicectomy

**Table 4: Results of surgery n=60**

Details	n (%)		Total
	OA n=30	LA n=30	
Pathology noted			
Normal	1 (3.33)	4 (13.33)	5 (8.33)
Inflamed	29 (96.66)	26 (86.66)	55 (91.66)
	30 (100)	30 (100)	60 (100)

OA: Open appendicectomy, LA: Laproscopic appendicectomy

8% showed normal appendix in LA group were operated because the patients were having tenderness in McBurneys point.

As per the reports of histopathology, inflamed appendix was noted in 86% of LA group and 96% in OA group.

Only one case was converted from LA to OA. The reason was intraoperative bleeding.

The mean pain on day 1 in OA group was 2.46 on VAS, whereas in LA group, it was 2.36.

The mean duration for return of bowel sounds in OA group was 53 h, whereas in LA, it was 44 h.

**Table 5: Duration of surgery n=60**

Parameter	OA n=30	LA n=30
Duration of surgery (min)	90.67	99.00
Range (in min)	60-120	60-150

OA: Open appendicectomy, LA: Laproscopic appendicectomy

**Table 6: Conversion to open n=60**

Parameter	Number of cases (%)
Conversion from LA to OA	1 (3.33)

OA: Open appendicectomy, LA: Laproscopic appendicectomy

**Table 7: Pain score n=60**

Details	n (%)	
	OA n=30	LA n=30
Pain score 0 to 4	28 (93.33)	29 (96.66)
Pain score 5 to 10	2 (6.66)	1 (3.33)
Mean scores	2.46	2.36

OA: Open appendicectomy, LA: Laproscopic appendicectomy

**Table 8: Return of bowel sounds n=60**

Parameter	OA n=30	LA n=30
Time taken to return of bowel sounds (in hrs)	53.33	44.67

OA: Open appendicectomy, LA: Laproscopic appendicectomy

**Table 9: Wound infection n=60**

Treatment	n (%)	
	OA n=30	LA n=30
Wound infection present	7 (23.33)	2 (6.66)

OA: Open appendicectomy, LA: Laproscopic appendicectomy

**Table 10: Duration of hospital stay n=60**

Parameter	OA n=30	LA n=30
Total duration of hospital stay (days)	8.03	4.26

OA: Open appendicectomy, LA: Laproscopic appendicectomy

Wound infection in OA group is 23% and in LA group is 7%.

The mean duration of hospital stay in OA group was 8.03 days, whereas it was 4.26 days in LA group (Tables 1-10).

## DISCUSSION

In this study, the mean duration for OA was 90 min, whereas for LA it was 99 min. It is comparable with other studies. Duration of surgery was dependent on competency and skill of the surgeon, availability of the equipment, trained staff, in most of the other studies including this study. However, one study is showing less time for LA (57.3 min)

than OA (62.4 min) as it was conducted in a well-equipped laparoscopic center. LA was associated with less pain in post-operative period in most studies. LA has less pain on VAS in post-operative period because the tissue handling, muscle cut, and nerve damage are less when compared to OA in other studies including this study.

Bowel sounds returned earlier in LA than in OA. LA allows early return of bowel sounds and early acceptance of solids.

Resumption of bowel sounds was earlier because there was less handling of bowels and nil exposure to external environment in LA when compared to OA.

Hence, acceptance of oral feeds will be earlier in LA (1.5 days) than OA (2.5 days) in this study and in other studies.

Wound infection is higher in OA group because of bacterial contamination, whereas they are less in LA group as appendix after separation from the base was placed in glove bag and was removed out. The infection rate is higher in OA group in this study as well as in other studies.

Wound infection is less in LA group in all studies. This helps in faster recovery of the patient and decreased hospital stay.

OA (8.03 days) has long duration of hospital stay because resumption of bowel movements is late, postop pain is more, wound infections are more when compared to LA (4.26 days) in this study and other studies.

LA patients are discharged earlier than OA group. This helps in earlier return to work.

Only one case was converted from LA to OA as there were adhesions and intraoperative bleeding and failure to progress in this study.

The most common reason for conversion was failure to progress due to adhesions.

## CONCLUSION

On analyzing the data, we find difference in outcome between LA and OA in selected patients.

The LA was better than OA with regards to post-operative pain, resumption of bowel sounds, post-operative complications, and duration of hospital stay. Even though, the duration of surgery was more than the OA.

All the above-mentioned are the advantages for the laparoscopic patients to resume back to their working hours at the earliest when compared to OA cases.

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# Obstetric Outcome of Teenage Pregnancy: A Prospective Study

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## Abstract

**Introduction:** Teenage pregnancy is high-risk pregnancy as it is associated with high incidence of preterm birth, low birth weight, and other complications to both fetus and the mother.

**Materials and Methods:** A prospective study was conducted in Government Theni Medical College during the period of 1 year from January 2015 to December 2015. Teenage mothers admitted in inpatient department were included and outcomes were compared with adult (20-24 years) pregnancies, selected randomly who had delivered during the same study period.

**Results:** There were total 5416 deliveries during the study period, out of which teenage pregnancy was 528 (9.7%). There were 138 (26%) teenage mothers of age 16-17 years and 390 (74%) of age group 18-19 years. As expected, maximum patients in the test group, i.e., teenagers were primigravida as compared to control group. As for mode of delivery, normal delivery in test and control was 82.9% versus 81.1%, and rate of cesarean delivery (10%) was similar in both the groups. Preterm delivery was in 8% teenage as compared to control which is 2.2%. The percentage of intrauterine fetal death was 0.7% versus 0% in test and control group. Proportion of low birth weight babies in test and control group was 7.2% versus 6%. Similarly, pregnancy related complications were also compared in teenage and control groups. It was found that postpartum hemorrhage occurred more in teenage pregnancy 1.8% versus 0.7% in test and control, respectively. The incidence of hypertensive disorders was 6.4% and 5.6% in test and control group. The proportion of babies with intrauterine growth restriction (IUGR) was 3% in test and 1.1% in control.

**Conclusions:** Teenage pregnancy can have IUGR as a major complication which is statistically proven in our study. Recognition of teenage pregnancies as high-risk and giving proper antenatal care can help these mothers to have good outcome on par with adult pregnancies.

**Key words:** Fetal outcome, Obstetric complications, Teenage pregnancy

## INTRODUCTION

Teenage pregnancy is high-risk pregnancy as it is associated with high incidence of preterm birth, low birth weight, and other complications to both fetus and the mother.<sup>1,2</sup> Younger girls are often immature physically and mentally and have lower body weight than older women<sup>3</sup> as growth may not have stopped among the girls.<sup>4</sup> They may require

more nutrients during pregnancy than older women.<sup>5</sup> The risk of death due to pregnancy related causes is double among women aged 15-19 years compared to women in their twenties.<sup>6,7</sup> In Theni, there is the tradition of childhood marriage and early pregnancy. Furthermore, lack of education and unawareness of contraceptive methods make the situation worse. The purpose of this study was to assess the extent of the problem in our hospital and to compare the outcome of teenage pregnancies with that of adult pregnancies.

## MATERIALS AND METHODS

This is a prospective study in Government Theni Medical College Teaching Hospital. All the teenage mothers

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who delivered during that period were included in the study period January 2015-December 2015, and the outcomes were compared with control group of 20-24 years selected randomly who had delivered during the same period. The maternal characteristics (age, gravidity, parity, and gestational age) and outcome (medical and obstetrical complications, mode of delivery, complications during delivery, fetal outcome, and fetal birth weight) were compared between the two groups statistical analysis were performed using pH Statz and Z-test for proportion.

## RESULTS

There were total 5416 deliveries during the study period out of which teenage pregnancy was 528. There were 138 (26%) teenagers between the age 16 and 17 years and 390 (74%) in the age group 18-19 years. Most of the teenagers were primigravida as compared to control group (Table 1).

The babies delivered preterm was 6.8% in teenage pregnancy as compared to 5.8% in control. As for mode of delivery, normal delivery in teenage and control was 82.9% versus 88.1%, respectively, and rate of cesarean delivery was similar and the incidence of instrumental delivery was more in control group. The percentage of intrauterine fetal death was 0.7% in teenage and 0 control group, respectively. As regard to low birth weight in teenage and control group, it was 7.2% versus 5.9%. Similarly, pregnancy related complications were compared in two groups. The incidence of postpartum hemorrhage was more in teenage pregnancy. Hypertension was 2.9% and 2 in teenage and control group, respectively. Furthermore, intrauterine growth restriction (IUGR) was in teenage and in control, which is the only outcome that was statistically significant (Tables 2-4).

**Table 1: Complications of teenage pregnancy compared to control group**

Complications	Teenage (%)	Control (%)	P value
Hypertension	34 (6.4)	30 (5.5)	NS
Eclampsia	4 (0.7)	6 (1.1)	NS
Postpartum hemorrhage	10 (1.8)	4 (0.7)	NS
IUGR	6 (1.1)	-	S
Congenital anomalies	4 (0.7)	2 (0.3)	NS

IUGR: Intrauterine growth restriction

**Table 2: Gestational age of teenage and control group**

Gestational age	<32 weeks (%)	32-36 weeks (%)	37-39 weeks (%)	40-42 weeks (%)	>42 weeks (%)
Teenage	10 (1.8)	26 (4.9)	254 (48.1)	228 (43.1)	10 (1.8)
Control	10 (1.8)	22 (4)	142 (44.8)	158 (47.7)	8 (1.4)

## DISCUSSION

In the developing world, one-third to one-half of the women become mothers before the age of 20 years and pregnancy related complications have become the leading cause of death among them.<sup>8,9</sup> Within South Asia, the recorded teenage pregnancy is highest in Bangladesh 35% followed by Nepal 21% and India 21%.<sup>10</sup> National Center for Health Statistics of America reported the incidence to be 13%.<sup>11,12</sup>

The incidence of the teenage pregnancy was 9.7% in our study. The range of age was between 16 and 19 years. Preterm delivery and low birth weight rates were almost similar in teenage and control groups. The rate of normal delivery was also similar between these two groups. Al-Ramahi and Saleh reported the rate of normal delivery more (83.9% vs. 79.4%) and rate of cesarean (7.1% vs. 16.8%) and instrumental delivery (4.5% vs. 1.4%) lesser in teenage pregnancy as compared to older mothers.<sup>13</sup>

Regarding pregnancy related complications such as postpartum hemorrhage, hypertension, and congenital anomalies, Ambadekar *et al.* found similar results between teenage and control groups.<sup>14,15</sup> The obstetric performance of both the test and control were almost same in our study. The only parameter that was significantly more in teenage pregnancy as compared to adult pregnancy was IUGR 4.92% versus 1.11% ( $P = 0.009$ ). The explanation for the similar result in recent studies may be due to earlier physical maturation of young girls to deal with pregnancy and labor just as the adult pregnant women do. Studies have explained earlier menarche with successive generations because of environmental changes like smaller family size, urbanization, change in life style, diet, and media and television.<sup>16-18</sup> IUGR was significantly more in teenage pregnancy group, we should work more toward reducing this problem by counseling about importance of good nutrition, providing the micronutrient such as iron, folic acid, and vitamin B complex to teenage pregnant girls. Orsin reported in their randomized trial of the effect on birth weight of a daily multiple micronutrient supplement given during pregnancy that there was average increase in birth weight of 77 g and a reduction of 25% in the rate of low birth weight who received iron and folate.<sup>19</sup> With early booking, regular antenatal visit, encouraging institutional delivery, and teenage pregnancy may not be a health problem after all.



**Table 3: Comparison of birth weight**

Birth weight	<1.5 kg (%)	1.5-2.4 kg (%)	2.5-4 kg (%)	>4 kg (%)
Teenage	4 (0.7)	34 (6.4)	486 (92)	4 (0.7)
Control	4 (0.7)	28 (5.2)	502 (92)	6 (1.1)

**Table 4: Comparison of type of delivery**

Type of delivery	Teenage (%)	Control (%)	P value
Normal delivery	432 (82.9)	448 (81)	0.56
Cesarean delivery	54 (10.2)	58 (10.7)	0.84
Delivery at home with retained placenta	18 (3.4)	6 (1.1)	0.07
Instrumental delivery	4 (0.3)	12 (2.2)	0.07
Delivery with intrauterine fetal death	0	4 (0.7)	0.67
Preterm delivery	36 (6.8)	32 (5.8)	0.67

## CONCLUSIONS

Teenage pregnancy itself is not a public health problem if regular antenatal visit and hospital delivery is encouraged. However, IUGR in teenage pregnancy is definitely a significant neonatal health problem which needs further research to reduce perinatal morbidity and mortality.

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# Comparative Study of Post-operative Analgesia Using Epidural Bupivacaine Versus Bupivacaine and Fentanyl Versus Bupivacaine and Neostigmine in Total Abdominal Hysterectomy

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## Abstract

**Introduction:** Post-operative pains following abdominal surgeries are of major concern as they cause psychological trauma and stress to the patients. Numerous studies involving multimodal post-operative analgesics strategies have been undertaken.

**Aim:** This study was undertaken in assessing efficacy of using epidural bupivacaine, bupivacaine with fentanyl and bupivacaine with neostigmine for patients undergoing total abdominal hysterectomy under general anesthesia.

**Materials and Methods:** A prospective, randomized, triple arm, single-blind, controlled study was conducted at Government Kilpauk Medical College Hospital and Government Royapettah Hospital, Chennai, for the patients undergoing total abdominal hysterectomy under general anesthesia. Informed consent from patients was obtained. The patients were divided into three groups of 20 in each based on computerized random number into Group B, Group BF, and Group BN. The patients in Group B received 10 ml of 0.125% bupivacaine, the patients in Group BF received solution containing 10 ml of 0.125% bupivacaine with fentanyl (1 mcg/kg), and the patients in Group BN received 10 ml of 0.125% bupivacaine with neostigmine (10 mcg/kg) epidurally at the start of surgical site closure. Time to first rescue analgesia, visual analog scale and Ramsay sedation score after giving epidural bolus dose, and the mean arterial blood pressure were monitored and compared.

**Results:** Mean time for first rescue analgesia in Group B was  $104.75 \pm 1.60$ , Group BF was  $289.25 \pm 3.23$ , and Group BN was  $261.00 \pm 4.13$ . The visual analog scale variation in the three groups had statistically significant difference in 60, 120, 180, and 240 min.

**Conclusion:** It was found that post-operative analgesia and other parameters were significantly advantageous in the groups of BF and BN when compared to Group B.

**Key words:** Bupivacaine, Epidural, Laparotomy, Neostigmine and fentanyl

## INTRODUCTION

Acute pain in the post-operative setting can have adverse physiological and psychological effects due to the stress

hormone response induced by anesthesia and surgery. The main objective of providing post-operative analgesia is to make the patient comfortable without pain, promote early ambulation, and improve respiratory function and early restoration of his/her routine life. In abdominal surgeries, the incidence of post-operative pain is higher causing restriction of the diaphragmatic movements.<sup>1</sup> This could result in basal atelectasis, respiratory tract infections due to decreased effort in coughing out the secretions, deep venous thrombosis due to poor ambulatory effort, all of which lead to increased duration of hospital stay, expenditure, morbidity and mortality. Providing epidural

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block with local anesthetic drugs in these patients can efficiently relieve post-operative pain.<sup>2</sup> Bupivacaine is one of the commonly used drugs for post-operative analgesia. Bupivacaine belongs to aminoacyl group of local anesthetics. It has a P<sub>ka</sub> of about 8.1 with protein binding capacity of 95%. It is highly potent has a slow onset and longer duration of action. 0.25% and lower concentrations of bupivacaine are preferred for use in obstetric patients and out patients for day care procedures. Usage of bupivacaine alone has its own disadvantages with regards to the dosing and concentration leading to subsequent hypotension that may ensue. Thus came the need for adjuvants such as opioids and alpha-2 agonists. Neostigmine has also been used in numerous studies and found advantageous in prolonging the duration of the epidural while reducing the concentration of bupivacaine. Fentanyl is 800 times more lipid soluble than morphine and rapidly is absorbed from the epidural space and cerebrospinal fluid (CSF). Its onset of action is very rapid which is about 15-30 min and its duration of action is 2-5 h.<sup>3,4</sup> The initial epidural bolus dose of fentanyl is 5 mcg/kg. Pruritus is the most common side effect. Neostigmine, an anticholinesterase drug, which is used to antagonize nondepolarizing muscle relaxants, has been tried for post-operative analgesia as an off-label use. Being a quaternary amine, it does not cross blood-brain barrier. Epidural neostigmine provides analgesia through M1 and M2 receptors in the spinal cord, inhibiting the breakdown of acetylcholine. It also prolongs and intensifies the analgesia increasing cyclic guanidino-mono phosphate by generating nitric oxide. It prolongs motor blockade when combined with a local anesthetic. Neostigmine also displays peripheral and supraspinal analgesic activity, however, the dose necessary to achieve this seems to be higher. Several studies have demonstrated that the use of epidural neostigmine is associated with lesser adverse effects and the proposed mechanism of analgesia is by drug spreading into CSF at the rate of 1/10<sup>th</sup> the epidural dose.<sup>5,6</sup>

### Aim

The aim of the study is to compare “The post-operative analgesic efficacy of epidural bupivacaine, bupivacaine plus fentanyl and bupivacaine plus neostigmine in adults is undergoing total abdominal hysterectomy under general anesthesia” by assessing:

1. Duration of post-operative analgesia, i.e., time interval between epidural drug bolus and time for first rescue analgesia
2. Visual analog scale after giving first epidural bolus dose
3. The Ramsay sedation score after giving first epidural bolus dose
4. Mean arterial blood pressure (MAP) perioperatively extending 12 h postoperatively.

## MATERIALS AND METHODS

A prospective, randomized, triple arm, single-blind, controlled study was conducted at Government Kilpauk Medical College Hospital and Government Royapettah Hospital, Chennai, for the patients undergoing total abdominal hysterectomy under general anesthesia. Informed consent from patients was obtained. Female patients aged 20-60 years, belonging to ASA PS I and II who have given valid informed consent and undergoing elective total abdominal hysterectomy under general anesthesia. The patients refusal, contraindications to epidural anesthesia, and patients with allergy or sensitivity to the drugs used were excluded from the study.

A total of 60 patients were included in the study. The patients were divided into three groups ( $n = 20$ ) in each based on computerized random number into Group B, Group BF, and Group BN. The patients in Group B received 10 ml of 0.125% bupivacaine, the patients in Group BF received solution containing 10 ml of 0.125% bupivacaine with fentanyl (1 mcg/kg), and patients in Group BN received 10 ml of 0.125% bupivacaine with neostigmine (10 mcg/kg) epidurally at the starting of surgical site closure. Routine monitoring included electrocardiogram, pulse oximetry, and noninvasive blood pressure. Intravenous (IV) cannulation was done with 18 G venflon. Premedication with injection of glycopyrrolate 6 mcg/kg IV, injection of midazolam 0.01 mg/kg IV, and injection of fentanyl 2 mcg/kg IV was administered. Under sterile aseptic precautions an epidural catheter was placed at the level of T12-L1 intervertebral space with 5 cm *in situ*. After ensuring that neither blood nor CSF was aspirated via catheter, a test dose of 3 ml 2% lignocaine with adrenaline (1:2,00,000) dilution was given.

Patients' vitals including heart rate, respiratory rate, MAP, and oxygen saturation are measured at the following time intervals 15, 30, 45, 60, 90, 120, and 180 min and hourly till 12 h in the post-operative period. Only surgeries completed within 200 min were taken for this study. Time for first rescue analgesia, visual analog scale and Ramsay sedation score after giving epidural bolus dose, and MAP were observed hourly till 12 h into the post-operative period.

The patient was then made to lie in supine position. Preoxygenated with 100% oxygen for 3 min. Then, it induced with injection of propofol 2 mg/kg and atracurium 0.5 mg/kg. The patient was intubated with appropriate sized endotracheal tube and secured after ensuring bilateral air entry. Maintenance was with nitrous oxide and oxygen in the ratio of 2:1 and sevoflurane 2 vol%. Injection of fentanyl was given 1 mc/kg 1 h after start of incision.

The epidural drug administration was given at the time of wound closure according to the patient belongs to. At the end of surgery, the patient was reversed and extubated after satisfying Aldrete criteria.

### Statistical Analysis

Descriptive statistics was done for all data and reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analyzed with the unpaired *t*-test and ANOVA single factor test. Categorical variables were analyzed with the Chi-square test and Fisher exact test. Statistical significance was taken as  $P < 0.05$ . The data were analyzed using SPSS version 16 and Microsoft Excel 2007.

## RESULTS

The pre-operative heart rate, respiratory rate, MAP, and oxygen saturation were recorded before administering epidural block.

Figure 1 shows mean time for first rescue analgesia in Group B was  $104.75 \pm 1.60$ , Group BF was  $289.25 \pm 3.23$ , and Group BN was  $261.00 \pm 4.13$ . The three groups were comparable with respect to the time for first rescue analgesia. Analysis of variants in Figure 1 showed they were highly statistically significant ( $P < 0.05$ ).

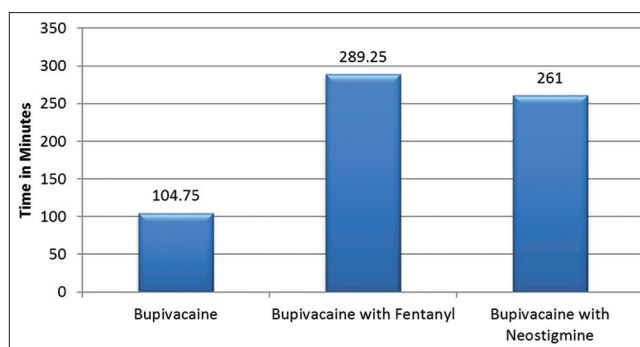
Visual analog scale variation in the three groups and the analysis of variants in Table 1 showed they were highly statistically significant.

Table 2 shows the Ramsay sedation score after giving epidural bolus dose in the three groups and they were found to be comparable. Analysis of variants in Table 3 showed they were highly statistically significant.

Table 3 shows the MAP variation in the three groups which were found comparable. There was no statistically significant difference in MAP neither intraoperatively nor postoperatively until 12 h of observation.

## DISCUSSION

Out of 60 patients ( $n = 20$ ) in this study, the results of our study showed there were no significant difference in age distribution, weight distribution, and gender status among the three groups ( $P > 0.05$ ). The time for first rescue analgesia in Group B was  $104.75 \pm 1.60$ , Group BF was  $289.25 \pm 3.23$ , and Group BN was  $261.00 \pm 4.13$ . Based on this evaluation, the duration of post-operative analgesia in Group BF and Group BN was found to be much higher when compared to Group B. Tekin *et al.*, compare the post-operative analgesic activity of the neostigmine and fentanyl when



**Figure 1: Comparison of average time for first rescue analgesia in Group B, Group BF, and Group BN**

used as an additive to bupivacaine in patients undergoing abdominal hysterectomy under general anesthesia showed that the duration of post-operative analgesia and total analgesic consumption was better when either fentanyl or neostigmine is added as additives to bupivacaine than bupivacaine alone.<sup>4</sup> Ross *et al.* did a randomized controlled study on a group of obstetric patients using bupivacaine and neostigmine as patient controlled epidural analgesia in 40 healthy patients posted for elective cesarean section. Epidural neostigmine infusion reduced bupivacaine requirement by 19% in all patients and 25% in those with  $>4$  h of treatment ( $P < 0.05$  for both). It was also found that these patients also experienced mild sedation.<sup>5</sup> Shehab and Salman conducted a study in women who underwent open abdominal hysterectomy for dysfunctional uterine bleeding under epidural combined with general anesthesia. The results showed that the mean duration of post-operative analgesia was significantly longer in the dexamethasone/levobupivacaine group compared with groups neostigmine/levobupivacaine and levobupivacaine, with significantly longer duration in the neostigmine/levobupivacaine group compared with group levobupivacaine.<sup>6</sup> Nakayama *et al.* evaluated the analgesic effects of epidural neostigmine in adult patients undergoing abdominal hysterectomy. 45 ASA I patients posted for elective abdominal hysterectomy were enrolled in this study. These patients were randomly divided into three groups. Here, the duration of post-operative analgesia was higher in the  $10 \mu\text{g}$  group than  $5 \mu\text{g}$  group.<sup>7</sup> Lauretti *et al.* compared the post-operative analgesic property of intra-articular and epidural neostigmine in patients undergoing knee surgery under combined spinal-epidural anesthesia. The time (min) for first rescue analgesia was much longer in both the  $1 \mu\text{g/kg}$  epidural neostigmine (EG) Group and  $500 \mu\text{g}$  intra-articular neostigmine (AG) groups ( $P < 0.05$ ). The pre-operative hemodynamic parameters were comparable between the three groups (Group B, Group BF, and Group BN). Post-operative sedation and visual analog scores were also significantly higher in Group BF and Group BN when compared to the Group B.<sup>8</sup> Cossu *et al.* found that neostigmine was used as an adjuvant to local anesthetics for neuraxial blockade

**Table 1: Comparison of visual analog scale after giving epidural bolus dose in Group B, Group BF, and Group BN**

Time after giving epidural dosage (in min)	Bupivacaine (Group B)	Bupivacaine with fentanyl (Group BF)	Bupivacaine with neostigmine (Group BN)	P value
60	3.55±0.95	0.25±0.12	0.45±0.14	<0.0001
120	7.85±0.41	0.60±0.18	1.15±0.17	<0.0001
180	5.50±0.36	0.75±0.16	1.25±0.18	<0.0001
240	4.75±0.23	1.55±0.44	3.75±0.68	<0.0001
300	4.80±0.26	6.30±0.65	6.55±0.47	0.028
360	4.60±0.26	4.80±0.42	4.70±0.29	0.912
420	4.80±0.24	3.90±0.24	3.90±0.22	0.009
480	4.55±0.24	3.60±0.29	4.05±0.22	0.036

**Table 2: Comparison of Ramsay sedation score after giving epidural bolus dose in Group B, Group BF and Group BN**

Time after giving epidural bolus dose in (min)	Bupivacaine (Group B)	Bupivacaine with fentanyl (Group BF)	Bupivacaine with neostigmine (Group BN)	P value
Baseline	2.00±0.00	2.00±0.00	2.00±0.00	1.000
60	1.85±0.08	2.60±0.15	2.10±0.07	<0.0001
120	2.00±0.00	3.15±0.15	2.00±0.00	<0.0001
180	2.00±0.00	3.45±0.11	2.00±0.00	<0.0001
240	2.00±0.00	3.10±0.07	2.00±0.00	<0.0001
300	2.00±0.00	2.60±0.11	2.00±0.00	<0.0001
360	2.00±0.00	2.35±0.11	2.00±0.00	<0.0001
420	2.00±0.00	2.00±0.00	2.00±0.00	1.000
480	2.00±0.00	2.00±0.00	2.00±0.00	1.000
540	2.00±0.00	2.00±0.00	2.00±0.00	1.000

**Table 3: Comparison of MAP changes in Group B, Group BF, and Group BN**

Time (in min)	Bupivacaine (Group B)	Bupivacaine with fentanyl (Group BF)	Bupivacaine with neostigmine (Group BN)	P value
Baseline	90.45±2.34	90.95±2.06	91.55±2.09	0.937
15	80.50±1.85	83.05±1.81	83.35±1.70	0.468
30	84.15±1.58	84.60±1.67	84.90±1.75	0.950
45	84.30±1.34	86.60±1.62	86.55±1.71	0.500
60	84.95±1.46	86.30±1.61	86.15±1.77	0.812
75	84.80±1.34	86.70±1.77	86.75±1.90	0.650
90	84.90±1.42	86.15±1.76	86.35±1.87	0.807
180	87.35±1.93	86.75±1.65	86.80±1.87	0.967
120	84.65±1.45	86.20±1.67	86.80±1.87	0.646
240	87.60±2.41	87.15±1.70	87.30±1.97	0.988
300	83.85±1.65	86.45±1.74	86.60±1.91	0.471
360	85.95±1.86	86.50±1.72	86.60±1.91	0.964
420	86.25±1.84	86.95±1.68	86.60±1.93	0.964
480	86.35±1.84	87.15±1.75	87.40±1.94	0.916
540	86.65±1.87	87.35±1.69	87.85±1.96	0.899
600	86.40±1.67	87.55±1.91	88.15±2.12	0.806
660	86.55±1.91	87.40±1.82	87.00±1.90	0.950
720	86.45±1.81	87.65±1.87	87.15±1.99	0.903

MAP: Mean arterial blood pressure

in obstetric patients to find out its efficacy in producing post-operative analgesia. From this study, they found that the epidural addition of neostigmine to local anesthetic like bupivacaine or ropivacaine resulted in greater analgesic response and greater patient tolerance when compared to the intrathecal administration of neostigmine. Post-operative requirement of subsequent doses of local

anesthetics was also significantly reduced ( $P < 0.05$ ).<sup>9</sup> Kaya *et al.* found that in patients posted for elective cesarean study under combined spinal-epidural using epidural neostigmine showed that total duration of post-operative analgesia and global pain satisfaction scores were reduced in the neostigmine group. There were no significant MAP variations found. The parameters were also statistically



significant when compared to the baseline values. Adverse effects such as pruritus and gastrointestinal side effects such as nausea and vomiting were significantly less in Group BN and Group B, but increased in Group BF where fentanyl was used.<sup>10</sup> Roelants and Lavand'homme studied the use of neostigmine and clonidine for labor analgesia in obstetric patients. They found that the post-operative analgesia was similar in both groups, the patients in neostigmine group had fewer side effects like hypotension.<sup>11</sup> In 2012, Jain *et al.* did a study in 45 patients posted for total knee replacement surgery. They compared the post-operative analgesic efficacy of low dose intrathecal neostigmine as an adjuvant to fentanyl and bupivacaine for total knee replacement and found out that the total duration of post-operative analgesia was significantly high in fentanyl and neostigmine group ( $P < 0.001$ ). The total number of rescue analgesia required was significantly higher in bupivacaine group ( $P < 0.05$ ). They also found that epidural neostigmine did not cause any adverse gastrointestinal side effects such as nausea and vomiting.<sup>12</sup>

## CONCLUSION

The duration of post-operative epidural analgesia was prolonged when either fentanyl or neostigmine was used as an adjuvant to epidural bupivacaine. However, it was found that fentanyl caused adverse effects such as pruritus, nausea, and vomiting. Thereby, epidural neostigmine may be considered as a safe adjuvant to bupivacaine, since the duration of post-operative analgesia was comparatively similar in both groups (Group BF and Group BN).

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# Efficiency of Pentazocine for Post-operative Analgesia: A Comparative Prospective Study

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## Abstract

**Background:** Pentazocine a relatively new, potent, opioid analgesic used for post-operative analgesia and appears to be longer lasting and has minimal side effects.

**Materials and Methodology:** Randomized comparative prospective study of 75 patients of the American Society of Anesthesiologist Physical Status I and II, aged between 25 and 45 years, of sexes and requiring general anesthesia particularly for upper abdominal surgery, received pentazocine by different routes. After surgery, when patients had Aldrete recovery score around 9-10 patients received pentazocine 300 mcg by various routes of administration as follow: Epidural, intramuscular, intravenous slow bolus over 10 min, continuous infusion over 12 h and sublingual tablets. The patients were studied for 48 h postoperatively. Observation was made half an hourly for 2 h and then hourly. Data collected, tables formulated as per meaningful duration of action observed and as per need of simplicity for analysis. Respiration, pulse rates and blood pressure was monitored. Assessment of pain was carried out with numeric rating scale.

**Results:** Meaningful duration of analgesia by different routes were as follows; epidural: 30-35 h in 53.33% of group population, intramuscular: 6-8 h in 86.67% of group population, intravenous bolus: 5-6 h in 73.33% of group population, intravenous infusion: 16-20 h in 60% of group population, and sublingual: 5-6 h in 66.66% of group population. Side effects observed due to pentazocine considering whole population as study sample were urinary retention in three patients (4%), nausea in five patients (6.67 %), vomiting in two patients (2.66%). No cardiorespiratory depression was observed in any of the patient and route of administration technique.

**Conclusion:** Pentazocine produces longer duration of meaningful analgesia by all techniques and where epidural route is best.

**Key words:** Epidural, Intramuscular, Intravenous bolus, Intravenous infusion, Pentazocine, Sublingual route

## INTRODUCTION

Pain is a subjective phenomenon which is perceived only by the sufferer and observer can assess its magnitude from what the sufferer tells him. It is fifth vital sign and pain free life is right of every patient. Any method of post-operative pain relief must be effective, safe, and feasible. Post-operative pain is often short lived through severe to bring a train of avoidable complications that may jeopardize the patient's recovery. Immobility induced

by fear, increases the liability to deep vein thrombosis,<sup>1</sup> bed sores, hypostatic pneumonia,<sup>2</sup> muscle wasting, urinary retention, and constipation<sup>3,4</sup> and it may substantially retard convalescence.<sup>5-7</sup> The optimal pain relief for upper abdominal surgery should ensure that pain should not affect depth and frequency of spontaneous breaths to avoid basal atelectasis and pneumonias.<sup>2</sup> It should also ensure that patient should not lose coughing ability due to sedation and should be comfortable in bed for initial 48 h after surgery when pain sensation is at peak. There are factors other than incision which also decides post-operative pain perception, e.g., age, sex, premedication, anesthetic agents used, and psychological factors. Hence, pain therapy should be multimodal<sup>6,7</sup> to take care of all aspects of pain pathophysiology. Recent advances in pharmacology have resulted in the introduction of few potent analgesics for post-operative pain, e.g. pentazocine. Several opioid drugs such as pethidine, pentazocine, morphine, and others have

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been used for post-operative pain relief and by different routes such as intramuscular, intravenous, sublingual intrathecal, and epidural. Our study includes pentazocine which is relatively newer opioid used for pain relief by various routes. In 1969, researchers at Reckitt and Colman had spent 10 years attempting to synthesize an opioid compound “with structures substantially more complex than morphine (that) could retain the desirable actions while shedding the undesirable side effects (addiction).”<sup>8</sup> Reckitt found success when researchers synthesized RX6029 which had showed success in reducing dependence in test animals. RX6029 was named pentazocine and began trials on humans in 1971.<sup>9</sup> By 1978 pentazocine was first launched in the UK as an injection to treat severe pain, with a sublingual formulation released in 1982. Pentazocine 0.2-0.4 mg intramuscularly gave pain relief probably as well as that of morphine 10 mg.<sup>10</sup> It is highly lipophilic thebaine derivative which is a narcotic antagonist with potent long lasting antinociceptive (agonist) action. Pentazocine hydrochloride is a white powder which is weakly acidic and with limited solubility in water. Pentazocine has low abuse potential, so the drug has potential for treating narcotic addiction. The most frequent side effects are drowsiness, nausea, vomiting, sweating and dizziness, respiratory depression, euphoria, miosis, and dry mouth. Treatment of adverse effects is naloxone.<sup>11</sup> Pentazocine, a relatively new drug has also been used for post-operative analgesia. It appears to be longer lasting than morphine and pethidine. One of the aims of this study is to show the importance of pentazocine as a post-operative analgesic.

This study consists of 75 patients undergoing various major general surgical procedures, particularly involves upper abdominal surgeries. Patients from both the sexes varying over a range of 25-45 years are considered. Randomly grouped into five group based on route of administration of pentazocine in post-operative period for analgesia. Aim of the study is to study pentazocine in relation to mean duration of analgesia by different routes, quality of analgesia based on predecided pain scale, side effects of drug with different routes and cardiorespiratory instability.

## MATERIALS AND METHODS

After obtaining institutional review board approval and written informed consent of patients, this prospective study was carried out in 75 the American Society of Anesthesiologist (ASA) Grade I and II adult who were planned for elective major surgical procedures, particularly involving upper abdomen. The patients were from both the sexes varying over a range of 25-45 years. 75 patients randomly grouped in five groups as per routes of pentazocine administered for study, e.g., epidural,

intramuscular (anterolateral aspect of thigh), intravenous bolus (over 10 min), intravenous continuous infusion (over 12 h), and sublingual. Each group includes 15 patients. When there was a recovery score of 9-10, each patient has given pentazocine either one of the technique which were mentioned above. Patients who were known to be hypersensitivity to drug, severe impairment of hepatic, pulmonary or renal function, myxedema or hypothyroidism, adrenal cortical insufficiency, central nervous system depression or coma, toxic psychosis, prostatic hypertrophy or urethral stricture, acute alcoholism, delirium tremors, and kyphoscoliosis were excluded from study. The presence of any medical disease other than the one for which they were being operated was ruled out. The patients were routinely investigated for hemoglobin, blood sugar, blood, urea, serum electrolytes, liver function test, X-ray chest, and electrocardiogram (ECG). Investigations were within normal limits.

After taking the patient on the operation table, a multipara monitor was attached and the baseline heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were noted down. A wide bore intravenous cannula was inserted for giving the intravenous fluids. After intravenous access, an infusion of ringer's lactate (10-15 ml/kg) comprised preloading. The patients were premedicated with glycopyrolate 5 mcg/kg, midazolam 30 mcg/kg, fentanyl 2 mcg/kg, ondansetron 4 mg 5 min before induction of anesthesia on the operation table. General anesthesia was induced with propofol 2 mg/kg, atracurium 0.5 mg/kg and after 3 min of induction, orotracheal intubation performed with cuffed endotracheal tube of adequate size. General anesthesia was maintained by oxygen, air, sevoflurane, and atracurium in closed circuit with soda lime. After operation, residual neuromuscular paralysis was reversed by neostigmine 50 mcg/kg with glycopyrolate 10 mcg/kg. The patients extubated after adequate recovery from anesthesia and shifted to recovery room. Postoperatively patients ECG, pulse, blood pressure, and respiration were monitored continuously with automated multipara monitors till recovery score was 9-10. Recovery score was monitored as per Aldrete and Kroulik<sup>12</sup> scoring system for adequate recovery in postanesthesia care unit.

Total score of 10, when recovery score was 9-10 each patient received pentazocine by one of the route mentioned above (Chart 1).

Epidural dose of pentazocine hydrochloride 300 mcg diluted to 10-12 ml with normal saline given through 20 G epidural catheter inserted in post-operative period in left lateral position with 18 G Tuohy needle by loss of resistance technique at L<sub>2-3</sub> spinal level. Catheter advanced

**Chart I: Aldrete and Kroulik index**

Assessment parameters	Condition	Grade
Muscle activity	Moves 4 extremities	2
	Moves 2 extremities	1
	Moves 0 extremities	0
Breathing	Deep, cough	2
	Limited, dyspnea	1
	Apnea	0
Consciousness	Fully awake	2
	Awakeness when called	1
	Does not respond to call	0
Circulation (AP)	±20% of preanesthesia level	2
	±20% to 49% of preanesthesia level	1
	±50% of preanesthesia level	0
SpO <sub>2</sub>	>92% at ambient air	2
	>90% with O <sub>2</sub>	1
	<90% with O <sub>2</sub>	0

SpO<sub>2</sub> - Percentage hemoglobin saturated with oxygen, AP- arterial pressure

4 cm inside epidural space and confirmed by 3 ml test dose with 2% xylocaine and adrenaline to avoid subarachnoid or intravascular malpositioning.

Intramuscular injection of pentazocine hydrochloride 300 mcg at anterolateral aspect of thigh.

Intravenous bolus of pentazocine hydrochloride 300 mcg slowly over 10 min through a intravenous line which was secured preoperatively (diluted in 100 ml of normal saline with infusion rate of 10 ml/min).

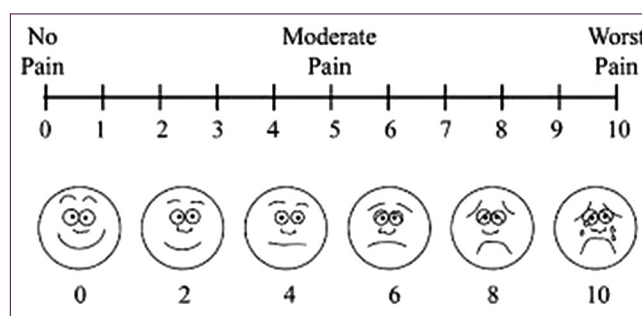
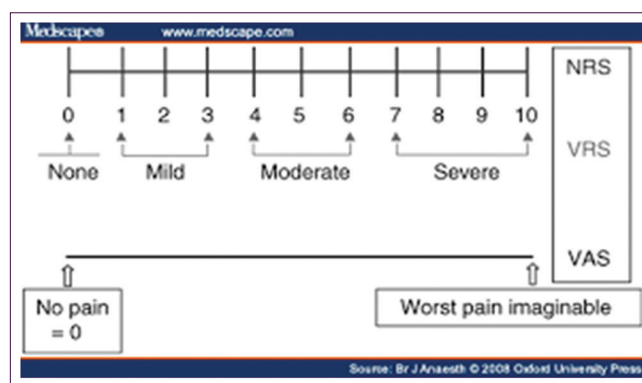
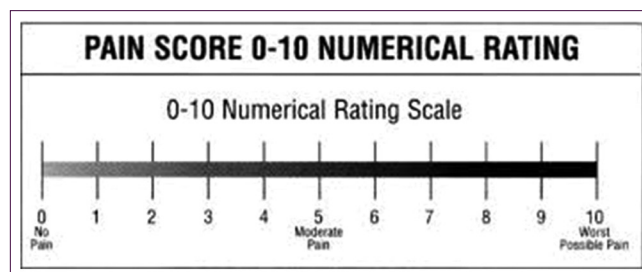
Intravenous continuous infusion of pentazocine hydrochloride 300 mcg over 12 h. For this separate vein was secured on the dorsum of hand with 20 G intravenous cannula. Infusion rate was adjusted in such a way that the infusion would run over 12 h and was labeled (pentazocine hydrochloride 300 mcg diluted in 96 ml of normal saline with infusion rate of 8 ml/h).

Sublingual pentazocine hydrochloride tablet (0.2 mg tablet, one and half tablet at a time) postoperatively.

The patients were studied for 24-48 h postoperatively. Throughout post-operative period intravenous fluids were given as per need of patients. Observation was made ½ hourly for initial 2 h and then hourly until the end. Respiratory rate and pulse rate were monitored manually by counting rate with wrist watch while blood pressure was measured with mercury sphygmomanometer.

Assessment of pain was carried out with numeric rating scale (NRS), which is similar to visual analog scale. Scale includes single line drawn on paper and evenly calibrated in 10 divisions. Scale starts from 0 (no pain) from extreme left to maximum scale of 10 (worst pain ever felt) on

extreme right of page. The patients are instructed to circle the number that represents the severity of pain they experiencing at the time of evaluation. NRS is validated pain scale for pain assesment.<sup>13</sup> Aim was to control pain and keep it minimal possible and tolerable level. Meaningful pain relief, when NRS score was 0-3. So for data collection and analysis pain score 0-3 is considered adequate pain relief, beyond that is not acceptable and was supplemented by other multimodal ways of analgesia.



Note was taken of side effects such as nausea, vomiting, itching, drowsiness, respiratory depression, retention of urine and any neurological deficit, sedation, and hypotension. The total duration of analgesia and quality of analgesia were noted. Surgeons were advised not to give any analgesics or sedation in post-operative period to avoid biases.

### Observations and Data

This is prospective study was carried out in 75 ASA Grade I and II adults who were planned for elective

major surgical procedures, particularly involving upper abdomen. 75 patients randomly grouped in five (each group includes 15 patients) groups as per routes of pentazocine administered. Results are expressed in percentage to compare with different groups. Duration of analgesia is in hours while the quality of analgesia is as per NRS score. Meaningful duration of analgesia means 50% or more of patients showing pain relief up to 0-3 NRS score of analgesia.

Table 1 shows young patients' age between 25 and 30 years has maximum part of study population, while older population is less in number. Pain threshold changes with age, so age distribution has impact on meaningful pain relief.

Table 2 shows male patients have maximum part of study population which is 72%, while females are less in number. Pain threshold changes with sex, so sex distribution has impact on meaningful pain relief.

Table 3 shows male and female patients' distribution in percentage in relation to age young males have maximum part of study population which is 21.33%, while old females are less in number. Pain threshold changes with age and sex, so age and sex distribution has impact on meaningful pain relief.

Table 4 shows types of operations done in male and female patients. Distribution in percentage in relation to surgery performed shows maximum number of surgeries were gastrojejunostomy with vagotomy and pyelolithotomy. Pain threshold and side effects change with type surgery. Hence, types of operations have impact on meaningful pain relief side effects.

Table 5 shows pain score after 30 min of pentazocine injection is considered for statistical analysis. Meaningful pain relief is NRT pain score 0-3.

53.33% patients show meaningful pain relief (NRS 0-3) for 30-35 h after single epidural bolus of 300 mcg pentazocine.

Table 6 shows pain score after 30 min of pentazocine injection is considered for statistical analysis. Meaningful pain relief is NRT pain score 0-3.

86.67% patients show meaningful pain relief (NRS 0-3) for 6-8 h after single intramuscular injection of 300 mcg pentazocine.

Table 7 shows pain score after 30 min of pentazocine injection is considered for statistical analysis. Meaningful pain relief is NRT pain score 0-3.

73.33% patients show meaningful pain relief (NRS 0-3) for 5-6 h after single intravenous bolus (over 10 min) of 300 mcg pentazocine.

**Table 1: Age distribution in the population studied**

Age group (in years)	Number of cases (%)
25-30	22 (29.33)
31-35	18 (24)
36-40	19 (25.33)
41-45	16 (21.33)
Total	75 (99.99)

**Table 2: Sex distribution in the population studied**

Sex	Number of cases (%)
Males	54 (72)
Females	21 (28)
Total	75 (100)

**Table 3: Distribution of males and females in the different age groups**

Age group in years	Number of cases (%)		
	Males	Females	Total
25-30	16 (21.33)	6 (8.0)	22 (29.33)
31-35	12 (16.00)	6 (8.0)	18 (24.00)
36-40	13 (17.33)	6 (8.0)	19 (25.33)
41-45	13 (17.33)	3 (4.0)	16 (21.33)
Total	54 (71.99)	21 (28.0)	75 (99.99)

**Table 4: Types of operations performed in this study**

Types of operation performed	Number of cases (%)
Gastrojejunostomy with vagotomy	29 (38.66)
Cholecystectomy	10 (13.33)
Pyelolithotomy	13 (17.33)
Exploratory laprotomy	06 (08.00)
Pyelerooplasty with vagotomy	04 (05.33)
Repair of epigastric hernia	06 (08.00)
Spleenectomy	01 (01.33)
Partial gastrectomy with resection anastomosis	02 (02.66)
Nephrectomy	02 (02.66)
Highly selective vagotomy	02 (02.66)
Total	75 (100)

Table 8 shows pain score after 30 min of pentazocine injection is considered for statistical analysis. Meaningful pain relief is NRT pain score 0-3.

60% patients show meaningful pain relief (NRS 0-3) for 16-20 h after intravenous infusion (over 12 h) of 300 mcg pentazocine.

Table 9 shows pain score after 30 min of pentazocine injection is considered for statistical analysis. Meaningful pain relief is NRT pain score 0-3.

66.66% patients show meaningful pain relief (NRS 0-3) for 5-6 h after sublingual 300 mcg pentazocine.

**Table 5: Duration and quality of analgesia with epidural pentazocine**

Duration of analgesia in (h)	Quality of analgesia (NRS pain score)	Number of cases (%)		Total cases (%)
		Males	Females	
0-5	2	-	1 (6.66)	1 (6.66)
6-10	1	-	2 (13.33)	2 (13.33)
11-15	1	-	2 (13.33)	2 (13.33)
16-20	1	1 (6.66)	2 (13.33)	3 (20)
21-25	1-2	1 (6.66)	2 (13.33)	3 (20)
26-30	2-3	4 (26.67)	2 (13.33)	6 (40)
30-35	3	4 (26.67)	4 (20)	8 (53.33)
36-48	>3 required rescue analgesics	4 (26.67)	5 (33.33)	9 (60)
Total		10 (66.67)	5 (33.33)	15 (100)

**Table 6: Duration and quality of analgesia with intramuscular pentazocine**

Duration of analgesia in (h)	Quality of analgesia (NRS pain score)	Number of cases (%)		Total (%)
		Males	Females	
0-2	2-3	3 (20)	1 (6.66)	4 (26.66)
3-5	2-3	5 (33.33)	1 (6.66)	6 (40)
6-8	3	8 (53.33)	5 (33.33)	13 (86.67)
9-11	>3 required rescue analgesics	9 (60)	5 (33.33)	13 (86.67)
12-48	>3 required rescue analgesics	9 (60)	5 (33.33)	14 (93.33)
Total		9 (60)	6 (40)	15 (100)

**Table 7: Duration and quality of analgesia with intravenous bolus of pentazocine**

Duration of analgesia in (h)	Quality of analgesia (NRS pain score)	Number of cases (%)		Total (%)
		Males	Females	
0-2	1	2 (13.33)	2 (13.33)	4 (26.66)
3-4	2-3	2 (13.33)	2 (13.33)	4 (26.66)
5-6	3	8 (53.33)	3 (20)	11 (73.33)
7-11	>3 required rescue analgesics	8 (53.33)	4 (26.66)	12 (80)
12-48	>3 required rescue analgesics	10 (66.66)	5 (33.33)	15 (100)
Total		10 (66.66)	5 (33.33)	15 (100)

NRS: Numeric rating scale

**Table 8: Duration and quality of analgesia with continuous intravenous infusion of pentazocine**

Duration of analgesia in (h)	Quality of analgesia (NRS pain score)	Number of cases (%)		Total (%)
		Males	Females	
0-5	1-2	3 (20)	0 (0)	3 (20)
6-10	0-1	4 (26.66)	0 (0)	4 (26.66)
11-15	2-3	5 (33.33)	1 (6.66)	6 (40)
16-20	3	8 (53.33)	1 (6.66)	9 (60)
21-25	>3 required rescue analgesics	8 (53.33)	2 (13.33)	10 (66.66)
26-48	>3 required rescue analgesics	9 (60)	2 (13.33)	11 (73.33)
Total		13 (86.66)	2 (13.34)	15 (100)

NRS: Numeric rating scale

**Table 9: Duration and quality of analgesia with sublingual pentazocine**

Duration of analgesia in (h)	Quality of analgesia (NRS pain score)	Number of cases (%)		Total (%)
		Males	Females	
0-2	2	1 (6.66)	2 (13.33)	3 (20)
3-4	2-3	2 (13.33)	2 (13.33)	4 (26.66)
5-6	3	7 (46.66)	3 (20)	10 (66.66)
7-11	>3 required rescue analgesics	8 (53.33)	4 (26.66)	12 (80)
12-48	>3 required rescue analgesics	11 (73.33)	4 (26.66)	15 (100)
Total		11 (73.33)	4 (26.66)	15 (100)

NRS: Numeric rating scale



Table 10 shows side effects observed due to pentazocine considering whole population as study sample were urinary retention in three patients (4%), nausea in five patients (6.67%), and vomiting in two patients (2.66%). No cardiorespiratory depression was observed in any of the patient and route of administration technique.

## DISCUSSION

In this study, we used pentazocine an opioid for pain relief by different routes to achieve good quality of analgesia and minimum side effect, which is possible because of its pharmacokinetic and physiochemical properties. It is an opioid, a semisynthetic derivative of thebaine, it is a mixed agonist-antagonist opioid receptor modulator that is used to treat opioid addiction in higher dosages. Available in solid and liquid form for different routes with minimum opioid-related side effects which can be reversed with available pure antagonists. It is potent, highly lipid soluble, and log acting, can administered with different routes with good bioavailability and protein binding with biliary and renal excretion. Most important factor is duration of action is long so frequency of administration decreases and the severity and frequency of side effects is low. This study was undertaken to evaluate pentazocine for post-operative analgesia by various techniques such as epidural, intramuscular, intravenous slow bolus, continuous intravenous infusion, and sublingual routes and results of the study are discussed for each of the above group in terms of duration and quality of analgesia.

Meaningful duration of analgesia means 50% or more of patients showing pain relief up to 0-3 NRS score was best achieved by epidural route with duration of 30-35 h in 53.33% patients in group (Table 5), which is close to study of Sanjay,<sup>14</sup> who found the mean duration of analgesia to be 31 h. With intramuscular route meaningful duration of analgesia was 6-8 h in 86.67% patients in group (Table 6), which is best among all groups. These results are comparable with results of Hovell,<sup>15</sup> who studied analgesic

effects of intramuscular pentazocine in 2 ug/kg, 4 ug/kg, and 8 ug/kg doses, which showed that 4-8 ug/kg dose gave longer duration of analgesia as in this study. Furthermore, Bilshack *et al.*,<sup>16</sup> results are in agreement with this study, this study obtained 6 h minimum analgesia with 4 ug/kg. Intravenous route slow bolus meaningful duration of analgesia was 5-6 h in 73.33% patients in group (Table 7). These results agree with the results of Kamel *et al.*<sup>17</sup> (1978), who also studied intravenous pentazocine 5 ug/kg and found that 6 h and more analgesia in 30 adult female patients. Continuous intravenous infusion meaningful duration of analgesia was 16-20 h in 60% patients in group (Table 8). This study approximately corroborates with the study of Fry *et al.*<sup>18</sup> who found that 80% patients did not require further analgesia for 12 h after stopping the drip. In this study, all 15 patients (100%) did not require additional analgesia for 12 h when the pentazocine drip was running, while Fry *et al.* results showed that 80% patients did not required additional analgesia for initial 12 h when the drip was running. The difference in this study may be due to the fact that this is made only with 15 patients whereas Fry *et al.* made a bigger sample size of 60 patients. Meaningful duration of analgesia by sublingual route was 5-6 h in 66.66% patients in group (Table 9). These results agree with the results of Chakraborty<sup>19</sup> who studied analgesic effects of 0.2 mg sublingual pentazocine and showed that it gives  $8.9 \pm 4.1$  (SD) hours of post-operative analgesia. This study was restricted to only gynecological operations while this study is restricted to upper abdominal surgery where severity of pain is more.

Common side effects observed in this study was urinary retention, seen in three patients (4%) out of 75 patients with only epidural techniques (Table 9). This urinary retention could be due to epidural technique itself or pentazocine. Gudi<sup>20</sup> (1986) studied 164 patients with single shot epidural lignocaine and buprenorphine for post-operative pain and found that nearly 6% of patients showed urinary retention. This study more or less corresponds with the above study. Five patients (6.67%) showed nausea of which two patients were operated for phylolithotomy with subcostal incision,

**Table 10: Side effects due to pentazocine by different routes of administration in study population**

Epidural route	Intravenous bolus route	Intravenous infusion route	Intramuscular route	Sublingual route	
In 3 patients (4% of study population)	Nil	Nil	Nil	Nil	Urinary retention
Nil	Nil	In 2 patients (2.66% of study population)	In 1 patient (1.33% of study population)	In 2 patients (2.66% of study population)	Nausea
Nil	In 1 patient (1.33% of study population)	Nil	In 1 patient (1.33% of study population)	Nil	Vomiting
Nil	Nil	Nil	Nil	Nil	Any other specific side effect



two patients operated for epigastric incisional hernia and one patient for exploratory laparotomy. Fry *et al.* found 11.66% of patients with nausea which is not similar to this study. This may be due to use of only continuous infusion route, where the continuous steady level of plasma pentazocine is maintained. They did not observe vomiting in any of their patients but in this study vomiting is seen with intramuscular and intravenous technique only, where the maximum plasma concentration is achieved within a short period which is not seen with epidural, continuous infusion, and sublingual routes. Hargus *et al.*<sup>21</sup> used pentazocine 0.3 mg and 0.6 mg intramuscularly and found respiratory depression in 42 patients (0.5%), observed euphoria in 17 patients (0.23%), and hallucination in 7 patients (0.09%). This observation was probably because of large number of patients studied 7,548. These side effects were not observed in any of the other studies including this study.

Considering the severity of post-operative pain and side effect of post-operative pain, longer duration of analgesia produced by epidural and continuous intravenous drip infusion would be better than other techniques where the facilities are available, which will avoid repeated supplementary doses. Moreover in comparison with longer duration of action in both the epidural and continuous infusion of pentazocine, the continuous infusion of pentazocine should be preferred because of ease of administration, less invasive, needing less skill, can be increased or decreased as per patients demand and less dependency on the nursing staff for subjective analysis and patient care.

## CONCLUSION

From this study, we conclude that pentazocine (300 mcg) produces excellent analgesia by all techniques which are used in this study. The average duration of meaningful (NRS pain score 0-3) analgesia produced by epidural route has maximum duration with acceptable minimal opioid-related side effects like urinary retention. Sublingual route has lowest duration of meaningful analgesia with nausea, while intramuscular route is associated with vomiting. No

cardiorespiratory depression or any other side effects such as itching, hallucination, euphoria, and constipation were observed in any of the technique.

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# Clinical Profile of Guillain-Barre Syndrome in a Tertiary Care Center

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## Abstract

**Background:** Guillain-Barre syndrome (GBS) is an acute, mostly demyelinating polyradiculoneuropathy of an autoimmune etiology. It is no longer called a pure demyelinating disorder and there are axonal variants of the same described as acute motor axonal neuropathy, acute sensory motor axonal neuropathy, and Miller Fisher variants.

**Materials and Methods:** All patients above the age of 18 presenting with acute flaccid paralysis were evaluated. Asbury's criteria was used to diagnose GBS. They were subjected to nerve conduction study and cerebrospinal fluid analysis. GBS disability scoring system (Erasmus GBS outcome score) was also assessed. Events occurring during the period of hospitalization were noted.

**Results:** A total of 50 patients with GBS were evaluated. Of these 76% were males and 24% were females. There were two peaks in the age wise distribution, one at 20-30 years and another at 40-60 years. The most common antecedent event was fever. The most common presenting signs and symptoms were motor weakness, followed by sensory symptoms such as tingling or numbness of the affected limbs. Respiratory difficulty as the presenting symptom was seen in 10 patients. Classical GBS was the most common presentation. A majority of the patients fulfilled 5-7 of Asbury's criteria. Evidence of protein cytological dissociation was seen in 88%. The majority of patients had demyelinating motor neuropathy with prolonged or absent F waves. 19 (38%) patients required intubation. Of these intubated patients, 26% died, 26% recovered, and 48% of them required tracheostomy. 42 patients received immunoglobulin therapy and eight patients underwent plasmapheresis. Six patients died in this study. Five of these patients died due to sepsis, predominantly respiratory. One person died due to intractable ventricular tachycardia.

**Conclusion:** Atypical GBS was uncommon. Most of the patients were managed with immunoglobulin. Mortality rate was higher and occurred mostly with a secondary sepsis.

**Key words:** Cerebrospinal fluid, Guillain-Barre syndrome, Immunoglobulin, Nerve conduction study, Plasmapheresis

## INTRODUCTION

Guillain-Barre (pronounced as Ghee-Yan-Bar-Ray) syndrome (GBS) is an acute and more often than not, demyelinating polyradiculoneuropathy of an autoimmune etiology. This disease has forever perplexed the minds of neurologists and physicians alike for its florid presentation and equally good recovery. With polio declared as being

eradicated from this country, GBS has now become the foremost diagnosis in patients presenting with acute flaccid paralysis. Although this disease has been identified a century ago, there are still many unanswered questions about it. For instance, though GBS has been classically described as an autoimmune disease, the molecular mimicry has never been attributed to any specific cause. The antecedent events that trigger this neurological disease are so vast and wide that it is difficult to pinpoint any specific event that serves as a hallmark for this disease. Over the last few decades our understanding of GBS has also changed, and we currently know that it is not a pure demyelinating disorder and there are axonal variants of the same described as acute motor axonal neuropathy, acute sensory motor axonal neuropathy, and Miller Fisher variants. Other variants of GBS such

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as pandysautonomia and polyneuritis cranialis occur so infrequently that no exact figure on their incidence or prevalence can be given. Even today the disease is best diagnosed by the clinical profile of patients who present with flaccid paralysis with areflexia, cerebrospinal fluid (CSF) analysis that shows protein cytological dissociation and nerve conduction studies (NCS) that show evidence of demyelination, with abnormal F waves. There is no single diagnostic test that confirms or rules out the possibility of GBS. In general, this disease carries good prognosis with mortality rates around 6% worldwide. Studies have been done to try and identify factors that could be considered as bad prognostic signs, but they have never been consistent.<sup>1,2</sup>

In this study, we look at the clinical profile of patients who presented with features of GBS to a tertiary care center and their clinical events in the hospital are recorded until the time of discharge.

## MATERIALS AND METHODS

All patients above the age of 18 presenting with acute flaccid paralysis were evaluated from June 2011 to June 2013. The patients were then subjected to Asbury's criteria for diagnosing GBS (Asbury Criteria features required for the diagnosis - symmetrical weakness in 4 limbs: Features strongly supporting the diagnosis - progression of symptoms over days to 4 weeks, relative symmetry of symptoms, mild sensory symptoms or signs, cranial nerve involvement especially facial nerve, recovery beginning 2-4 weeks after progression ceases, autonomic dysfunction, absence of fever at onset, high concentration of protein in CSF, and typical electrodiagnostic features). Laboratory investigations such as complete blood count, random blood sugar, urine analysis, renal and liver function tests, and serum electrolytes were done in all cases. Two-dimensional echocardiography was done in specific patients as required. The patients were subjected to NCS and CSF analysis. An account of the antecedent events of clinical importance was recorded. The patients were then subjected to GBS disability scoring system (Erasmus GBS outcome score [EGOS]). The patients were monitored daily. Their disability score was reassessed every week till discharge. The need for ventilation was assessed on a day to day basis and if required tracheostomy was performed. The time and type of therapeutic intervention (including intravenous immunoglobulin [IVIg] and plasmapheresis) were recorded. This was done till the patient was discharged or a terminal event occurred.

## RESULTS

The patients presenting with acute flaccid paralysis from June 2011 to July 2013 were identified and among them 50 patients had GBS. Of these 76% were males and 24% were females. There were two peaks in the age wise distribution of this disease, one at 20-30 years and another at 40-60 years (Table 1).

Eight patients each had diabetes and hypertension, three had coronary artery disease. GBS patients presented throughout the year. There was a sharp rise in the incidence of GBS in the months of October (10 patients) and November (six patients). The majority of patients had no antecedent events (23 patients), and the most common antecedent event that was found was fever (10 patients) followed by loose stools (eight patients).

The most common presenting signs and symptoms were motor weakness, which was followed by sensory symptoms such as tingling and numbness of the affected limbs. Respiratory difficulty as the presenting symptom was seen in 10 patients (Table 2).

Asbury's scoring system for diagnosis was graded from 1 to 9. Most of the patients scored around 5-7 (Table 3).

Most of the patients presented with EGOS scale score of 2 (Table 4).

88% of people had evidence of protein cytological dissociation. NCS was done for all patients admitted with GBS. Most of the patients had demyelinating motor neuropathy with prolonged or absent F waves. Some

**Table 1: The study profile**

Age	Male	Female	Total
<20	0	3	3
20-29	6	3	9
30-39	4	0	4
40-49	10	1	11
50-59	9	2	11
60-69	6	2	8
>70	3	1	4

**Table 2: The presenting symptoms and signs**

Presenting signs and symptoms	Symptoms
Weakness of limbs	48
Sensory symptoms	20
Respiratory difficulty	10
Facial nerve involvement	7
Ptosis/ophthalmoplegia	3
Bulbar symptoms	1

**Table 3: Asbury score**

Score	Number of patients
1	0
2	0
3	0
4	6
5	10
6	18
7	15
8	1
9	0

**Table 4: EGOS disability score on admission**

Score	Number of people
1	1
2	22
3	6
4	13
5	8

EGOS: Erasmus Guillain-Barre syndrome outcome score

had more than one type of conduction abnormalities (Table 5).

19 (38%) patients required intubation. Of these intubated patients, 26% died, 26% recovered, and 48% of them required tracheostomy. 42 patients received immunoglobulin therapy and eight patients underwent plasmapheresis. Six patients died in this study. Five of these patients died due to sepsis, predominantly respiratory. One person died due to intractable ventricular tachycardia. Patients with low Asbury score had a poor prognosis than with a higher score. The EGOS scoring of patients at the time of discharge was also documented. Most of them scored 0 or 1 at the time of discharge meaning normal or near normal recovery (Table 6).

## DISCUSSION

GBS has always been considered a disease with a very low incidence which is estimated at around 0.7-1.5/100,000 population.<sup>3</sup> This being an observational study at a tertiary care center, the incidence or prevalence of this disease could not be estimated. Most of the studies that have looked at the epidemiology of GBS have noticed that this disease seems to occur more often in males than in females.<sup>4,5</sup> This has been true with this study also; 76% of our GBS patients were males and 24% were females. The disease was seen in all age groups, but there were two peaks of distribution that was seen, one at 20-30 years and another at 40-60. This was consistent with previous studies which had also described similar peaks.<sup>6,7</sup> However, the second peak seemed to occur much earlier in this study. A very interesting observation that was made in this study was the pattern of distribution

**Table 5: NCS findings**

NCS	Number of patients
Demyelinating motor neuropathy with prolonged or absent F waves	48
Demyelinating sensory neuropathy	4
Facial NCS abnormalities	2
Axonopathy	1

NCS: Nerve conduction study

**Table 6: EGOS disability score on discharge**

Score	Number of patients
0	16
1	21
2	3
3	1
4	3
5	0
6	6

EGOS: Erasmus Guillain-Barre syndrome outcome score

of the incidence of the disease during the calendar months of a year. There was a significant peak in the occurrence of this disease in the months of October and November. This also corresponded to the distribution of rainfall in Chennai during the period of study.

Most of the previous studies have shown that patients present with an antecedent event even up to 6 weeks before the neurological symptoms. In this study, 55% of them had antecedent event before getting admitted to the hospital. This was consistent with studies that had been published earlier.<sup>8</sup> Among the antecedent events that were reported by the patients, fever was the most common one (19%) followed by loose stools (16%). After motor weakness, the next common presentation was sensory disturbances which were seen in 20 patients. Such sensory disturbances have also been reported in previous studies.<sup>9</sup> The most common cranial nerve that was involved was the facial nerve which was also consistent with the previous studies.<sup>9</sup> Respiratory failure was seen as a presenting complaint in 20% of the patients. This correlated with the incidence of respiratory failure that has been previously documented with GBS (10-30%).<sup>10</sup>

Protein cytological dissociation was seen in 88% of the patients. This was consistent with previous studies.<sup>11</sup> Previous studies had shown that demyelinating form of GBS was the most common in European countries and in the US,<sup>12</sup> and the axonopathy variant was more common in China and Japan.<sup>13</sup> However, in this study, the demyelinating variant was the most common (96%). Most of the patients were administered IVIg (84%). The prognosis of the patient based on IVIg treatment could not be assessed because many patients had received treatment elsewhere



before being admitted in this hospital, which served as a confounding factor. Moreover, the decision as to whether IVIg needed to be administered was based solely on the treating physician and Neurologist's discretion. Of the types of GBS that were seen in this study, demyelinating variety was the most common, followed by Miller Fisher variant, and then, axonopathy.

In this study patients with poor prognosis were distributed throughout all ages. This was not correlating with previous studies which had quoted older age to be a marker of poor prognosis of patients.<sup>14</sup> In this study, it was found that patients with a lower score in Asbury's scale had worse prognosis than patients with a higher score. At the time of discharge most of the patients had no or minimal residual neurological deficit (EGOS Scale - 0 or 1) - 74%. Mortality rate was 12% which was higher than the ones shown in other studies worldwide (4%).<sup>15</sup> This was mostly due to sepsis.

## CONCLUSION

Our study showed GBS to be more frequent in males, with classical GBS being the predominant type. NCS and CSF findings were the most specific for diagnosis of GBS. Asbury criteria on admission had no correlation with the prognosis. We were not able to ascertain which line of treatment was superior as 84% were given immunoglobulin therapy and only 16% underwent plasmapheresis. Mortality was seen only in patients who developed secondary complications such as respiratory sepsis.

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# Serum Electrolyte Profile in Subjects Admitted with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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## Abstract

**Introduction:** Chronic obstructive pulmonary disease (COPD) affects 6-10% of the adult population and is a leading cause of morbidity and mortality responsible for 5.1% of all deaths worldwide. It is important to identify factors associated with acute exacerbation of COPD and poor outcome among exacerbation cases.

**Materials and Methods:** The study was conducted in the Department of General Medicine, Krishna Rajendra Hospital, Mysore. It was a cross-sectional study done till adequate sample size patients were enrolled. Permission from the Institutional Ethical Committee was obtained for the proposed study. The study included 100 COPD patients and 100 healthy controls.

**Results:** In our study, we found that there was a statistically significant difference ( $P < 0.001$ ) between serum levels of sodium in patients with acute exacerbation of COPD ( $131.7 \pm 5.07$  mEq/L) as compared to healthy controls ( $138.66 \pm 3.83$  mEq/L). Furthermore, serum potassium levels in COPD exacerbation cases ( $3.31 \pm 0.33$  mEq/L) was significantly low ( $P < 0.001$ ) as compared to that of controls ( $3.87 \pm 0.36$  mEq/L).

**Conclusion:** Serum electrolyte levels were significantly low among patients of acute exacerbation of COPD. Hence screening for these abnormalities may improve outcome.

**Key words:** Chronic obstructive pulmonary disease, Potassium, Serum electrolytes, Sodium

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by progressive airflow limitation that is not fully reversible. COPD affects 6-10% of the adult population and is a leading cause of morbidity and mortality responsible for 5.1% of all deaths worldwide.<sup>1,2</sup>

Exacerbations are the most common cause of hospitalization among COPD patients.<sup>3</sup> The economic and social burden created by acute exacerbations of COPD are extremely

high. Thus, it is important to identify factors associated with exacerbation. It is also important to identify factors associated with poor outcome among COPD exacerbation cases. Since electrolytes are important for nerve conduction as well as smooth muscle and skeletal muscle contraction, it may significantly alter the outcome of COPD exacerbation if untreated. Thus, this study aims at evaluating serum electrolyte levels in acute exacerbation of COPD.

## MATERIALS AND METHODS

The study was conducted in the Department of General Medicine, Krishna Rajendra Hospital, Mysore. It was a cross-sectional study done till adequate sample size patients were enrolled. Permission from the Institutional Ethical Committee was obtained for the proposed study. The study included 100 COPD patients and 100 healthy controls. COPD diagnosis was made based on history, clinical examination, chest X-ray, and pulmonary function

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test. Age and sex matched healthy controls were enrolled from patients attendants/hospital staff.

### Inclusion Criteria

All cases of COPD patients presenting to outpatient department or emergency with acute exacerbation.

### Exclusion Criteria

1. COPD patients admitted for causes other than COPD exacerbation
2. COPD patients requiring mechanical ventilation
3. Patients with pre-existing renal, hepatic, endocrinal or cardiac illness.

All subjects undergoing the study were given necessary information and informed consent taken in a standard proforma. Detailed history was taken. After thorough clinical examination, necessary investigations for the confirmation of COPD were done. Under strict aseptic conditions, 2 ml of fasting blood was collected. Blood was centrifuged and serum was separated. Serum electrolyte levels measured by ion specific electrode method. Study was analyzed by SPSS software. Statistical significance analyzed by Student's *t*-test ( $P < 0.005$  was considered as statistically significant).

## RESULTS

The mean age of cases was  $57.92 \pm 12.91$  years and mean age of controls was  $53.73 \pm 8.98$  years. Mean serum levels of sodium among cases and controls were  $131.7 \pm 5.07$  mEq/L and  $138.66 \pm 3.82$  mEq/L, respectively. There was a statistically significant difference in mean serum sodium levels among cases and controls ( $P < 0.001$ ).

Mean serum potassium levels among cases and controls were  $3.3081 \pm 3.3126$  mEq/L and  $3.8740 \pm 3.6003$  mEq/L, respectively. The patients with acute exacerbation of COPD had significantly low serum potassium levels ( $P < 0.001$ ).

## DISCUSSION

COPD is a leading cause of morbidity and mortality worldwide. With increasing industrialization and smoking, the prevalence of COPD is increasing. Exacerbations are the most common cause of hospitalization among COPD patients.<sup>3</sup>

The economic and social burden created by acute exacerbations of COPD are extremely high. Thus, it is important to identify factors associated with exacerbation and poor outcome. Common causes of deranged serum sodium levels include hyperglycemia, use of thiazides or

nonsteroidal anti-inflammatory drug, congestive cardiac failure, chronic renal failure, and low dietary salt intake.<sup>4</sup> Common causes of hypokalemia include diarrhea, laxative abuse, vomiting, certain diuretics, drugs like insulin,  $\beta$  agonists, and theophylline.<sup>5</sup> Thus, COPD patients *per se* are predisposed to electrolyte imbalance. In turn electrolyte imbalance can cause respiratory muscle weakness, cardiac arrhythmia, low cardiac output, etc.<sup>6</sup> Thus the presence of electrolyte imbalance leads to significantly poor outcome among COPD patients. This study aimed at evaluating serum electrolyte levels in patients with acute exacerbation of COPD.

In this study 100 patients with COPD acute exacerbation and 100 healthy controls were enrolled. The mean age of cases was  $57.92 \pm 12.91$  years and the mean age of controls was  $53.73 \pm 8.98$  years.

Serum sodium and potassium levels were measured in cases as well as healthy controls. Mean serum levels of sodium among cases were  $131.7 \pm 5.07$  mEq/L and among controls were  $138.66 \pm 3.82$  mEq/L. There was a statistically significant difference in mean serum sodium levels among cases and controls ( $P < 0.001$ ).

Mean serum potassium levels among cases were  $3.3081 \pm 3.3126$  mEq/L and among controls were  $3.8740 \pm 3.6003$  mEq/L. The patients with acute exacerbation of COPD had significantly low serum potassium levels ( $P < 0.001$ ).

Parameter	Age		P value
	Group I	Group II	
Age (mean $\pm$ SD)	57.92 $\pm$ 12.92	53.73 $\pm$ 8.98	0.008
Sex (Male/Female)	12/88	14/86	0.674
Serum sodium (mean $\pm$ SD)	131.7 $\pm$ 5.07	138.66 $\pm$ 3.83	0.000
Serum potassium (mean $\pm$ SD)	3.31 $\pm$ 0.33	3.87 $\pm$ 0.36	0.000

SD: Standard deviation

Our study results were similar to that of Das *et al.* who conducted the study on 64 acute exacerbations of COPD cases and 20 healthy controls. Average levels of serum sodium and potassium in COPD patients were  $133 \pm 6.86$  and  $3.39 \pm 0.96$  mEq/L, respectively. Serum sodium and potassium levels in the control group were  $142 \pm 2.28$  and  $4.52 \pm 0.02$  mEq/L, respectively.<sup>7</sup> The study concluded that it is important to identify electrolyte imbalance among COPD acute exacerbation cases to prevent adverse outcome.

Thus, although there are no established guidelines which advice for routine screening of serum electrolyte levels in COPD acute exacerbation cases, it is important to screen the patients for the same. Correction of serum electrolyte levels among acute exacerbation of COPD cases may actually improve the outcome.

## CONCLUSION

Patients of acute exacerbation of COPD should be screened for electrolyte imbalance. Correction of these electrolyte imbalance could improve outcome of exacerbation.

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# Hashimoto's Thyroiditis - Diagnostic Accuracy of Antimicrosomal Antibodies

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## Abstract

**Introduction:** Hashimoto's thyroiditis (HT) is an autoimmune disease in which the thyroid gland is gradually destroyed by a variety of cell- and antibody-mediated immune processes.

**Objectives:** To compare the sensitivity, specificity, and diagnostic accuracy of antimicrosomal antibody and fine needle aspiration cytology (FNAC), and ultrasonography in diagnosis in HT.

**Materials and Methods:** Descriptive study with diagnostic test evaluation of 200 patients was carried out in the Department of Surgery in Thiruvananthapuram Medical College, and in whom thyroidectomy being done during the period 2013-2014 for the duration of 18 months. 100 patients were with HT and 100 patients were taken as control.

**Results:** The result indicates that in people with nodular goiter, sensitivity and specificity of antithyroid peroxidase antibody (TPO-Ab) test to detect HT were estimated to be 88% and 89%, respectively, with an overall accuracy of 88.5%. The positive predictive values (PPVs) and negative predictive values (NPVs) were 88.9% and 88.1%, respectively, and in patients with nodular goiter, the sensitivity and specificity of FNAC to detect HT were estimated to be 88% and 91%, respectively, with an overall accuracy of 89.5%. The PPV and NPVs were 90.7% and 88.3%, respectively.

**Conclusion:** There is a high degree of concordance between serological and cytological findings of HT in people with nodular goiter. Assays of anti-TPO-Abs in this study have a high sensitivity, specificity, and accuracy to detect HT which justifies the use of anti-TPO-Abs as a screening test in the evaluation of patients with nodular goiter.

**Key words:** Accuracy, Antibodies, Antithyroid peroxidase, Fine needle aspiration cytology, Hashimoto's thyroiditis, Positive and negative predictive value

## INTRODUCTION

The first report of chronic thyroiditis, struma lymphomatosa was described by Hakaru Hashimoto in 1912.<sup>1-3</sup> Hashimoto's thyroiditis (HT) is an autoimmune disease in which the thyroid gland is gradually destroyed by a variety of cell- and antibody-mediated immune processes.<sup>2</sup> The first report of chronic thyroiditis, struma lymphomatosa was described by Hakaru Hashimoto in 1912.<sup>1-3</sup> It was the first disease to be recognized as an autoimmune disease. The mean annual

incidence rate of autoimmune hypothyroidism is up to 4 per 1000 women and 1 per 1000 men.<sup>2</sup>

A family history of thyroid disorders is common; HLA-DR3, HLA-DR4, and HLA-DR5 are the best documented genetic risk factors.<sup>2</sup> Hashimoto's may be associated with CTLA-4 gene. Gross examination, the thyroid gland is usually mildly enlarged throughout and has a pale gray tan cut surface that is granular nodular and firm.<sup>4</sup> On microscopy, the gland is diffusely infiltrated by small lymphocytes and plasma cell and occasionally show well developed germinal centers. Thyroid follicles are smaller than normal with reduced amount of colloid and increased interstitial connective tissue (Figure 1). The follicles are lined by Hurthle or Askanazy cells (Figure 2) which are characterized by abundant eosinophilic granular cytoplasm.<sup>4</sup> Follicular cell destruction often with mononuclear cell invasion of the follicular spaces is a diagnostic pathological finding.<sup>3</sup>

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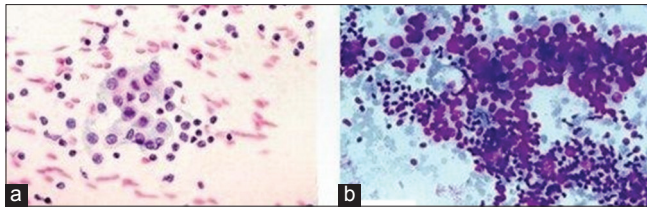


Figure 1: (a and b) Hashimoto's thyroiditis cytology images

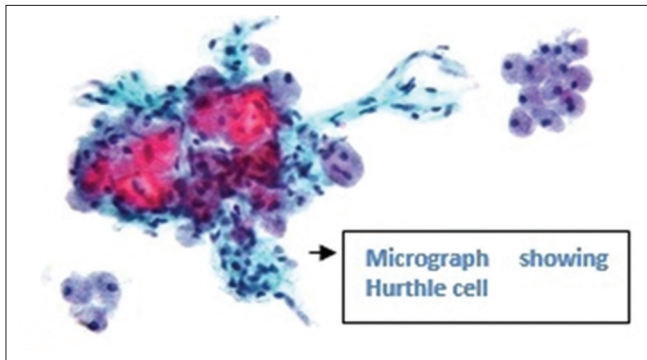


Figure 2: Hurthle cell

The diagnosis of HT can be made only by histopathology.<sup>5,6</sup> Antimicrosomal antibody represents an important tool in the diagnosis of autoimmune thyroiditis.<sup>3</sup> Antimicrosomal antibody test is less invasive and can be used to assess disease activity in patients that have developed such antibodies. Value  $>34.0$  IU/ml generally are associated with autoimmune thyroiditis.<sup>5</sup> The median disappearance time is 6.3 years for thyroid peroxidase antibodies (TPO-Abs).<sup>7</sup> High TPO-Abs is associated with poor physical and psychological well-being and appears to predict future health perception in hypothyroidism patients.<sup>6</sup> HT patients benefit from surgery at least for palliation and to relieve the persistence of symptoms.<sup>8</sup> Hashimoto's thyroiditis has a predisposition to turn into malignant thyroid tumors especially differentiated thyroid cancer.

### Aim and Objectives

To compare the sensitivity, specificity, and diagnostic accuracy of antimicrosomal antibody and fine needle aspiration cytology (FNAC) and ultrasonography (USG) in diagnosis in HT.

## MATERIALS AND METHODS

A prospective observational study was conducted at Medical College Thiruvananthapuram.

### Inclusion Criteria

All patients above 12 years of age admitted in the Department of Surgery in Trivandrum medical college and in whom thyroidectomy being done. Thyroidectomy patients with clinical or cytological or serological

pre-operative diagnosis of HT will be the subject of study. Incidentally detected HT from thyroidectomy specimens will also be included.

### Exclusion Criteria

Those not willing to participate in the study and patients with history of thyroid surgery or radioiodine therapy patients with radiation exposure to neck are excluded from the study.

- Study period is from March 21, 2012 to September 20, 2013.
- Study tool is antimicrosomal antibody titer.

Based on sensitivity and specificity and concerting PSM Department, sample size. I have taken 100 cases of histologically proven HT and 100 cases of histologically negative HT. Thyroid stimulating hormone (TSH) was measured by immunochemiluminometric assay with analytical sensitivity 0.01 mIU/ml. The serum anti-TPO-Abs were measured by immunochemiluminescent assay with a reference range value  $<34$  IU/ml as negative.<sup>5</sup>

Following steps were followed during analysis of anti-TPO-Abs:

1. 1<sup>st</sup> incubation: 20  $\mu$ l of sample are incubated with anti-TPO-Abs labeled with a ruthenium complexa
2. 2<sup>nd</sup> incubation: After addition of biotinylated TPO and streptavidin-coated microparticles, the anti-TPO-Abs in the sample compete with the ruthenium-labeled anti-TPO-Abs for the biotinylated TPO antigen. The entire complex becomes bound to the solid phase via interaction of biotin and streptavidin.
3. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with Procell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
4. Results are determined via a calibration curve which is instrument-specific generated by 2-point calibration and a master curve is provided via the reagent barcode.

Thyroid FNAC was performed on one or both lobes of the gland. Each aspiration was expelled and smeared on glass slides. The slides were immediately wet-fixed in 95% ethyl alcohol for Papanicolaou staining. Satisfactory smear was defined as one that contained five to six groups of well-preserved cells with at least 10-15 cells in each group. The diagnosis of HT for FNAC was made based on the presence of lymphocytes, plasma cells, and Hurthle cells.

### Statistical Method Analysis

The normally distributed data were expressed as means, while the variables with a skewed distribution were reported



as median (interquartile range). The sensitivity, specificity, and receiver operating characteristic (ROC) curves were calculated by a two-by-two contingency table, and the optimal cut-off point was yielded from the closest point to the left upper corner of the ROC curve. All statistical analyses were performed with the SPSS Statistical Package (version 13.0). Values of  $P < 0.05$  were considered statistically significant.

### Ethics

This study was approved from the Human Ethics Committee, Medical College, Thiruvananthapuram on date March 21, 2012. Informed written consent was obtained from all participants.

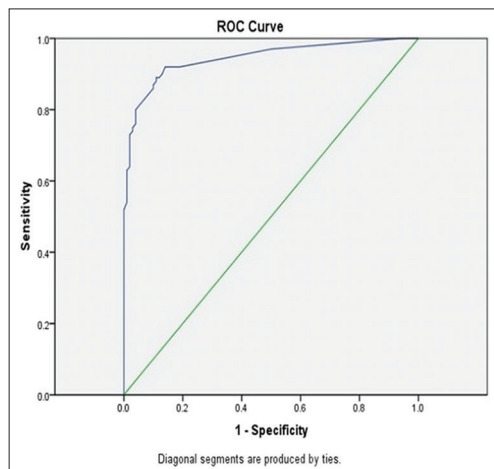
## RESULTS

The total of 200 patients participated in the study. 100 patients with histologically proven HT and age and sex matched 100 patients with histologically negative HT after informed consent were enrolled in the study.

When results of antimicrosomal antibodies were plotted in ROC curve, the area under curve was 0.944, which is suggestive of assays of anti-TPO-Abs in this study have a high sensitivity, specificity, and accuracy to detect HT (Figure 3).

The results indicate that in people with goiter, the sensitivity, specificity of positive antimicrosomal antibody in diagnosis of HT were 88% and 89%, respectively, with an overall accuracy of 88.5% and positive predictive values (PPVs) and negative predictive value (NPV) were 88.9% and 88.1%, respectively, (Table 1).

Sensitivity, specificity, overall accuracy, PPV of FNAC in diagnosis of HT is 88%, 91%, 90.7%, 88.3% and 89.5% respectively (Table 2).



**Figure 3: Receiver operating characteristic curve of results of antimicrobial antibodies**

Sensitivity, specificity, PPV, NPV, and accuracy of USG neck in diagnosis of HT is 75%, 82%, 80.6%, 76.6%, and 78.5%, respectively, (Table 3).

## DISCUSSION

HT is an autoimmune disease in which the thyroid gland is gradually destroyed by a variety of cell- and antibody-mediated immune processes over a period. The study on 100 patients of HT showed the following facts. HT is about 15-20 times more common in women than in men and frequently involves people between the ages of 30 and 50 years of age. In this study also, patients were mainly young females with mean age of 41.12 years (Tables 4 and 5). This is similar to most of the available literature although there are studies, which differ in the age of presentation of the diagnosis of HT. In a previous study<sup>9</sup> from the United Kingdom, patients were mainly older women with mean age at diagnosis being 59 years.

Most of our patients had symptoms of hypothyroidism with a diffuse goiter although nodular presentation was also noted in few cases. Friedman *et al.*<sup>10</sup> found nodular presentation in as many as 80% of their patients.

TSH was elevated in all with either decreased or normal T3, T4. Studies have suggested that impairments of physical, mental, and psychic well-being in patients with HT, but these impairments have been shown to be independent of

**Table 1: Comparison of test result to reference standard ("gold standard") for antimicrosomal antibody**

Antimicrosomal antibody	HPR HT positive	HPR HT negative
Positive	88	11
Negative	12	89

Statistical analysis value of  $P=0.000$  ( $<0.05$ ) for this study. HPR: Histopathological report, HT: Hashimoto's thyroiditis

**Table 2: Comparison of test result to reference standard ("gold standard") for FNAC**

FNAC	HPR HT positive	HPR HT negative
Positive	88	9
Negative	12	91

HPR: Histopathological report, FNAC: Fine needle aspiration cytology, HT: Hashimoto's thyroiditis

**Table 3: Comparison of test result to reference standard ("gold standard") for USG neck**

USG neck	HPR HT positive	HPR HT negative
Positive	75	18
Negative	25	82

USG: Ultrasonography, HPR: Histopathological report, HT: Hashimoto's thyroiditis

**Table 4: Age distribution of patients/age interval (in years)**

Age (in years)	Hashimoto positive	Control
<21	5	4
21-30	19	15
31-40	38	31
41-50	19	30
51-60	9	11
61-70	7	5
>70	3	4

**Table 5: Sex distribution of patients**

Study patients	Female	Male
Hashimoto positive	88	12
Control	89	11

thyroid dysfunction. HT patients' positive for TPO-Abs showed poorer results when assessed for symptomatic distress as well as in the three domains: Somatization, obsessive compulsive symptoms, and depression (all  $P \leq 0.02$ ). TPO-Abs positivity, defined as TPO-Abs >100 IU/L, significantly predicted poorer physical and psychosocial well-being.<sup>6</sup>

In a study by Ott *et al.*, symptoms such as chronic fatigue, dry hair, chronic irritability, chronic nervousness, a history of breast cancer and early miscarriage, and lower quality of life levels were significantly associated with anti-TPO levels exceeding the cut-off point ( $P < 0.05$ ).<sup>11</sup>

In the previous study, "The incidence of Hashimoto's disease in nodular goiter: The concordance in serological and cytological findings" by Chehade<sup>12</sup> the sensitivity and specificity of anti-TPO-Ab test to detect HT in nodular goiter were estimated to be 76.38% and 94.23%, respectively. The data in my study shows that the sensitivity, specificity of positive antimicrosomal antibody in diagnosis of HT were 88% and 89%, respectively.

In the previous study by Rho, TPO-Ab titer was significantly associated with the degree of inflammation and the specificity of TPO-Ab detection for HT diagnosis was found to be 96.9%.<sup>13</sup> These results are almost comparable to my study.

The role of USG neck in evaluating HT is also not well-defined. A characteristic USG neck finding in HT is the diffuse hypoechogenic pattern seen in up to 77% of individuals.<sup>14</sup> The data in my study shows that the sensitivity of USG neck is 75%.

This study emphasizes routine pre-operative assessment of antimicrosomal antibodies in diagnostic evaluation of

patients suspected to have HT. This study also proved that in the south Indian population, antimicrosomal antibodies as almost as accurate as histopathology in diagnosing HT.

Antimicrosomal antibodies can be used as a screening tool also in diagnosing subclinical cases owing to its high specificity (89%) which is comparable to invasive histopathology (91%). Being a noninvasive and easily available test, application of this test on large scale is feasible on contrary to histopathology. Although TSH levels are usually elevated in HT, but can be normal in few cases. In these types of cases where diagnosis of Hashimoto is suspected clinically, but TSH is normal, antimicrosomal antibodies can be used preoperatively to diagnose HT because of its high sensitivity and specificity in diagnosing this disease.

## CONCLUSION

Anti-microsomal antibodies can be used as a screening test because of its noninvasive nature and high specificity. Statistical analysis value of  $P = 0.000$  ( $<0.05$ ) for this study. Histopathology is invasive, so cannot be used as screening test but its remains as "Gold standard" test because of its highest sensitivity and specificity.

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# Histopathological Study of Spectrum of Lesions Seen in Surgically Resected Specimens of Fallopian Tube

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## Abstract

**Background:** Fallopian tubes are common surgical specimen in the pathology laboratory; still there is a lack of data to describe the frequency of various histopathological findings.

**Aims and Objectives:** (1) To study the histopathological lesions seen in surgically resected specimens of fallopian tube, (2) to study the frequency of various pathological lesions of fallopian tube and their age distributions.

**Materials and Methods:** A total of 185 fallopian tube specimens over a period of 1 year either from hysterectomy with salpingo-oophorectomy specimens, salpingo-oophorectomy specimens or salpingectomy specimens were reviewed thoroughly on the basis of gross and microscopic findings.

**Results:** Among 63.78%, i.e., 118 cases had some tubal pathology with acute salpingitis forming the major group (55 cases) of tubal pathologies followed by paratubal cysts (21 cases). Primary neoplastic lesions of fallopian tube were rare as compared to secondary malignancies.

**Conclusion:** Although the fallopian tubes remain unremarkable in a majority of the surgical pathological specimens, they must be subjected for histopathological examination to evaluate various pathological lesions.

**Key words:** Fallopian tube lesions, Histopathology, Tumors

## INTRODUCTION

The fallopian tube are complex structures that connect ovaries to endometrial cavity. They are sites of various interactions necessary for normal pregnancy.<sup>1</sup> It is a common specimen in a pathology laboratory and may be examined either alone as a salpingectomy specimen or as a part of a more complex specimen from a hysterectomy and/or oophorectomy operation.<sup>2</sup> Although fallopian tube is affected by a wide spectrum of diseases, literature search reveals that there are only occasional studies documenting

histologic changes in fallopian tube removed for all reasons. The aims and objectives of this study is to describe various histopathological lesions seen in surgically resected specimens of fallopian tube and to study the frequency of various pathological lesions of fallopian tube and their age distributions.

## MATERIALS AND METHODS

A one year prospective study was done from March 2015 to February 2016 at Pt. Jawahar Lal Nehru Memorial Medical College and Dr. B. R. A. M. Hospital, Raipur, Chhattisgarh. During this period, a study of 185 fallopian tubes cases was done. All the specimens of salpingectomy either done for TAH with bilateral salpingo-oophorectomy (BSO), unilateral salpingectomy or salpingo-oophorectomy were included in the study. Tubectomy specimens were excluded from the study. A minimum of three cross sections of each

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tube, from proximal, mid, and distal portions should be taken for microscopic examination. The proximal fallopian tube is serially cross-sectioned at 2.0-3.0 mm intervals, and the distal fimbriated end is longitudinally sectioned for maximal exposure of the fimbrial epithelium. It is processed routinely to obtain paraffin sections of 4-5  $\mu$  size and then stained with hematoxylin and eosin. After this, microscopic features were studied.

## RESULTS

A total of 185 specimens consisting of various gynecological lesions were studied thoroughly. In the majority of the cases, the clinical diagnosis was carcinoma ovary (44/185) followed by uterine fibroid (31/185) (Table 1). The maximum number of cases belonged to the age group of 41-50 years, followed by 31-40 years of age group with vaginal bleeding as their most common presenting complaint. The youngest patient was 12-year-old female where BSO was done for ovarian mass, and the eldest was 72 years who underwent hysterectomy for endometrial carcinoma.

As shown in Table 2, most common age group of tubal lesions was 41-50 years in which 23.78% (44/185) cases were seen followed by 31-40 years of age group in which 15.67% (29/185) cases were seen. As shown in Table 3, in majority of the cases the fallopian tube showed abnormal pathological findings (63.78%) which included salpingitis, hydrosalpinx, hematosalpinx, salpingitis isthmica nodosa, endometriosis, ectopic pregnancy, paratubal

cyst and tumors. In 36.21% cases, fallopian tube were unremarkable.

Maximum numbers of cases were of acute salpingitis, constituting 29.72% (55/185) of cases. The majority of the cases of acute salpingitis were seen in the age group of 41-50 years (22/55) (Table 2). In most of the cases, acute salpingitis was observed as an incidental finding in tubes removed along with uterus (panhysterectomy) for treating various gynecological disorders.

The next major group was of paratubal cysts, constituting 11.35% (21/185) of cases. The majority of the cases were seen in the age group of 41-50 years (15/21) (Table 2).

Ectopic pregnancy was seen in 10.27% (19/185) cases. The majority of the cases were seen in the age group of 21-30 years (13/19) (Table 2). One case of ectopic pregnancy was associated with chronic salpingitis in the same tube and two cases of ectopic pregnancy were associated with acute salpingitis in the same tube.

Primary fallopian tube carcinoma was seen in 2 (1.08%) cases. One case was diagnosed in a 53-year-old female and it was reported as endometrioid adenocarcinoma. Another case was diagnosed in a 25-year-old female and it was reported as serous tubal intraepithelial carcinoma (Figure 1).

Metastasis to the fallopian tube was seen in 5 (2.70%) cases. The metastasis to the fallopian tube was from ovarian primary in three cases, uterus primary in one case, and gastrointestinal tract (GIT) primary in one case. Among ovarian neoplasms, two were dysgerminoma and one was mucinous carcinoma. Among uterus (endometrium), it was endometrioid carcinoma. Among GIT (Krukenberg tumor), it was moderately differentiated mucinous intestinal type adenocarcinoma (Figure 2).

## DISCUSSION

In this study, 67 (36.21%) cases were reported unremarkable and 118 (63.78%) cases were reported having tubal pathology. In most of the studies, cases with unremarkable tubes outnumbered the cases with tubal pathology.<sup>3-7</sup> However, in this study, cases with tubal pathology has outnumbered the cases with unremarkable tubes.

The most common histopathological finding in this study is acute salpingitis (29.72%) and all the cases are found incidentally on histopathological examination. In this study, the incidence of acute salpingitis was higher as compared to other studies.<sup>3-7</sup>

**Table 1: Distribution of cases according to clinical diagnosis**

Clinical diagnosis	Number of cases	Incidence (%)
Carcinoma ovary	44	23.78
Fibroid	31	16.75
Ectopic pregnancy	19	10.27
Ovarian cyst	17	9.18
Carcinoma cervix	16	8.64
Menorrhagia	15	8.10
Carcinoma endometrium	13	7.02
Ovarian cystadenoma	07	3.78
DUB	05	2.70
Endometrial hyperplasia	04	2.16
Adenomyosis	04	2.16
PID	03	1.62
Rupture uterus	02	1.08
Adnexal mass	01	0.54
Tubo-ovarian mass	01	0.54
Ovarian endometriosis	01	0.54
Carcinoma fallopian tube	01	0.54
Krukenberg tumor	01	0.54
Tubectomy	00	00
Total	185	100

DUB: Dysfunctional uterine bleeding, PID: Pelvic inflammatory disease



**Table 3: Age-wise distribution of tubal lesions seen during histopathological examination**

Tubal lesions	11-20 years	21-30 years	31-40 years	41-50 years	51-60 years	61-70 years	71-80 years	Total	%
Acute salpingitis	5	5	14	22	7	2	-	55	29.72
Chronic salpingitis	-	-	1	3	1	-	-	5	2.70
Acute on chronic salpingitis	-	-	-	1	-	-	-	1	0.54
Granulomatous/tuberculous salpingitis	-	1	-	-	-	-	-	1	0.54
Hydrosalpinx	-	-	3	-	-	-	-	3	1.62
Hematosalpinx	-	2	-	-	-	-	-	2	1.08
Salpingitis isthmica nodosa	-	-	-	1	1	-	-	2	1.08
Endometriosis	-	-	2	-	-	-	-	2	1.08
Ectopic pregnancy	1	13	4	1	-	-	-	19	10.27
Paratubal cysts	-	1	4	15	1	-	-	21	11.35
Tumors									
Malignant primary	-	1	-	-	1	-	-	2	1.08
Malignant secondary	1	1	1	1	1	-	-	5	2.70
Total	7	24	29	44	12	2	-	118	100

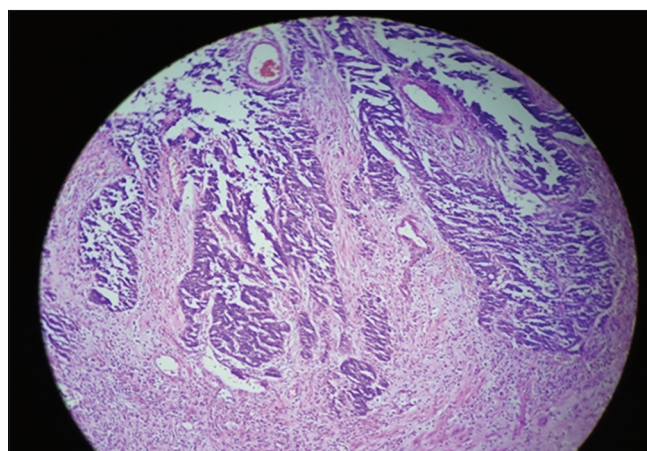
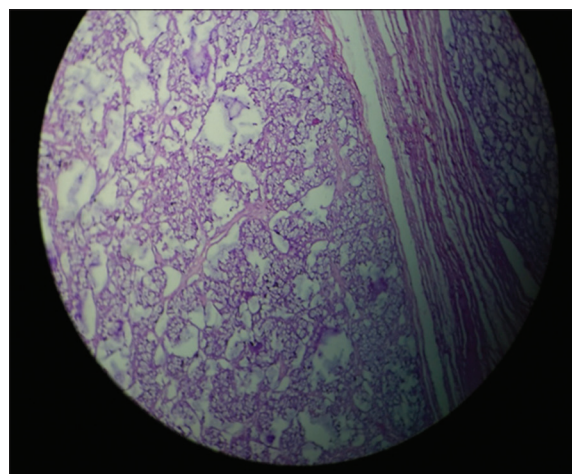
**Table 2: Distribution of various tubal lesions encountered in this study**

Fallopian tube lesions	Number of cases	Incidence (%)
Normal	67	36.21
Abnormal	118	63.78
Salpingitis	62	33.51
Acute salpingitis	55	29.72
Chronic salpingitis	05	2.70
Acute on chronic salpingitis	01	0.54
Granulomatous/tuberculous salpingitis	01	0.54
Hydrosalpinx	03	1.62
Hematosalpinx	02	1.08
Salpingitis isthmica nodosa	02	1.08
Endometriosis	02	1.08
Ectopic pregnancy	19	10.27
Paratubal cyst	21	11.35
Tumors	07	3.78
Malignant primary	02	1.08
Malignant secondary	05	2.70
Total	185	100

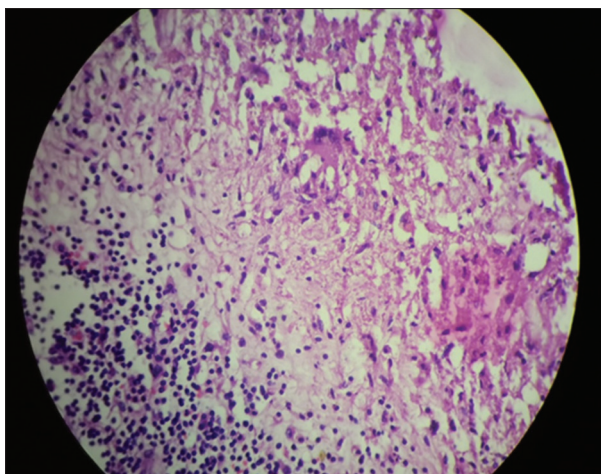
In this study, chronic salpingitis was seen in 5 (2.70%) cases. The incidence of chronic salpingitis was lower in this study as compared to other studies.<sup>3-7</sup>

In this study, acute on chronic salpingitis was seen in 1 (0.54%) case. In this study, the incidence of acute on chronic salpingitis was lower as compared to other studies.<sup>3,7</sup>

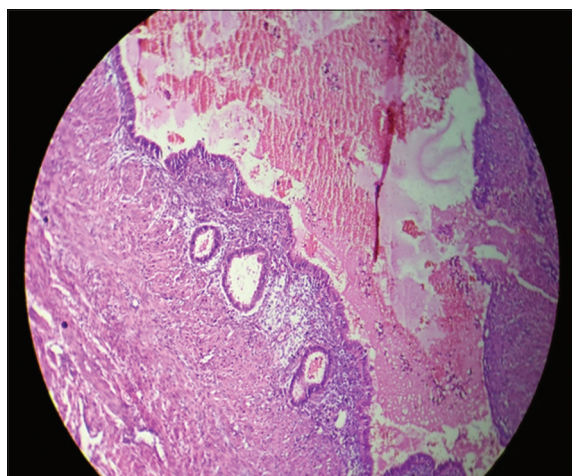
In this study, tuberculous salpingitis is seen in 1 (0.54%) case. Lakshmi *et al.*<sup>5</sup> observed almost equal incidence of tuberculous salpingitis (0.59%). Tuberculosis of fallopian tube develops commonly by hematogenous spread of the organism, usually from a primary pulmonary infection and rarely by direct extension from adjacent organs or lymphatic spread from intestinal tuberculosis. Agarwal and Gupta<sup>8</sup> in their study of female genital tract tuberculosis, found the incidence declining from 1.8% in 1974 to 0.8% in 1989 and

**Figure 1: Histopathology section of right fallopian tube showing primary endometrioid adenocarcinoma (H and E, x100)****Figure 2: Histopathology section of right fallopian tube showing metastasis of mucinous carcinoma of ovary (H and E, x100)**

onward. They noted the involvement of endometrium in 99.5%, fallopian tubes in 94.7%, cervix in 81.5%, ovaries in 62.5%, and vagina in 0.2% cases (Figure 3).



**Figure 3: Histopathology section of fallopian tube showing tuberculous salpingitis (H and E, x100)**



**Figure 4: Histopathology section of fallopian tube showing endometriosis (H and E, x100)**

The second most common finding in this study is paratubal cysts (11.35%). In this study, the incidence of paratubal cysts was higher as compared to other studies.<sup>3,5,7</sup>

In this study, ectopic pregnancy was seen in 19 (10.27%) cases. The incidence of ectopic pregnancy was higher in this study. Bagwan *et al.*<sup>3</sup> observed almost similar incidence of ectopic pregnancy (11.79%). Most of the patients in this study were in the age group of 21-30 years, with 13 cases (68.42%), which was consistent with the study by Dahiya *et al.*<sup>9</sup> in which, most of the cases were between the age group of 25 and 29 years.

In this study, salpingitis isthmica nodosa was seen in 2 (1.08%) cases. In this study, the incidence was higher as compared to other studies.<sup>3-7</sup>

In this study, hydrosalpinx was seen in 3 (1.62%) cases. In this study, the incidence of hydrosalpinx was lower as compared to other studies.<sup>3-7</sup>

In this study, hematosalpinx was seen in 2 (1.08%) cases. Gon *et al.*<sup>4</sup> observed almost closer incidence of hematosalpinx (0.85%) (Figure 4).

In this study, endometriosis was seen in 2 (1.08%) cases. In this study, the incidence of endometriosis was higher as compared to other studies.<sup>3-7</sup>

In this study, the incidence of primary fallopian tube carcinoma was higher as compared to other studies.<sup>3-6</sup>

In this study, the incidence of metastatic tubal malignancy was higher than primary tubal malignancy. This finding is correlated with this study and previous study conducted by Bagwan *et al.*<sup>3</sup> and Gon *et al.*<sup>4</sup> In this study, the incidence of metastatic tumors was higher as compared to other studies.<sup>3,4</sup>

## CONCLUSION

Although the fallopian tubes remain unremarkable in majority of the surgical pathological specimens, it must be subjected for histopathological examination to demonstrate the pathological lesion, and also, it is essential for the pathologist to section the fallopian tubes serially and submit all the representative tissue for microscopic examination so that the diagnosis of these pathological entities is not missed. The role of distal fallopian tube as organ of serous carcinogenesis is an emerging concept. Routine histological examination of the fimbria provides the opportunity to detect these early malignant changes.

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# Histomorphological Study of a Spectrum of Breast Diseases in Association with Immunohistochemistry in Vadodara, Gujarat, India

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## Abstract

**Introduction:** Breast lumps are a cause for concern, both for the patient and surgeon, because of the risk of cancer. In this study, a total of 350 cases of breast pathology were studied which included cases of all ages and histological types. The main purpose of this study was to analyze the spectrum of breast lesions in SSG Hospital, Vadodara, while highlighting the common uses of immunohistochemistry (ICH) in diagnostic breast pathology.

**Materials and Methods:** This observational study was conducted in histopathology section of the Department of Pathology, SSG Hospital, Vadodara. The specimens were grossly examined followed by processing, sectioning from paraffin-embedded blocks, and staining with hematoxylin and eosin. ICH markers were applied on the cases wherever applicable and required from a diagnostic point of view.

**Results:** The most common type of inflammatory lesion of breast was granulomatous mastitis, benign breast lesion was fibroadenoma, and breast malignancy was infiltrating ductal carcinoma-not otherwise specified type. Triple-positive breast cancers in this study were 1.7%. Triple-negative breast cancers in this study were 36.75%. E-cadherin was used in 8 cases. Loss of E-cadherin indicates lobular type. Myoepithelial markers were used in 8 cases in our study. Positivity of these markers confirms the benign nature of the lesion.

**Conclusion:** Microscopy has always been the mainstay of histological diagnosis in breast pathology. However, the growing use of ICH has proved to be advantageous and an incredible aid in the diagnosis. Several cases of diagnostic dilemma such as invasion or pseudoinvasion, ductal or lobular type, and *in situ* or invasion can be reliably diagnosed by the judicious use of ICH markers.

**Key words:** Breast diseases, Histomorphology, Immunohistochemistry

## INTRODUCTION

Breast diseases are showing a rising trend worldwide. A number of studies have been done to know the magnitude of the problem. There is a wide variation in the spectrum of breast diseases in various countries or ethnic groups. Breast lumps are a cause for concern, both for the patient and surgeon, because of the risk of cancer.

Benign breast diseases are more prevalent as compared to malignant and inflammatory lesions, as seen throughout the world. In India, breast cancer forms the second most common malignancy after cervical cancer and is detected in 20/1, 00,000 women.

## Aims of the Study

1. To evaluate the histopathological profile of different breast diseases in SSG Hospital based on hematoxylin and eosin (H and E) sections.
2. To know the frequency of various breast diseases in relation to the age of occurrence in our institute.
3. To distinguish usual ductal hyperplasia from atypical ductal hyperplasia or low-grade carcinoma *in situ* using immunohistochemical (ICH) markers.
4. For the distinction of ductal carcinoma *in situ* (DCIS)

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and lobular carcinoma *in situ* (LCIS), and of invasive ductal carcinoma-not otherwise specified (NOS) and invasive lobular carcinoma using ICH markers.

5. To differentiate *in situ* versus invasive carcinoma; invasion versus pseudoinvasion using myoepithelial markers.
6. To evaluate the prognosis of malignant breast lesions using ICH markers.

## MATERIALS AND METHODS

The present study was conducted at the Department of Pathology, Medical College Baroda and SSG Hospital. The test population comprised patients with breast pathology, between September 2013 and October 2015. The protocol was approved by the local Ethics Committee.

Data for the study were obtained from the departmental records (for retrospective study) and tissue specimens received in the histopathology section (for prospective study) in the specified period of study.

### Tissue Collection

The tissues of the test population submitted were evaluated by histopathological processing and examination (HPE). Pro forma designed to gather uniform necessary information was used for every case. After that, the most suitable tissue block was selected for IHC evaluation.

### Tissue Processing

Tissues were fixed in 10% buffered formalin overnight, for an average period of 16-24 h. The tissue was grossed and representative blocks were processed in the histokinete with a cycle of 24 h, after which the processed tissue was embedded into paraffin wax blocks and then chunked onto wooden chucks. The wax blocks were trimmed using a rotary microtome. Sections were taken onto slides and stained by the routine H and E stain. During the HPE reporting, most of the cases were diagnosed by light microscopy and subsequently, estrogen receptor (ER), progesterone receptor (PR), and Her2 were done on the best section representing the tumor. Only in certain cases where there was diagnostic dilemma, other IHC markers were applied.

### IHC Procedure

The selected tissue block sections were taken up on poly-L-lysine-coated slides for IHC procedure. The slides were deparaffinized in xylene, thereafter brought down to water after passing through increasing grades of alcohol. The peroxidase antiperoxidase method of IHC was followed. Biogenex reagents were used for the antigen retrieval and IHC staining process. The heating cycles followed in the Biogenex temperature-controlled microwave were two cycles of 10 min and 5 min each at 95°C, with intermittent refilling of the antigen retrieval solution.

After that, the slides were brought down to room temperature and taken through the steps of wash with TRIS buffer, peroxide block, power block, and monoclonal antibodies. After this, slides were again washed in TRIS buffer, the secondary antibody exhibited, thereafter DAB chromogen was added. The slides were then washed with water, counterstained with hematoxylin, and blued. Then, the slides were serially dehydrated in alcohol, cleared in xylene, and thereafter mounted using DPX. After drying, the test slides were examined along with the control sections stained simultaneously.

## RESULTS

All the 340 cases were evaluated histopathologically, and 124 cases were subsequently evaluated ICH. The following observations were made.

In our study, the age of patients ranged from 13 to 85 years, with a mean age of 40.5 years. Maximum number of cases were seen in the age group of 41-50 years ( $n = 80$ , 23.53%) followed by the age group of 31-40 years ( $n = 72$ , 21.18%) (Table 1).

Totally 2 cases of borderline phyllodes were found which cannot be classified into either of the above-mentioned categories, resulting in little disparity in the total number of cases.

About 331 out of the 340 cases in our study were females, constituting 97.35% of the total patients (Table 2).

The most common inflammatory lesion in our study was found to be granulomatous mastitis ( $n = 7$ , 43.75% of the total inflammatory lesion cases) (Figure 3) followed by breast abscess ( $n = 6$ , 37.50%) (Figure 1) and duct ectasia ( $n = 2$ , 12.5%) (Figure 2). One case of chronic mastitis was found whereas we did not confront any case of fat necrosis in our study (Table 3).

Table 4 shows that most common benign breast disease in our study was fibroadenoma forming the major bulk with 103 cases out of the total 138 cases of benign breast diseases (74.64%) (Figures 5 and 6). It was followed by 8 cases of fibrocystic disease (6.02%) and 6 cases of gynecomastia (4.51%) (Figure 4). There were 4 cases of phyllodes tumor (Figure 13) (3%), 3 cases each of sclerosing adenosis (Figure 9), lactating adenoma (Figure 7), and intraductal papilloma (Figure 11), 2 cases each of ductal adenosis and galactocoele (Figure 14), and 1 case each of tubular adenoma (Figure 8), florid ductal adenoma (Figure 10), atypical ductal hyperplasia, and radial scar (Figure 12). We did not encounter any case of lipoma, fibromatosis, and lobular hyperplasia in our study.



Out of the 184 cases of malignant lesion in our study, the most common (150) was infiltrating ductal carcinoma (IDC)-NOS (Figure 16), forming 80.64% of the total malignant cases. There were 6 cases of mucinous carcinoma (3.47%) (Figure 18), 5 cases of DCIS (2.89%) (Figure 15), 4 cases of metaplastic carcinoma (2.31%) (Figure 23), 2 cases each of mixed IDC and ILC (Figure 17), medullary carcinoma, metastatic adenocarcinoma (Figure 27), and stromal sarcoma, (Figure 26) and 1 case each of invasive micropapillary carcinoma (Figure 22), papillary carcinoma (Figure 21), secretory carcinoma (Figure 19), and malignant phyllodes (Figure 25). There were no cases of LCIS, ILC, and lymphoma in our study. (Table 5)

Table 1 and 6 shows that most of the benign breast diseases occurred in the age group of 21-30 years ( $n = 49$ ). Of these, 44 were females and 5 were males. It was closely followed by 43 benign cases in the age group of 11-20 years. (Tables 1 and 2)

Whereas, the most common age group facing the malignant breast lesion was 41-50 years ( $n = 64$ ), of which all were females. The age group with second highest frequency of malignant lesions was 51-60 years ( $n = 44$ ), of which 1 was male (diagnosed as IDC-NOS). (Tables 1 and 2)

Thus, out of the total neoplastic cases studied, 93.98% of benign and 99.52% of malignant lesions were seen in females.

**Table 1: Distribution of cases according to age**

Age group	Total (%)	Inflammatory (%)	Benign (%)	Malignant (%)
11-20	43 (12.65)	0 (0)	43 (100)	0 (0)
21-30	64 (18.82)	9 (14.06)	49 (76.56)	16 (25.00)
31-40	72 (21.18)	3 (4.17)	30 (41.67)	39 (54.17)
41-50	80 (23.53)	2 (2.50)	12 (15.0)	64 (82.50)
51-60	44 (12.94)	0 (0)	0 (0)	44 (100)
61-70	30 (8.82)	2 (6.67)	3 (10.00)	25 (83.33)
71-80	6 (1.76)	0 (0)	1 (16.67)	5 (83.34)
81-90	1 (0.29)	0 (0)	0 (0)	1 (100)
Total	340	16 (4.70)	138 (40.59)	184 (54.71)

**Table 2: Distribution of cases according to gender**

Gender	Number of cases (%)
Male	9 (2.65)
Female	331 (97.35)

**Table 3: Incidence of inflammatory lesions**

Type of lesion	Number of cases (%)
Breast abscess	6 (37.50)
Chronic mastitis	1 (6.25)
Granulomatous mastitis	7 (43.75)
Duct ectasia	2 (12.50)
Fat necrosis	0 (0)

Table 7 shows that out of the total 117 cases, those which came out to be ER positive in this study were 37 (31.62%), total PR-positive cases were 35 (29.91%), and Her2neu-positive cases were 36 (30.77%). Whereas, the total number

**Table 4: Incidence of benign lesions**

Type of lesion	Number of cases (%)
Fibroadenoma	103 (74.64)
Fibrocystic disease	8 (6.02)
Sclerosing adenosis	3 (2.26)
Ductal adenosis	2 (1.50)
Lactating adenoma	3 (2.26)
Tubular adenoma	1 (0.75)
Florid ductal adenoma	1 (0.75)
Benign phyllodes tumor	4 (3)
Intraductal papilloma	3 (2.26)
Lipoma	0 (0)
Atypical ductal hyperplasia	1 (0.75)
Fibromatosis	0 (0)
Galactocele	2 (1.50)
Lobular hyperplasia	0 (0)
Radial scar	1 (0.75)
Gynecomastia	6 (4.51)

**Table 5: Incidence of malignant lesions**

Type of lesion	Number of cases (%)
Intraductal carcinoma <i>in situ</i>	5 (2.89)
Lobular carcinoma <i>in situ</i>	0 (0)
Infiltrating duct carcinoma-NOS	150 (80.64)
Invasive lobular carcinoma	0 (0)
IDC+ILC	2 (1.16)
Invasive micropapillary carcinoma	1 (0.58)
Papillary carcinoma	1 (0.58)
Mucinous carcinoma	6 (3.47)
Secretory carcinoma	1 (0.58)
Medullary carcinoma	2 (1.16)
Metaplastic carcinoma	4 (2.31)
Malignant phyllodes	1 (0.58)
Stromal sarcoma	2 (1.16)
Metastatic adenocarcinoma	2 (1.16)
Lymphoma	0 (0)

IDC: Infiltrating ductal carcinoma, NOS: Not otherwise specified

**Table 6: Age and sex distribution in benign and malignant neoplasm**

Age interval (in years)	Benign neoplasm			Malignant neoplasm		
	Number of cases (%)			Number of cases (%)		
	Female	Male	Total cases	Female	Male	Total cases
11-20	41 (95.35)	2 (4.65)	43	0 (0)	0 (0)	0
21-30	44 (89.79)	5 (10.20)	49	16 (100)	0 (0)	16
31-40	29 (96.67)	1 (3.33)	30	39 (100)	0 (0)	39
41-50	12 (100)	0 (0)	12	64 (100)	0 (0)	64
51-60	0 (0)	0 (0)	0	43 (97.73)	1 (2.27)	44
61-70	3 (100)	0 (0)	3	25 (100)	0 (0)	25
71-80	1 (100)	0 (0)	1	5 (100)	0 (0)	5
81-90	0 (0)	0 (0)	0	1 (100)	0 (0)	1
Total	130 (93.98)	8 (6.02)	138	183 (99.52)	1 (0.48)	184

of cases negative for ER, PR, and Her2neu were 80, 82, and 81, respectively.

Table 8 shows the distribution of malignant lesions according to the combined ER/PR status. The number of tumors positive for both ER and PR was 30 (25.64%). Those which were positive for either ER or PR were very few. However, majority of the breast carcinomas in this study came out to be negative for both ER and PR.

**Table 7: Distribution of cases according to ER, PR, and Her2neu status**

IHC marker	Positive cases (%)	Negative cases (%)
ER	37 (31.62)	80 (68.38)
PR	35 (29.91)	82 (70.09)
Her2neu	36 (30.77)	81 (69.23)

IHC: Immunohistochemistry, ER: Estrogen receptor, PR: Progesterone receptor

**Table 8: Distribution of cases according to ER and PR status**

ER/PR status	Number of cases (%)
ER+PR+	30 (25.64)
ER+PR-	7 (5.98)
ER-PR+	6 (5.13)
ER-PR-	74 (63.25)

PR: Progesterone receptor, ER: Estrogen receptor

**Table 9: Distribution of cases as per IHC group results**

IHC status	Number of cases
ER+, PR+, Her2+	2 (1.70)
ER+, PR+, Her2-	27 (23.08)
ER+, PR-, Her2+	3 (2.56)
ER+, PR-, Her2-	4 (3.42)
ER-, PR+, Her2+	1 (0.85)
ER-, PR+, Her2-	7 (5.98)
ER-, PR-, Her2+	30 (25.64)
ER-, PR-, Her2-	43 (36.75)

IHC: Immunohistochemistry, PR: Progesterone receptor, ER: Estrogen receptor

**Table 10: Comparison of distribution of cases according to age**

Criteria	Mansoor (2001) <sup>1</sup>	Prajapati et al. (2014) <sup>2</sup>	Present study (2015)
Mean age in years	35.7 years	37.5 years	40.5 years

**Table 11: Comparison of distribution of cases according to gender**

Sex	Prajapati et al. (2014) <sup>2</sup>	Rahman et al. (2014) <sup>3</sup>	Present study (2015)
Male (%)	0.4	1	2.65
Female (%)	99.6	99	97.35

From Table 9, it can be concluded that majority of the cases in our study were negative for all the three receptors ( $n = 43$ , 36.75%), referred to as triple-negative breast carcinomas. The second majority group was ER-/PR-/Her2+ which comprised 30 cases forming a total of 25.64%. It was followed by ER+/PR+/Her2- group of tumors which occupied 23.08% ( $n = 27$ ). Rest of the tumors constituted about 12% in total.

- In 17 cases of diagnostic dilemma from the histopathological point of view, IHC markers other than ER, PR, and Her2neu were applied. These were as follows:

- Use of E-cadherin was done in 8 cases for distinguishing between ductal and lobular carcinoma. Of these, 6 came out to be IDC-NOS while 2 came out to be mixed ductal and lobular carcinoma (Figure 28).
- Myoepithelial markers were applied in 8 cases to confirm invasion or pseudoinvasion in cases. These were 2 cases of breast papilloma and one each of ductal adenosis, radial scar, and fibroadenoma. In all these cases, myoepithelial markers were positive. In 3 cases, these markers were negative and were diagnosed as IDC (Figures 11, 12 and 15).
- There was one case of secretory carcinoma which was confirmed with the help of IHC markers. The results were positive for S100, polyCEA, and EMA whereas CK5/6, Type IV collagen, and gross cystic disease fluid protein (GCDFP) were negative (Figure 19).
- In one case of triple-negative IDC, basal cell IHC markers were applied and they came out to be positive, confirming the basal-like carcinoma of breast (Figure 24).
- Two cases had a differential diagnosis of lymphoma, melanoma, and neuroendocrine carcinoma. However, the respective markers, i.e., CD45, CD20, HMB45, synaptophysin, and chromogranin were found to be negative. Hence, the diagnosis of IDC-NOS was made (Figure 29).

## DISCUSSION

In the present study, the age of patients ranged from 13 to 85 years, with a mean age group of 40.5 years (Table 10). Maximum number of cases were seen in the age group of 41-50 years (23.53%). This is probably because, in our study, malignant cases were more than the benign and inflammatory lesions combined. Hence, the load of breast lesions is tilted toward the higher age.

In the present study, out of 340 cases, only 9 (2.65%) cases were males and the remaining 331 (97.35%) cases were females (Table 11). The male-to-female ratio was 1:37.

**Table 12: Comparison of incidence of inflammatory lesions**

Criteria	Mansoor (2001) <sup>1</sup>	Aslam <i>et al.</i> (2013) <sup>4</sup>	Rahman <i>et al.</i> (2014) <sup>3</sup>	Present study (2015)
Percentage of cases (%)	10.7	11.8	19.24	4.70

**Table 13: Comparison of distribution of benign lesions**

Criteria	Mansoor (2001) <sup>1</sup>	Shanthi <i>et al.</i> (2011) <sup>5</sup>	Aslam <i>et al.</i> (2013) <sup>4</sup>	Rahman <i>et al.</i> (2014) <sup>3</sup>	Present study (2015)
Percentage of cases out of the total number of cases (%)	56.87	68	75.30	76.66	40.59
Most common (percentage of total benign cases)	Fibroadenoma (66.86%)	Fibroadenoma (70.83%)	Fibroadenoma (71.3%)	Fibroadenoma (70.88%)	Fibroadenoma (74.64%)

**Table 14: Comparison of distribution of malignant breast lesions**

Criteria	Mansoor (2001) <sup>1</sup>	Shanthi <i>et al.</i> (2011) <sup>5</sup>	Aslam <i>et al.</i> (2013) <sup>4</sup>	Rahman <i>et al.</i> (2014) <sup>3</sup>	Present study (2015)
Percentage of cases out of the total number of cases	32.42	24	11.80	23.34	54.71
Most common (percentage of total malignant cases)	IDC-NOS (87.70)	IDC-NOS (78.57)	IDC-NOS (100)	IDC-NOS (94.59)	IDC-NOS (80.64)

NOS: Not otherwise specified, IDC: Infiltrating ductal carcinoma

**Table 15: Comparison of distribution of cases according to ER, PR, and Her2neu status**

Marker	Ambrose <i>et al.</i> (2010) <sup>6</sup>	Ali <i>et al.</i> (2014) <sup>8</sup>	Doval <i>et al.</i> (2015) <sup>7</sup>	Present study
ER+ (%)	59	78.7	30.12	31.62
PR+ (%)	51	76.4	27.95	29.91
Her2neu+ (%)	27	13.2	23.0	30.77
Triple negative (%)	20.67	15.5	23.8	36.75

PR: Progesterone receptor, ER: Estrogen receptor

Universally, the breast cancer gender ratio of male:female is in the range of 1:99. The present study had one case of male breast cancer which automatically pushed the incidence to above 2%. This is very much in accordance with the past studies done by Prajapati *et al.*<sup>2</sup> in 2014 and Rahman *et al.*<sup>3</sup> in 2014.

In the present study, out of the 340 cases studied, inflammatory lesions' group contained 16 cases (4.70%) (Table 12). Of these, the most common inflammatory lesion was granulomatous mastitis ( $n = 7$ , 43.75%) and the most common age group was 21-30 years. The probable reason behind this is that most of the inflammatory lesions in our tertiary setup are diagnosed by fine-needle aspiration cytology and biopsy is not sent to the laboratory.

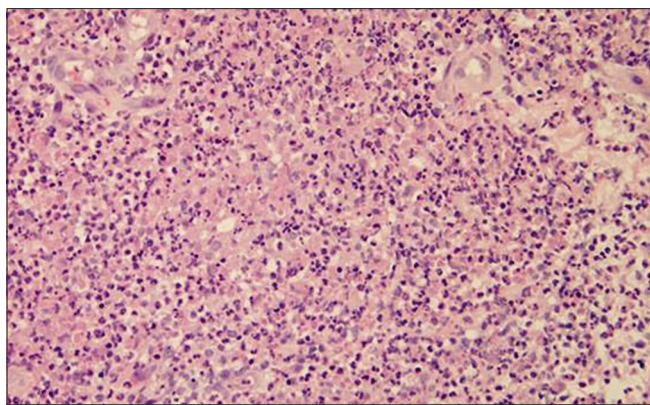
In the present study, out of the 340 cases, 138 were benign (40.59%). Most of the benign cases fell in the age group of 21-30 years ( $n = 49$ ) closely followed by 11-20 years ( $n = 43$ ). In accordance with the past studies, in the present study also, the most common benign breast lesion was found to be fibroadenoma constituting a total of 103 cases (74.64% of the total benign breast diseases and 30.29% of

the total breast lesions). Fibroadenoma occupied 66.86% of the total benign cases studied by Mansoor, 70.83% in a study by Shanthi *et al.*, 71.3% in a study by Aslam *et al.*, and 70.88% in a study carried out by Rahman *et al.* This clearly concludes that fibroadenoma is the most common benign breast lesion. (Table 13)

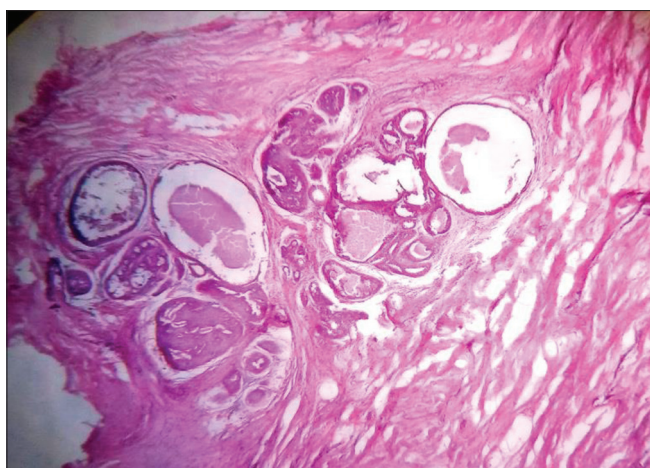
In the present study, out of the 340 cases, 186 were malignant (54.71%). The finding that breast cancer was slightly more common than benign breast lesions in this study is at variance with most studies, probably because being a tertiary health-care facility, most of the patients admitted here are referred as malignant cases from the periphery and the growing environment of private-owned hospitals by general practitioners where most of the benign lesions are probably managed. In this study, most of the malignant cases were found to be in the age group of 41-50 years ( $n = 64$ , 82.5%). The most common breast cancer was found to be IDC-NOS, constituting a total of 150 cases (80.64%). This is similar to the past studies conducted by Mansoor in 2001, Shanthi *et al.* in 2011, Aslam *et al.* in 2013, and Rahman *et al.* in 2014. From the above data, we can conclude that IDC-NOS is the most common breast carcinoma. However, a large variety of cases were seen in this study in variable numbers. (Table 14)

Expression of both ER and PR was specifically nuclear while positive expression of HER2 was demonstrated as continuous membranous immunoreaction. In our study, total cases positive for ER, PR, and Her2 were 31.62%, 29.91%, and 30.77%, respectively. These results were 59%, 51%, and 27% in the study conducted by Ambrose *et al.*, 78.7%, 76.4%, and 13.2% as per Ali *et al.*, and 30.12%,

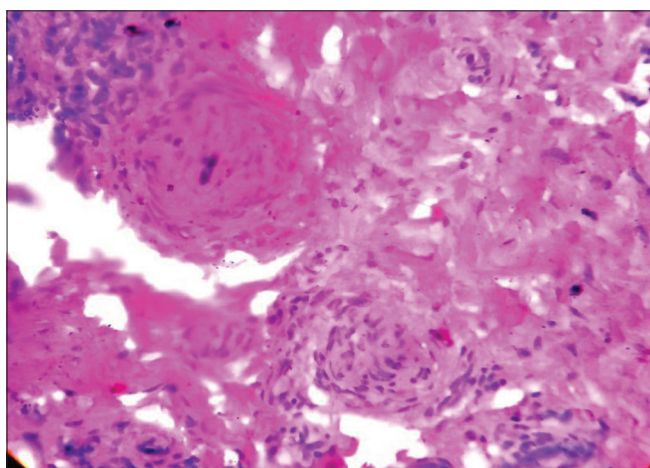




**Figure 1: Breast abscess showing plenty of neutrophils and obliteration of lobular pattern (H and E; x100)**



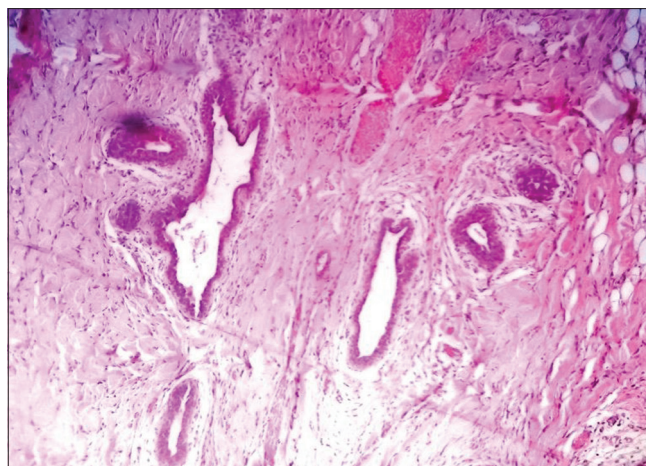
**Figure 2: Duct ectasia showing dilated large ducts with fatty detritus in lumen and fibrous thickening of wall (H and E; x100)**



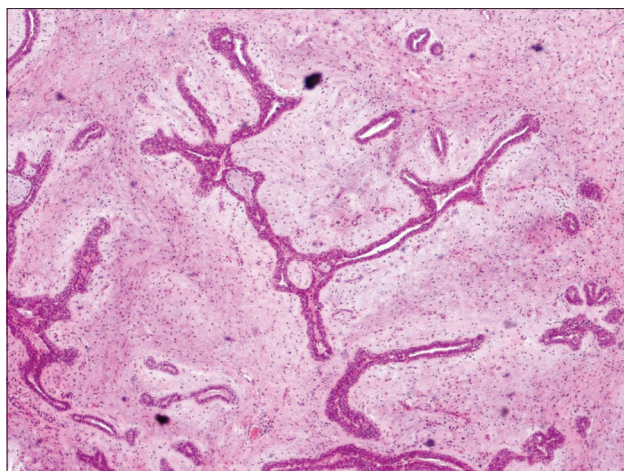
**Figure 3: Granulomatous mastitis showing foreign body granulomas (H and E; x100)**

27.95%, and 23% in the study done by Doval *et al.* for ER, PR, and Her2 positivity, respectively. (Table 15)

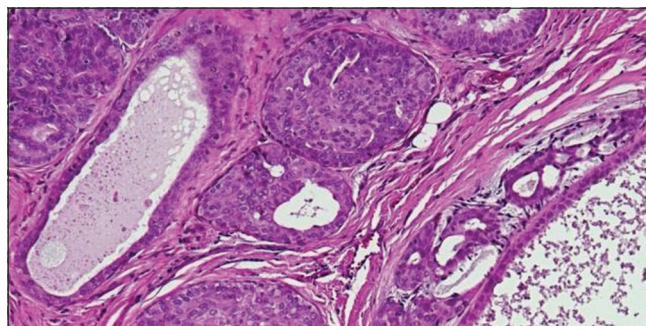
In our study, as far as triple-negative breast carcinomas are concerned, 36.75% of the total breast malignancies were



**Figure 4: Gynecomastia showing epithelial proliferation surrounded by edematous stroma (H and E; x100)**



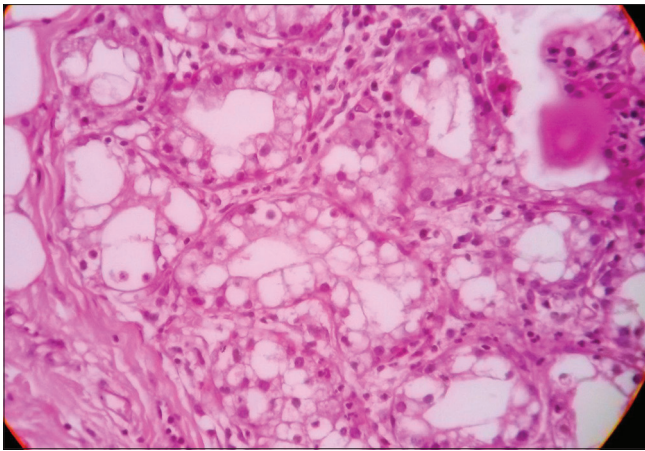
**Figure 5: Fibroadenoma showing tubular glandular formations lined by ductal epithelial and myoepithelial cells surrounded by loose connective tissue (H and E; x100)**



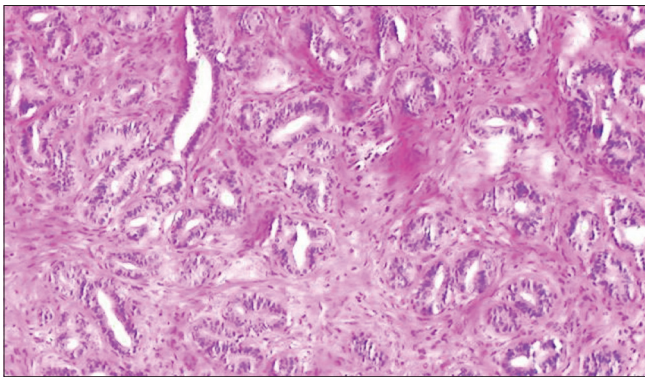
**Figure 6: Fibrocystic disease of breast showing cystic dilation, apocrine metaplasia and florid ductal hyperplasia (H and E; x400)**

negative for ER, PR, as well as Her2neu. They presented with a mean age group of 50 years, and majority of the patients were aged between 40 and 65 years. Similar results were obtained by Doval *et al.* (2015)<sup>7</sup>. According to their study, the patients with triple-negative tumors presented at a mean age of 50 years and majority of the patients (51.5%)

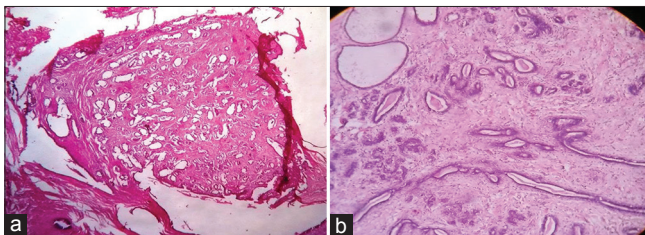




**Figure 7: Lactating adenoma of breast showing proliferated glands lined by actively secreting cuboidal cells with marked cytoplasmic vacuolation (H and E; x400)**



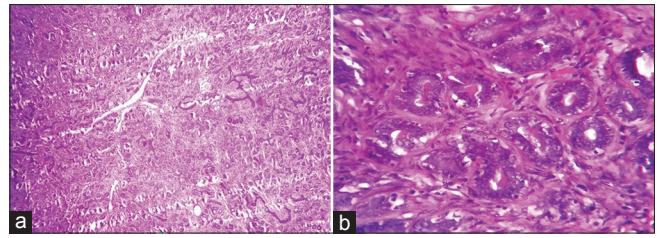
**Figure 8: Tubular adenoma showing closely packed uniform small tubules lined by epithelial and myoepithelial cells (H and E; x100)**



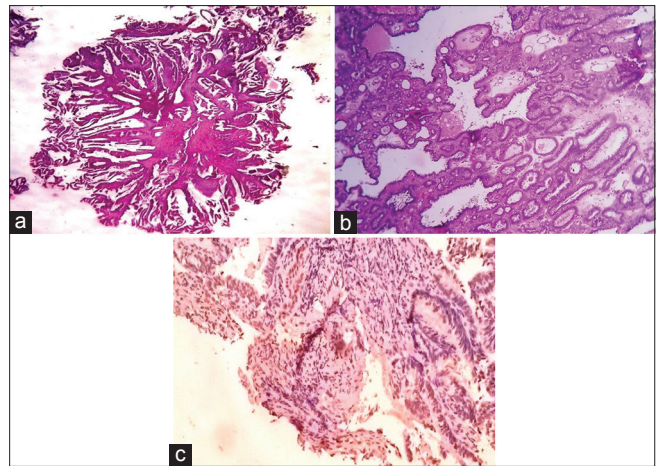
**Figure 9: (a) Histomorphology of sclerosing adenosis of breast showing nodular architecture (H and E; x40), and (b) atrophy of epithelial cells, cystically dilated glands and increased intralobular stroma (H and E; x100)**

were in the age group of 20-50 years as compared to the non-triple-negative tumor group. In the study conducted by Basu *et al.* (2008)<sup>9</sup>, “triple-negative” group comprised 14.08% of the total study population. The age of the patients with this subtype of tumor ranged from 33 years to 75 years.

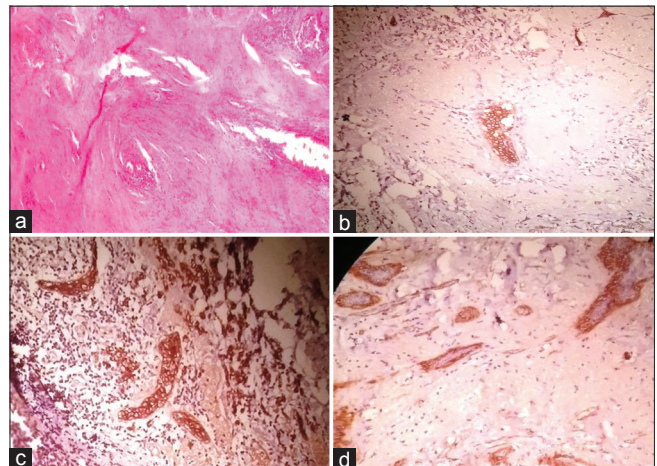
- There were 17 cases in our study where IHC markers other than ER, PR, and Her2neu were applied. These are discussed as follows:



**Figure 10: (a and b) Histomorphology of florid ductal adenoma of breast showing effaced architecture due to increased proliferation of glands (H and E; a - x100 and b - x400)**



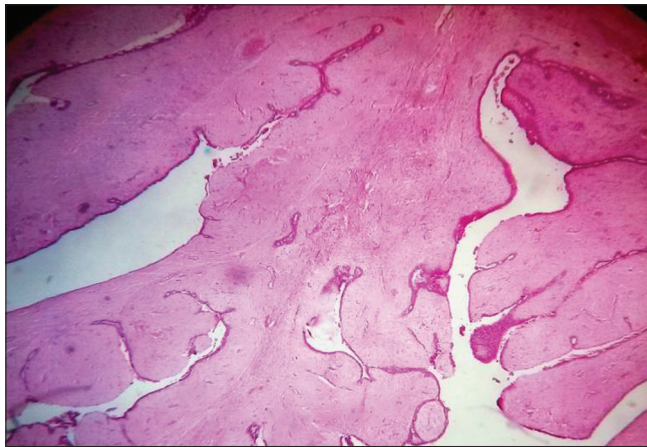
**Figure 11: (a) Histomorphology of benign intraductal papilloma of breast showing complex arborizing architecture (H and E; x40), and (b) well defined dual cell composition (H and E; x100), and (c) well defined row of myoepithelial cells highlighted by p63 positivity**



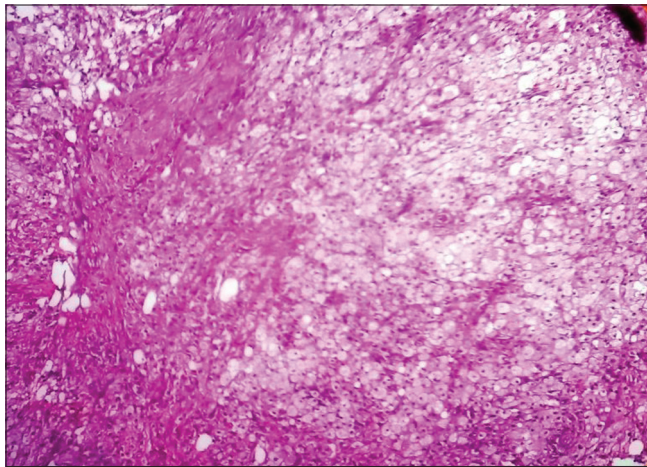
**Figure 12: (a) Histomorphology of radial scar of breast showing stellate shaped central fibrous core and variable degree of epithelial distortion and proliferation (H and E; x100), (b) The entrapped ductular cells show positivity for CK7, (c) Pankeratin, and (d) myoepithelial cells stain for S100**

- In 8 cases, E-cadherin was applied to differentiate between ductal and lobular carcinoma. Of these, 6 came out to be IDC-NOS while 2 came out to be mixed ductal and lobular carcinoma. According

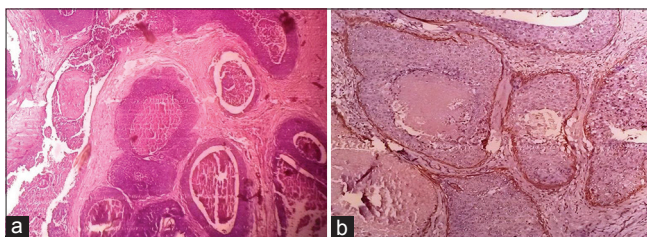




**Figure 13: Benign phyllodes tumor of breast showing stromal hypercellularity and benign glandular elements (H and E;  $\times 100$ )**

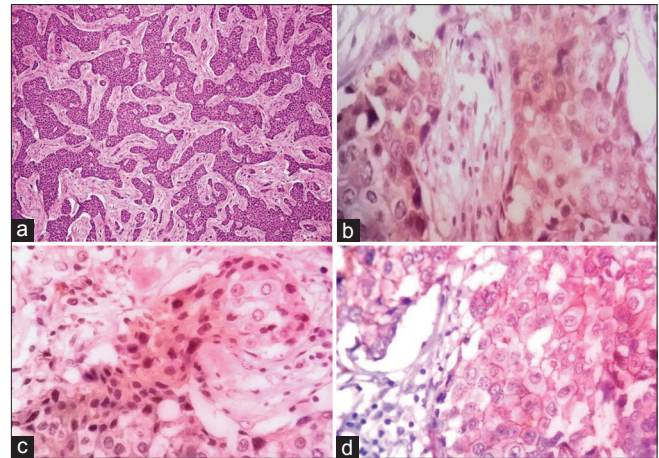


**Figure 14: Galactocoele showing dilated, anastomosing, epithelium lined channels with secretory activity (H and E;  $\times 400$ )**

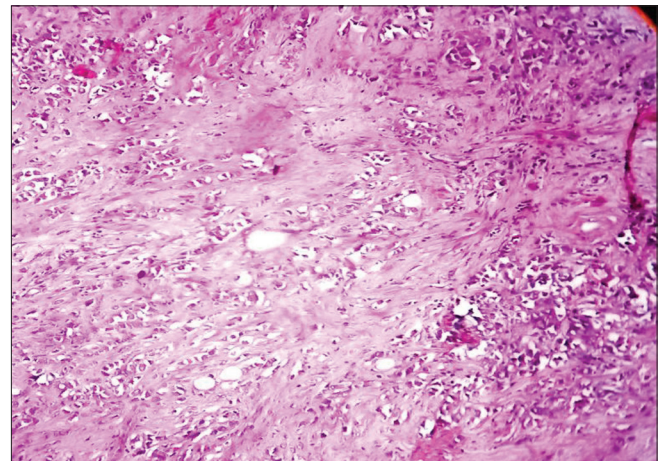


**Figure 15: (a) Histomorphology of ductal carcinoma *in situ* of breast, Comedo type showing ducts with solid growth of large, pleomorphic tumor cells along with comedo type of central necrosis (H and E;  $\times 100$ ), and (b) presence of myoepithelial cells confirmed by calponin**

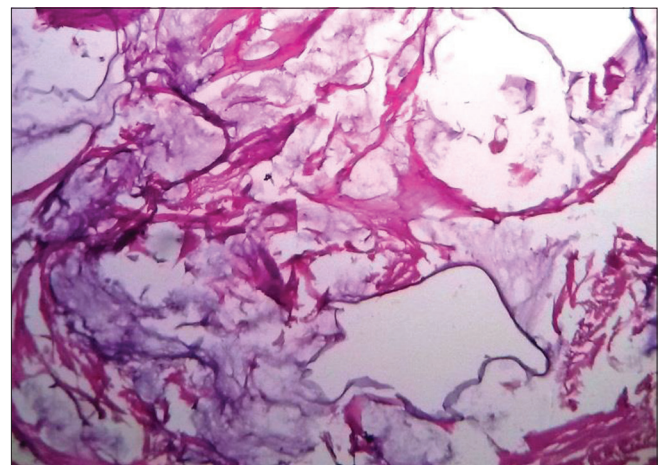
to an article published in the Arch Pathology Laboratory Medicine, 2008<sup>10</sup>, E-cadherin, a cell-cohesion protein encoded by a gene on chromosome 16q22.1, is the current marker of choice to help discriminate between lobular and ductal carcinoma. The majority of usual ductal carcinomas express cytoplasmic E-cadherin, whereas most *in situ* and



**Figure 16: (a) Histomorphology of invasive ductal carcinoma of breast- not otherwise specified showing large pleomorphic ductal epithelial cells in sheets and cords having prominent nuclei with surrounding desmoplasia (H and E;  $\times 100$ ), (b) Estrogen receptor positivity, (c) Progesterone receptor positivity, and (d) Her2 positivity**

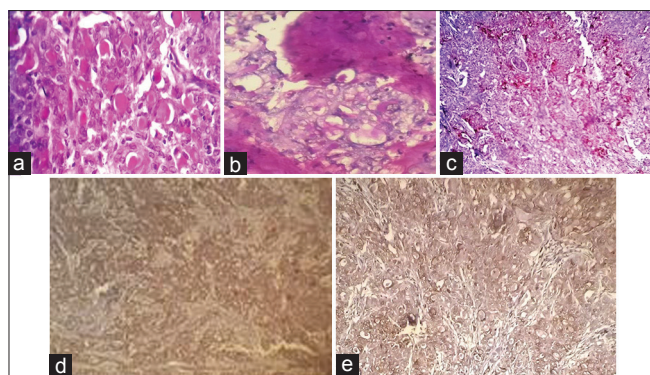


**Figure 17: Mixed infiltrating ductal carcinoma and ILC of breast- right corner shows infiltrating ductal carcinoma component and central part shows ILC component**

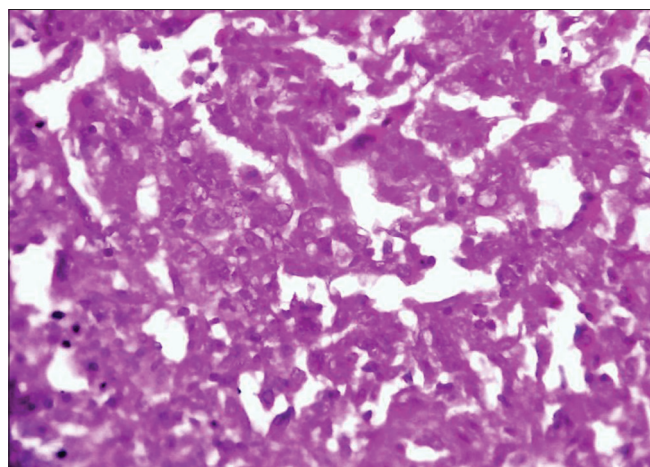


**Figure 18: Mucinous carcinoma of breast showing tumor cells in pools of extracellular mucin (H and E;  $\times 100$ )**

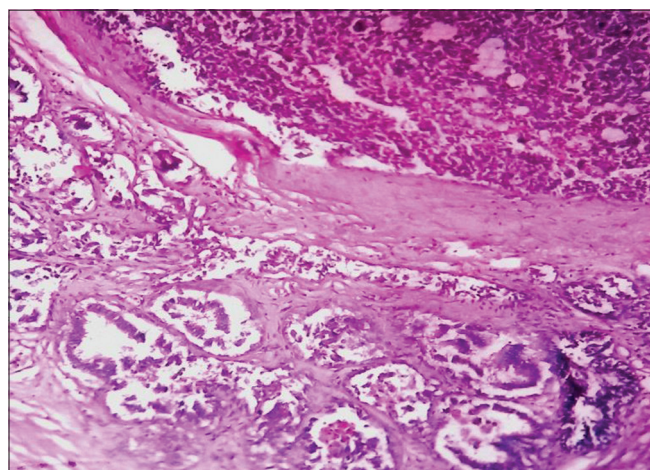




**Figure 19:** (a) Histomorphology of Secretory carcinoma of breast- showing tubuloalveolar formations lined by cells with vacuolated cytoplasm forming lumina filled with eosinophilic PAS positive secretions (A; H and E;  $\times 400$ ), (b) PAS stain, (c) Strong reactivity for S100, (d), polyCEA, and (e) EMA

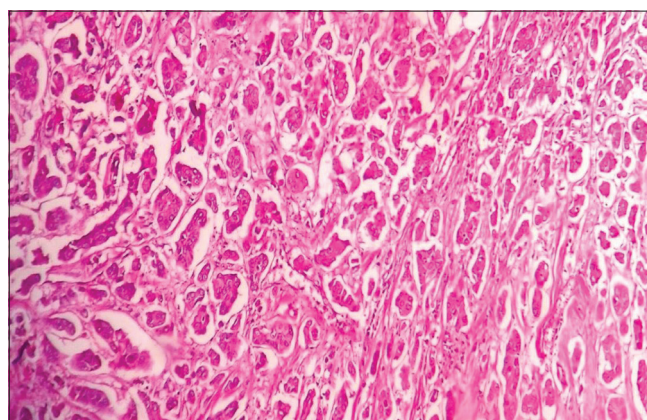


**Figure 20:** Medullary carcinoma of breast showing large tumor cells in syncytial pattern surrounded by stroma infiltrated by lymphocytes (H and E;  $\times 400$ )

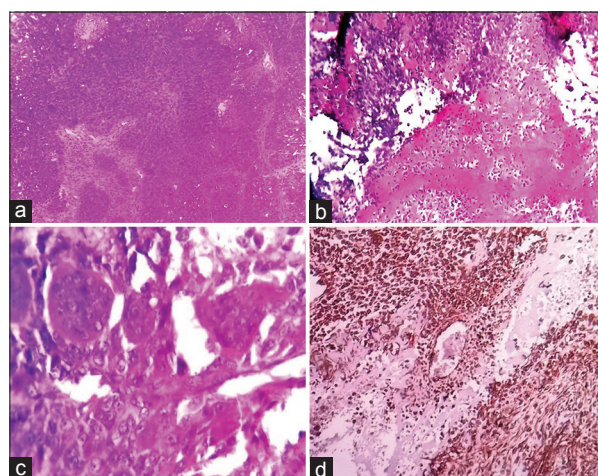


**Figure 21:** Papillary carcinoma of breast showing papillary formations with fibrovascular core (H and E;  $\times 400$ )

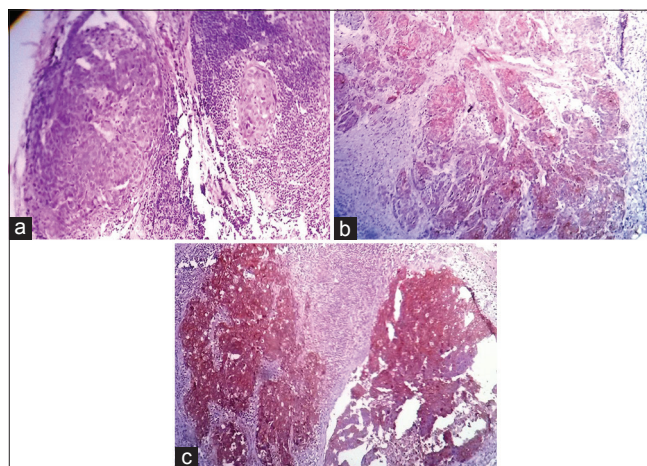
invasive lobular carcinomas, both classic and pleomorphic types, lack expression.



**Figure 22:** Invasive micropapillary carcinoma of breast showing pseudopapillary structures lacking fibrovascular core and tubular structures free floating in clear empty spaces (H and E;  $\times 400$ )

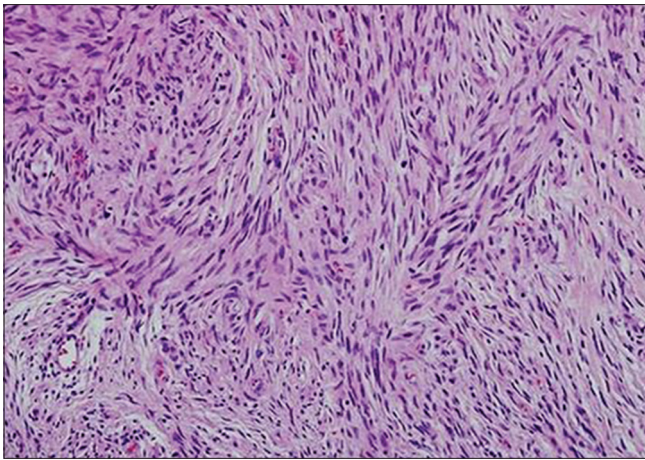


**Figure 23:** (a) Histomorphology of Metaplastic carcinoma of breast- showing squamous differentiation (H and E;  $\times 100$ ), (b) chondroid differentiation (H and E;  $\times 100$ ), (c) osteoclastic giant cells (H and E;  $\times 400$ ), and (d) vimentin positivity

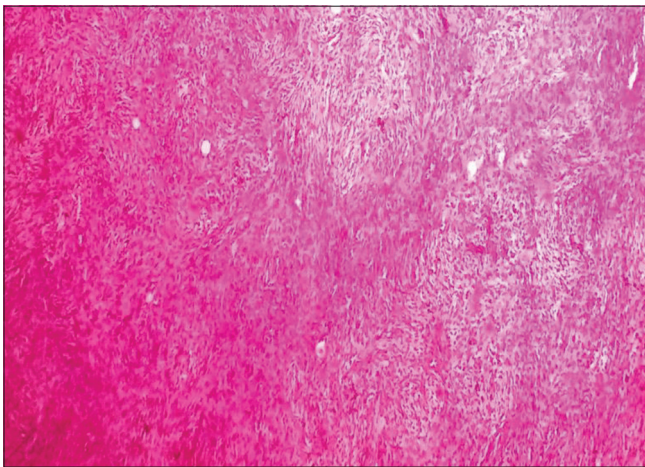


**Figure 24:** (a) Histomorphology of Basal like infiltrating ductal carcinoma of breast- showing high grade tumor with necrosis and lymphocytic response (H and E;  $\times 100$ ), and (b) positivity for basal like keratins CK5/6, and (c) EGFR, (d) These are triple negative tumors

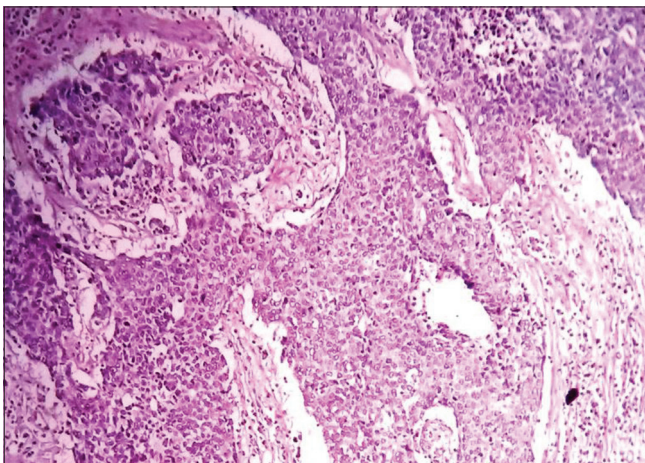




**Figure 25: Malignant phylloides tumor of breast showing markedly hypercellular stroma (H and E; x100)**

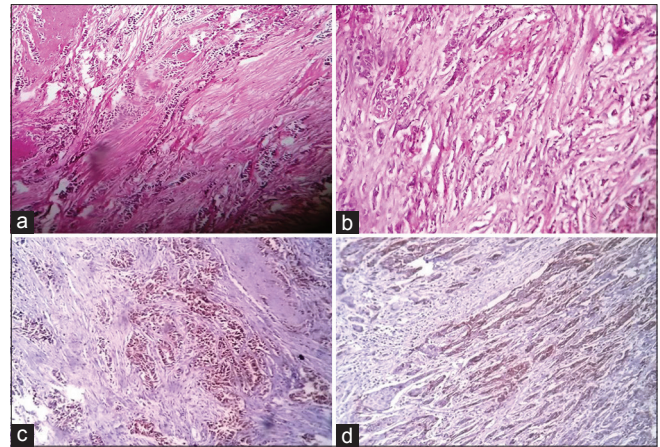


**Figure 26: Stromal sarcoma of breast**

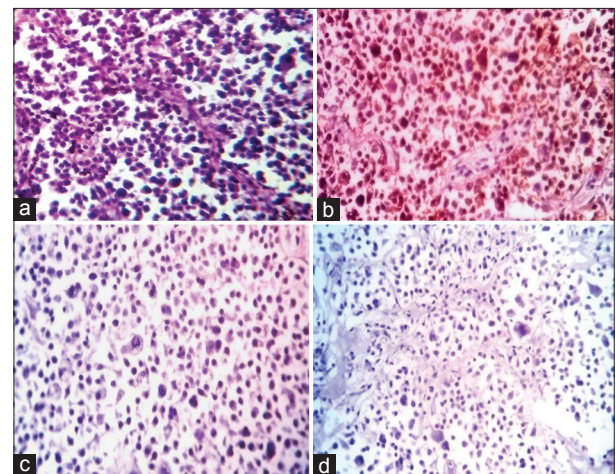


**Figure 27: Metastatic adenosquamous carcinoma of breast**

II. Myoepithelial markers were applied in 8 cases to confirm invasion or pseudoinvasion in cases. About 5 cases showed the presence of myoepithelial cells confirming the benign nature of the lesion. These were 2 cases of breast



**Figure 28: Diagnostic dilemma between infiltrating ductal carcinoma and ILC of breast (H and E; a and b), solved by E cadherin positivity, (c and d) which represents presence of cohesiveness in infiltrating ductal carcinoma**



**Figure 29: (a) Diagnostic dilemma between poorly differentiated infiltrating ductal carcinoma of breast and melanoma or lymphoma (H and E; x400), (b) was solved by E cadherin positivity, (c), lack of HMB45 reactivity, (d) lack of CD20 reactivity**

papilloma and one case each of ductal adenosis, radial scar, and fibroadenoma. In 3 cases, these markers were negative and were diagnosed as IDC. In addition to penetrating basement membrane, invasive carcinomas lack the mucoepithelial carcinoma layer that normally surrounds benign breast glands. This observation is the basis of using myoepithelial markers to distinguish invasive carcinoma from infiltrative mimics.<sup>11,12</sup>

III. One case of secretory carcinoma was confirmed by positive S100, polyCEA, and EMA. GCDFP usually shows variable positivity in secretory carcinoma. However, in our case, it was negative. In the past, some of the cases of microglandular adenosis were misdiagnosed as secretory carcinoma. Hence, Type IV collagen and CK5/6 were applied but they came out to be negative, confirming the absence of basement membrane.<sup>13</sup>



- IV. In another case which was negative for ER, PR, and Her2 (triple negative), epidermal growth factor receptor and CK5/6 were applied which showed positive results. Such kind of ICH profile is shown by basal-like carcinomas. According to a study done by Abd El-Rehim *et al.*<sup>14</sup> on the expression of luminal and basal cytokeratins in human breast carcinoma, the tumors expressing a basal phenotype or a mixed basal/luminal phenotype have a worse prognosis. The basal phenotype correlates with high-grade IDC-NOS, as well as with medullary carcinomas, adenoid cystic carcinomas, and squamous differentiation (metaplastic carcinomas).
- V. High-grade IDC-NOS can be difficult to distinguish from lymphoma, melanoma, and neuroendocrine carcinoma. In this study, 2 such cases were confirmed immunohistochemically by their respective markers, i.e., CD45, CD20, HMB45, synaptophysin, and chromogranin. These all were found to be negative.

## CONCLUSION

This study comprised 340 cases of breast lesion. The cases presented to SSG Hospital and Medical College Baroda. The surgical specimens were then evaluated histopathologically, and 124 cases were analyzed ICH.

Based on the above study, the following conclusions were drawn:

- The age group of patients ranged from 13 to 85 years, with a mean age of 40.5 years.
- Male-to-female ratio in this study was 1:37.
- The incidence rate of inflammatory lesions was 4.7%.
- The most common presenting age group for inflammatory lesions was 21-30 years (9 cases).
- The most common type of inflammatory lesion of breast was granulomatous mastitis (7 cases, 43.75% of the total cases of inflammatory lesions).
- The incidence rate of benign lesion was 40.59%.
- The most common presenting age group for benign breast lesion was 21-30 years (49 cases).
- The most common histopathological type of benign breast lesion was fibroadenoma (103 cases, 74.64% of the total benign breast diseases).
- The incidence rate of malignant lesions was 54.71%.
- Most of the malignant cases presented at the age group of 41-50 years (64 cases).
- The most common histopathological subtype of breast

malignancy was IDC-NOS type (150 cases, 80.64% of the total cases with malignant lesion).

- Two cases of borderline phyllodes were found.
- Percentage of ER positivity in this study was 31.62%.
- Percentage of PR positivity in this study was 29.91%.
- Percentage of Her2neu positivity in this study was 30.77%.
- Triple-positive breast cancers in this study were 1.7%.
- Triple-negative breast cancers in this study were 36.75%.
- E-cadherin is helpful in differentiating IDC from ILC as in 8 cases in our study. Loss of E-cadherin indicates lobular type.
- Myoepithelial markers can aid in ruling out invasion or pseudoinvasion. This was used in 8 cases in our study. Positivity of these markers confirms the benign nature of the lesion.

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# A Study of Lipid Profile in Diabetes Mellitus

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## Abstract

**Background and Objectives:** Diabetes mellitus (DM) is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized, producing hyperglycemia. Furthermore, it is proposed that underutilization of glucose is associated with changes in lipid profile. Changes in lipid profile are also well related with severity of DM as adjudged by glycated hemoglobin (HbA1c). The study intends to find any correlation among above factors.

**Methods:** This study involved 40 participants of which 20 were patients admitted with diagnosis of DM, and other 20 were age and sex matched healthy controls who fulfilled inclusion criteria. Blood samples were drawn under aseptic precautions from cases of DM and healthy controls. Necessary investigations were carried out and values were tabulated for cases, and controls separately for statistical evaluation.

**Results:** In DM patients compared to controls significant increase in following parameters was observed. Fasting blood sugar (FBS), post prandial blood sugar (PPBS), HbA1c, and lipoprotein(a) levels increased significantly ( $P < 0.001$ ). HbA1c/high-density lipoprotein (HDL), HbA1c/low density lipoprotein (LDL), and HbA1c/cholesterol ratios also increased significantly ( $P < 0.001$ ). Furthermore, the levels of triacylglycerol (TAG), very LDL (VLDL), and cholesterol/HDL were significantly increased with  $P < 0.008$ ,  $P < 0.011$ , and  $P < 0.003$ , respectively. The levels of HDL were significantly reduced in patients with DM compared to controls with  $P < 0.001$ . There is no significant change observed in cholesterol, LDL, and HbA1c/lipoprotein(a) levels.

**Conclusions:** There is a statistically significant large effect in FBS, PPBS, HbA1c, TAG, VLDL, HDL, and lipoprotein(a) levels of cases compared with controls, whereas LDL and cholesterol levels are no significant. Increased cholesterol/HDL ratio is well-known risk factors of coronary artery disease. HDL, LDL, cholesterol, and TAG levels were well associated with HbA1c, whereas lipoprotein(a) levels are not associated with HbA1c. Hence, our conclusion is that lipoprotein(a) may not be a dependable risk factor for coronary heart disease.

**Key words:** Cholesterol, Diabetes mellitus, Glycated hemoglobin, Lipid profile, Lipoprotein(a)

## INTRODUCTION

Diabetes mellitus (DM) is the most common metabolic disorder affecting the people worldwide. Even though diabetes has been known since antiquity, only in the last few decades new discoveries have provided great hopes to minimize morbidity and mortality. It is estimated that for one diagnosed diabetes there is undetected diabetes. The diabetic ketoacidosis was major fatal complication of diabetes has virtually come down with advent of insulin.

However, the vascular complications have remained same and they have replaced diabetic ketoacidosis as the frequent cause death in diabetes.

Dyslipidemia is commonly seen diabetes. Type 2 DM is one of the most common secondary causes of hyperlipidemia. The relationship between hyperlipidemia and vascular complication of diabetes has long been of interest because both tend to occur with greater frequency in Type 2 DM. Insulin resistance and obesity combine to cause dyslipidemia and hyperglycemia and hyperlipidemia have additive cardiovascular risk. It is recommended that patients with DM should be treated as if they already have coronary artery disease.

Hence identification, critical evaluation, and follow-up of serum lipid profile in Type 2 DM continue to be important.<sup>1-4</sup>

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## MATERIALS AND METHODS

### Source of Data

The subjects for the study are selected from patients who are admitted to tertiary care hospital.

### Method of Collection of Data

From the patients admitted 50 representative cases with H/O Type 2 DM are taken as subjects for the study. Age and sex matches 50 nondiabetic are taken as controls. The diagnosis of diabetes is based on revised criteria according to consensus panel of experts from the National Diabetes Data Group and WHO.

### Inclusion Criteria

1. Patients with Type 2 DM of more than 40 years
2. Duration of diabetes more than 4 years.

### Exclusion Criteria

Type 2 diabetes patients with concomitant diseases or condition affecting the lipid levels such as hypothyroidism, on lipostatic drugs, and thiazides.

- A detailed history and careful physical examination
- Routine blood and urine examination
- Biochemical analysis for fasting blood sugar (FBS) and post prandial blood sugar (PPBS)
- Fasting serum triglycerides (TGs)
- Total cholesterol (TC)
- High-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C).

### Blood Sampling and Preparation of Serum

The blood samples were drawn in the fasting state. The venepuncture was done in the cubital fossa. Tourniquet was used but was released just before sampling to avoid artificial increase in the concentration of serum lipids. About 10 ml of blood was drawn using perfectly dry and sterile syringes, and the blood was transferred to dried glass vials.

Serum was separated within 2 h of collection to prevent artificial changes in concentration of HDL. The blood was centrifuged at 5000 rpm for 10 min. The supernatant clear serum was then pipette out using dry piston pipettes with disposable tips and stored in dry thin walled vials at 4°C. The samples were analyzed the same day. Care was taken to exclude the hemolyzed serum.

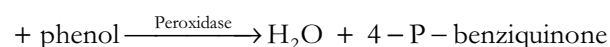
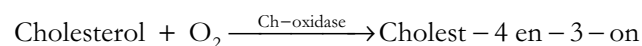
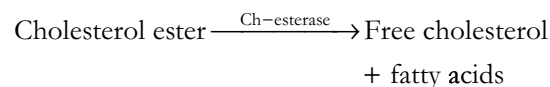
### Laboratory Procedure

The lipid and lipoprotein assay was done using Dr. Lange LP 700 equipment.

### Estimation of TC

Method - CHOD - DAP method.

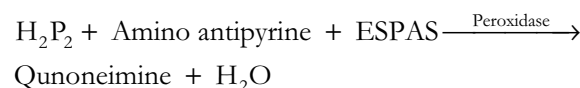
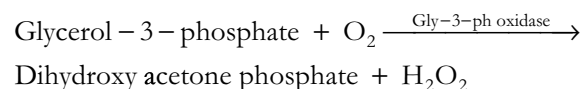
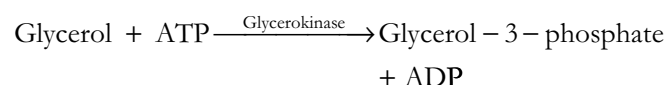
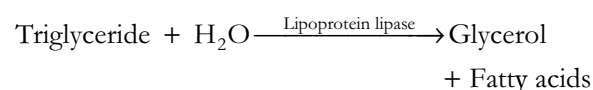
Principle-enzymatic estimation:



### Estimation of total TGs

Method: GPO-DAP method.

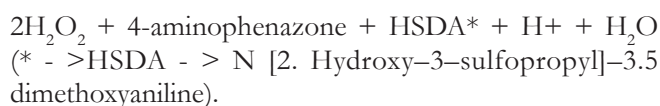
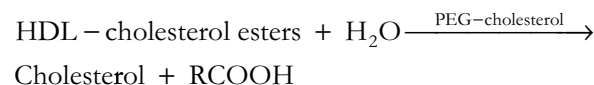
Principle-enzymatic estimation:



### Estimation of HDL-C

Principle: Enzymatic estimation.

Determination of HDL-C in serum and plasma using polyethane glycol (PEG) modified enzymes, sulfated and cyclodextrin and dextran sulfate. When cholesterol esterase and cholesterol oxidase enzymes are modified by PEG, they show selective catalytic activities toward lipoprotein fractions, with the reactivity increasing in the order LDL < very LDL (VLDL) = Chylomicrons < HDL. In the presence of magnesium ions, sulfated alpha - cyclodextrin reduces the reactivity of cholesterol especially in chylomicrons and VLDL without the need for precipitation of lipoprotein aggregate.



### Test Principle

Chylomicrons, VLDL, and LDL are precipitated by adding phosphotungstic acid and magnesium ions to the sample. Centrifugation leaves only the HDL in the supernatant. Their cholesterol content is determined enzymatically.

Clinical interpretation: Normal range - 35-55 mg/dl.

It is considered as a risk factor if HDL-C level was <35 mg/dl.

### References

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### LDL Cholesterol (LDL-C) Estimation

$LDL = TC - HDL - \text{serum TG}/5$ .

### VLDL-C

In the absence of chylomicrons, only three forms of lipoproteins are present in the sera - VLDL, LDL, and HDL. Since VLDL is the primary TG carrying form in the fasting state, its concentration can be approximated by dividing the amount of plasma TGs by described by Friedewald in 1972.

### Statement of Limitations

Lipoprotein(a) is not evaluated in the study.

Vascular complications are not documented by more appropriate investigations like angiography, Doppler study.

### Statistical Analysis

The mean levels of various fractions were correlated with basal reference values for normal individuals. Relevant statistical methods like “Z significant test” (The manual of statistical methods for use in health and nutrition) were used to see the significance of deference in mean values between groups and to know the correlation between inter and intergroup variations.

## OBSERVATION RESULT

A total number of 50 patients suffering from Type 2 DM were studied results of various clinical and biochemical parameters and their interrelationship are as follows Table 1 and Graph 1.

### Duration of Diabetes

The average duration of diabetes ranged from 4 to 12. The majority of the patients had diabetes of between 5 and 10 years and few had diabetes more than 10 years.

### Types of Treatment

24 patients out of 50 were taking only oral hypoglycemic drugs (OHDs), 10 were taking both OHD and insulin. The remaining 10 were taking only insulin.

### Degree of Control of Diabetics

The distribution of patients according to the degree of glycemic control based on glycated hemoglobin (HbA1c) level is shown in the Table 2 and Graph 2.

- 18 patients had Grade I severity
- 26 patients had Grade II severity
- 6 patients had Grade III severity.

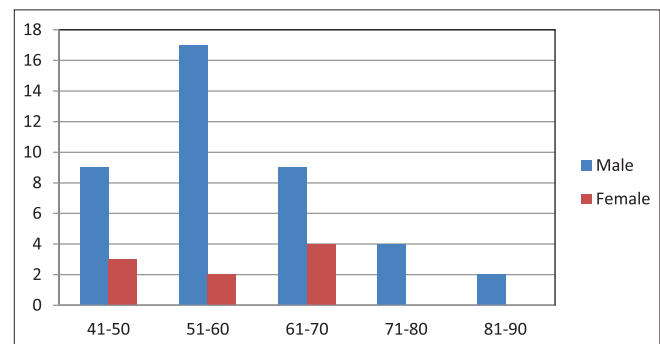
**Table 1: Age and sex distribution**

Age	Male	Female
41-50	9	3
51-60	17	2
61-70	9	4
71-80	4	0
81-90	2	0

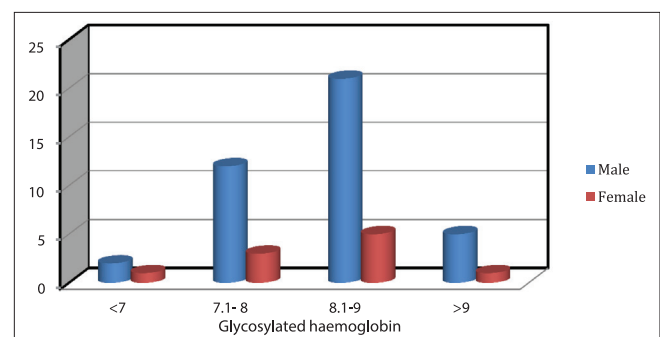
**Table 2: Degree of control of diabetics**

HbA1c	Male	Female
<7	2	1
7.1-8	12	3
8.1-9	21	5
>9	5	1

HbA1c: Glycated hemoglobin



**Graph 1: Age and sex distribution**



**Graph 2: Degree of control of diabetics**

### Incidence of Various Complications

The incidence of various complications observed in this study is in the Table 3 and Graph 3. It is observed from the study that retinopathy and peripheral neuropathy were the most common complication 52% and 40%, respectively. Next common was ischemic heart diseases 28%. The list common was cerebrovascular accident. 14% of patients of the study group had no complications.

### Comparison of Various Lipid Levels between Diabetes (Study) and Control Group

The Table 4 shows the mean values with standard deviation of various lipid traction of diabetes in comparison to that controls.

If can be seen that mean value all range of lipid fractions except HDL-C are higher in diabetes when compared to controls. However, statistical significance is high for TG, HDL-C, VLDL-C, and low power TC, LDL-C.

### Duration of Diabetes and Lipid Profile

Table 5 show the mean value and standard deviation of lipid fraction on different groups diabetes of different duration. Diabetes grouped into four groups duration interval of 3 years in can be observed from the Table 5 that mean values of TG show an increase with increase

**Table 3: Incidence of various complications**

Complications	Male	Female	Total
Retinopathy	24	6	30
Neuropathy	16	4	20
Nephropathy	5	4	9
Ischemic heart diseases	9	5	14
Cerebrovascular accident	6	1	7
No complications	6	1	7

**Table 4: Comparison of various lipid levels between diabetes (study) and control group**

Lipid level	Diabetic	Control	P value
TG	183.86±52	183.86±48	<0.001
HDL-C	31.8±6.33	41.20±8.10	<0.001
TC	214.78±43.12	166.88±34.8	<0.001
LDL-C	149.9±11.01	96.9±32	<0.001
VLDL	33±10.1	28.64±8.99	<0.01

**Table 5: Duration of diabetes and lipid profile**

Duration	TG	TC	HDL
4-6	160.86±46.91	131.93±46.41	32.73±1.03
8-9	191.35±43.80	158.25±47.16	31.60±6.3
10-12	200.08±43.28	216.00±8.4	31.00±0.00
>12	207.5±3.5	183.16±41.91	30.23±0.00
P value	<0.001	<0.001	<0.001

TG: Triglyceride, TC: Total cholesterol, HDL: High-density lipoprotein

duration of illness. HDL-C shows trend of decrement in their levels. TC shows an increase initially but later decrease in the trend.

### SEVERITY OF DIABETES AND SERUM LIPIDS

Table 6 show mean and standard deviation of various serum lipid fraction in relation to severity of diabetes assed by HbA1c levels. It can observe from that there is increase in levels of TGs, TC, LDL-C, and VLDL-C, with increasing severity of diabetes. The difference in values of these lipid fractions were statistically significant. HDL-C levels decreased to significant levels with increasing severity.

### DISCUSSION

Type 2 DM has emerged one of the most common causes of dislipidemie vascular complications are believed to be critical for prognosis of DM and there development, in turn, is believed to depend on several factors such as duration, degree of control, and dyslipidemia in diabetes.

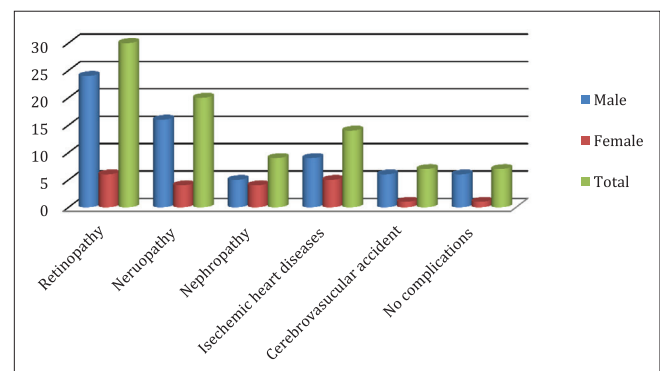
It is been found that Type 2 DM suffer from dyslipidemia intune leading to various vascular complication (All Bright *et al.* 1989).

### Age and Sex distribution

Several workers in India (Ajagnakar and Sathi *et al.* 1989; Vaishnava *et al.* 1989; Shankar *et al.*) have reported that in the incidence of diabetes is greater in male then females. In our study, it is observed that 82% were males 18% were females.

### Duration of Diabetes

In our study, the average duration Type 2 DM in the study group was 8 years. This is because criteria for inclusion of patients suffering from diabetes more than 4 years.



**Graph 3: Incidence of various complications**

**Table 6: Severity of diabetes and serum lipids**

Hb1Ac	TG	TC	LDL-C	HDL-C	VLDC
<7	153.5±9.19	180.66±67.88	118.60±67.88	33.66±6.7	29.00±11.3
7.1-8	171.77±33.76	192.88±33.83	133.22±51.57	32.72±5.67	26.94±10.17
8.1-9	197.04±44.0	241.63±37.83	176.72±52.61	27.6±5.6	37.31±9.09
>9	224.20±23.19	250.05±57.51	186.4±29.21	24.5±4.5	39.6±6.5
P value	<0.01	<0.001	<0.01	<0.001	<0.001

TG: Triglyceride, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, VLDC: Very low-density lipoprotein

### Incidence of Various Complications

In this study, retinopathy was the most common complications followed by neuropathy. Retinopathy was seen in 52% of the study group. According to the American diabetic association, at the 10 and 15 years the diabetic retinopathy was 58% and 18%, respectively. The incidence of peripheral neuropathy seen in this study more are similarly to published reports,

- Mohan *et al.* - 1999 - 34.1%
- Ramachandran *et al.* 2000 - 23.7%.

The above two authors have documented lower incidence of retinopathy.

This could be because in your study most them had nonproliferative or back ground retinopathy and duration of diabetes was slightly higher. In our study, the incidence neuropathy was 40% which coincidence with the study of Niskament *et al.* 1997 - 30%. Other incidence presents in the study coincidence the studies done by Surie *et al.*

### Serum Lipid in Diabetes and Control Groups

This study has shown that TG, TC, LDL-C, and VLDL-C, the lipid profile are higher significantly in diabetes than and HDL-C was significantly lower in diabetics than control groups.

According Fredrick *et al.* 1994, Michel *et al.* 1989, in Type 2 DM there is significant elevation of TG, VLDL-C, and decreasing in HDL-C. Our study has shown similar results except for TC, LDL-C which are significantly elevated. The reasons for increasing TC LDL-C are increasing in the incidence of the obesity, sedentary life lack of physical activity, the diet, and risk factors like hypertension.

### Severity of Diabetes and Lipid Levels

In our study, severity of diabetes was classified according to the levels of HbA1c a better marker of glucose levels than FBS and PPBS. Here, more than 50% of the patient had more than 8. And also this study shows an significant increasing levels of TG, TC, LDL-C, and VLDL-C and significant decrease in level of HDL-C has the severity of diabetes or HbA1c increased similar results were observed Ahuja *et al.* din 1992; Gossion *et al.* 1986; Pfeifer *et al.* 1987

found similar relationship between HbA1c and various lipid fraction.

### Duration of Diabetes and Lipid Levels

This study showed good correlation between duration of diabetes and lipid abnormalities. Similar results were by author Barbara V Howard *et al.* 1984; James S Reitman *et al.* 1987; but some authors, Baker *et al.* (1982), have observed variant observation where there was no correlation between the two.

The study includes Type 2 DM patients who smoke, consume alcohol, and hypertensive. These are risk factors for dyslipidemia. Hence, further study needs to done excluding these risk factors. This study controls were also smokers, alcoholic, and hypertensive. Hence, baseline characters are matched with patients. There is significant increase in LDL-C levels which is not observed in Type 2 DM. Hence, these needs to be further studied to confirm whether Type 2 DM effect LDL-C.<sup>5-8</sup>

## SUMMARY

The serum lipid profile of 50 Type 2 DM patients was studied and compared with age and sex matched nondiabetic healthy controls. The serum lipid levels were correlated with various clinical profiles of diabetes such as sex, duration, and severity of diabetes.

In this study group, the average duration of diabetes was 8 years. Of 50 patients, 82% were males and 18% were females. The average duration of diabetes was 8 years. 24 patients were on OHDs, 16 were taking both oral hypoglycemic and insulin, and 10 were on only insulin.

Among the complications, diabetic retinopathy was the most common complication 52%, the second most common was neuropathy 40%. Ischemic heart disease was seen in 28%, nephropathy was seen in 18%, and cerebrovascular accident in 14%.

The mean values of the entire lipid fraction TG, TC, LDL-C, and VLDL-C, were statistically significantly higher in diabetes than healthy controls. There was correlation between lipid levels and duration of diabetes for all lipid

fractions which were significant. All lipid fractions showed a progressive increase severity of diabetes. The difference was statistically significant.

Degree of control diabetes was inadequate as more than 50% had high HbA<sub>1c</sub>. This probably the main reason for significant dyslipidemia and as well as complication.

## CONCLUSION

From this study, it was evident that DM has a real impact on lipid metabolism. This was substantiated by the fact that all the lipid fractions were elevated in diabetes when compared to healthy controls. Hence, hyperlipidemia is quite common in diabetes and hypertriglyceridemia is the most common abnormality.

The age and sex of the patients did not have much influence on serum lipids. The duration of diabetes and the severity of diabetes had marked influence on lipid levels. Hence, good control of diabetes would help to check the alterations in lipid levels.

Diabetic patients with complications tend to have higher levels of lipid fractions (TGs, cholesterol, and LDL-C) and lower levels of HDL-C. This suggests that there appears to be some relation between the genesis of various vascular complications (micro vascular and macro vascular), and the presence of lipid abnormality. It is difficult to

point out a particular factor as the cause as multiple mutually interacting factors determine the presence or development of these complications. As good control of diabetes is shown to keep the lipid levels in near normal range, it appears important to aim at critical control of DM to prevent or at least postpone the onset of various complications.

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# Histopathology of Skin Adnexal Tumors - A Two Year Retrospective Study at a Tertiary Care Hospital

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## Abstract

**Introduction:** Skin adnexal neoplasms are rare neoplasms which differentiate toward or arise from the skin adnexa, viz., hair follicles, sweat glands or sebaceous glands. They present diagnostic difficulties because of their wide variations on histopathology. Benign adnexal neoplasms are more common than malignant lesions. Histopathology is the gold standard.

**Aim:** The aim of this study was analysis of skin adnexal tumors in our institution with respect to age, sex, location, histopathology, and incidence.

**Materials and Methods:** All cases of skin adnexal tumors for May 2014-June 2016 were retrieved from department registries and analyzed.

**Results:** A total of 23 cases were included. Majority of the tumors were benign (73.91%) and of hair follicle origin (34.78%). Incidence was found to be higher in females compared to males (male: female=1:3.53) with maximum cases in the age group 41-50 years (34.78%) and the head and neck region was the most common location (56.52%). Nodular hidradenoma was the most common benign tumor overall (4/17). Sebaceous carcinoma comprised the bulk of the malignant tumors (2/6). Others were eccrine spiradenocarcinoma, malignant proliferating pilar tumor, malignant proliferating trichilemmal tumor, and malignant nodular hidradenoma. Overall incidence of skin adnexal tumors was found to be 0.25%.

**Conclusion:** Skin adnexal tumors are relatively rare neoplasms. Benign tumors are more common than malignant lesions. Histopathology is essential to confirm the diagnosis.

**Key words:** Histopathology, Malignant eccrine spiradenoma, Skin adnexal tumors

## INTRODUCTION

Skin adnexal tumors present a wide spectrum of morphology, which often defies precise classification making them one of the most challenging areas of pathology. They have been correctly termed by cotton as “troublesome tumors” due to the difficulty in classifying them on clinical basis alone.<sup>1</sup> The histogenesis of mixed adnexal tumors is still uncertain and origin from pluripotent

stem cells within epidermis is suggested.<sup>2</sup> They can occur as single-lineage neoplasms or may show overlapping morphological features of different lineages such as hair follicles, sebaceous glands, eccrine, and apocrine glands.<sup>3,4</sup> Diagnosis of these tumors is difficult because of their wide spectrum and variants, their rarity, differentiation along two or more adnexal lines and their complicated nomenclature. Most skin adnexal tumors are benign and cured by simple excision, however, their malignant counterparts are rare, locally aggressive with propensity for nodal and distant metastasis having poor clinical outcome. Diagnosis of these malignant tumors becomes doubly important with a view toward treatment and prognosis.<sup>3</sup> Histopathology is the gold standard of diagnosis with immunohistochemistry playing a limited role. Our study is a retrospective analysis of skin adnexal tumors with respect to their anatomical location, age and sex of the individuals affected, their

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histopathological features and to determine their incidence in our institution over a period of 2 years.

## MATERIALS AND METHODS

The study was a hospital-based retrospective study conducted in the Department of Pathology, Gauhati Medical College and Hospital from May 2014 to June 2016. All cases of skin adnexal tumors diagnosed during this period were included. The clinical details were obtained from accompanying requisition forms and department registries. The slides and blocks were retrieved from the archives and analyzed. The slides were stained using routine Hematoxylin and eosin staining and confirmed with special stains were required.

## RESULTS

A total of 23 skin adnexal tumors were diagnosed during the study period out of 9303 cases of surgical pathology reported. The incidence of skin adnexal tumors was found to be 0.25%. There were 6 males (26.08%) and 17 females (73.92%) with a male: female ratio of 1:3.53. Of the 23 cases documented, 17 were benign (73.92%) and 6 were malignant (26.08%). The age distribution is shown in Figure 1. The maximum cases were in the age group of 41-50 years (34.78%). With respect to anatomical location, the head and neck region was found to be the most common (78.26%) with predominance in the scalp (56.52%). The anatomical locations are shown in Table 1.

The tumors were further divided into hair follicle, sebaceous, eccrine, and apocrine gland differentiation. The most common tumors were of hair follicle origin - 10 (43.48%) (Table 2). The most common benign tumor was nodular hidradenoma (4/17) followed by pilomatrixoma and trichilemmal tumor (3/17 each). The frequency and percentage of the different skin adnexal tumors, benign and malignant are shown in Tables 3 and 4. Malignant adnexal tumors were rare with only 6 cases in our study out of which 2 were sebaceous carcinoma making it the most common type and one case each of eccrine spiradenocarcinoma, malignant nodular hidradenoma, malignant proliferating pilar tumor, and malignant trichilemmal tumor.

## DISCUSSION

Adnexal tumors of the skin are rare neoplasms which show differentiation toward pilar, sebaceous, eccrine or apocrine structures. They are believed to originate from pluripotent stem cells in epidermal niches and a single tumor can show more than one line of differentiation.<sup>2</sup>

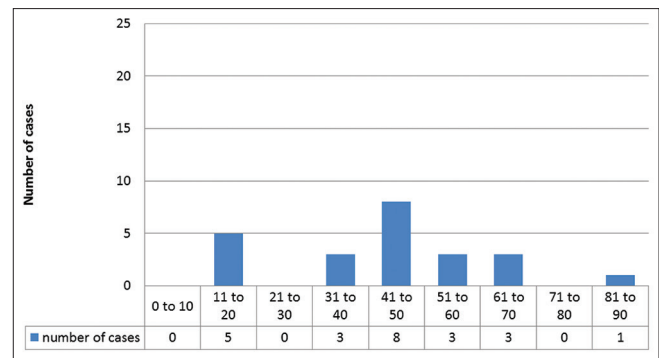


Figure 1: Distribution of cases based on age

Table 1: Distribution of cases based on anatomical locations

Anatomical location	Number of cases (%)
1. Head and neck	18 (78.26)
Scalp	13 (56.52)
Forehead	1 (4.35)
Eyelid	2 (8.70)
Cheek	1 (4.35)
Chin	1 (4.35)
2. Trunk	1 (4.35)
3. Lower limb	2 (8.69)
4. Upper limb	1 (4.35)
5. Perianal region	1 (4.35)
Total	23 (100)

Table 2: Distribution of tumors based on differentiation

Differentiation of appendageal tumors	Total number (%)
Hair follicle	10 (43.48)
Sebaceous gland	4 (17.39)
Eccrine gland	7 (30.44)
Apocrine gland	2 (8.69)
Total	23 (100)

Table 3: Benign skin adnexal tumors with frequency

Appendageal tumors	Benign tumor types	Number of cases (%)
Hair follicle	Pilomatrixoma	3 (17.65)
	Trichilemmal cyst	3 (17.65)
	Trichofolliculoma	2 (11.76)
Sebaceous	Naevus sebaceous	2 (11.76)
Eccrine	Nodular hidradenoma	4 (23.51)
	Chondroid syringoma	1 (5.89)
Apocrine	Apocrine hidrocystoma	1 (5.89)
	Hidradenoma papilliferum	1 (5.89)
Total		17 (100)

Skin adnexal tumors have a wide range of age distribution. Sharma *et al.*<sup>5</sup> found the maximum cases in the age group of 51-60 years whereas Radhika *et al.*<sup>6</sup> reported the third decade to be the most common. In our study, the maximum

cases were in the age group of 41-50 years (34.78%) which coincides with the findings of Vani *et al.*<sup>7</sup> (21.56%).

Male:female ratio was reported to be 1.07:1 by Sharma *et al.*<sup>5</sup> In our study, the male: female ratio was found to be 1:3.53 (Figure 1) which was in concordance with Vani *et al.*, Nair and Saha *et al.* who reported a male: female ratio of 1:1.68, 1:2.3, and 1: 1.88, respectively.<sup>7-9</sup>

Sharma *et al.*, Radhika *et al.*, and Vani *et al.* observed that head and neck region was the most common site of occurrence, which was also noted in our study (78.26%).<sup>5-7</sup>

The incidence of skin adnexal tumors in our study was found to be 0.25%. This is similar to observations by Samaila (0.9%)<sup>10</sup> and Jindal and Patel (0.37%).<sup>11</sup>

The incidence of benign adnexal tumors is more compared to malignant tumors. We found 73.92% benign and 26.08% malignant cases in our study. This coincided with the findings of Sharma *et al.*, Radhika *et al.*, Vani *et al.*, and Samaila who reported 77.14%, 80.36%, 74.50%, and 88.5% benign and 29.63%, 19.64%, 25.49%, and 11.5% malignant lesions, respectively.<sup>5-7,10</sup>

In our study, tumors of hair follicular origin were the most common (43.48%) of which pilomatrixoma and trichilemmal cyst were maximum in number (3 cases each). This coincides with the findings of Kant *et al.*<sup>12</sup> and Jayalakshmi and Looi<sup>13</sup> who found hair follicular tumors to be 64.29% and 63.4% of skin adnexal tumors but is in contrast to the findings of Sharma *et al.*, Vani *et al.*, and Nair who found tumors of sweat gland origin to be the most common.<sup>5,7,8</sup>

The most common benign tumor overall was nodular hidradenoma (4/17 cases) which is similar to the observations of Sharma *et al.*, Radhika *et al.*, and Vani *et al.*<sup>5-7</sup>

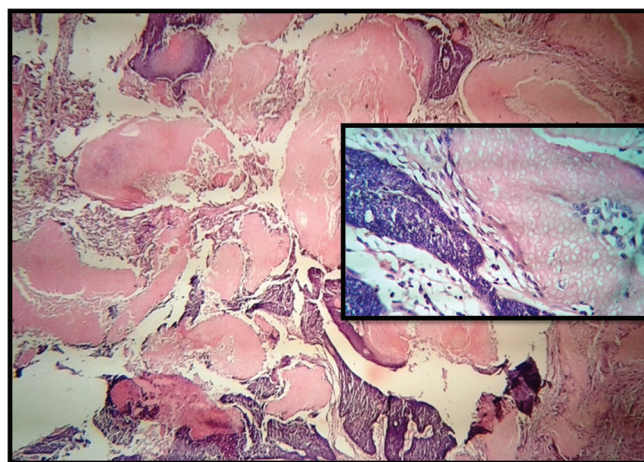
Pilomatrixoma was the second most common benign tumor (3 cases) with microscopy showing biphasic pattern of keratinized ghost cells and basaloid cells. One of the cases showed giant cell reaction and calcium deposition (Figure 2).

We found 2 cases of trichofolliculoma, one in the chin and other in the cheek. Both revealed microscopic features of dilated hair follicle arising from surface epithelium with numerous secondary hair follicles arising from it. Numerous sebaceous gland cells were found embedded in the walls of the secondary hair follicles (Figure 3).

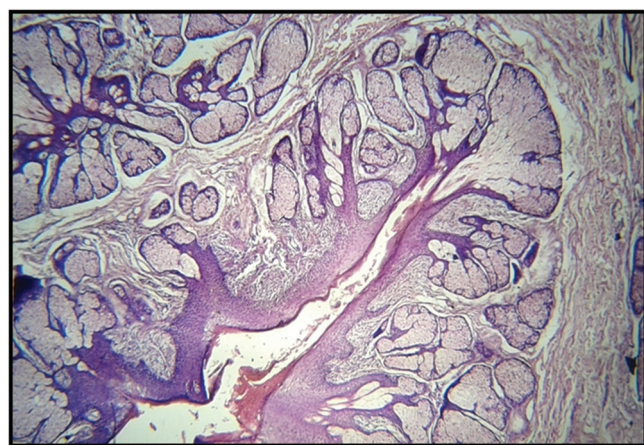
Chondroid syringoma or mixed tumor of the skin is a rare cutaneous adnexal neoplasm mostly reported as isolated case reports.<sup>14</sup> It may be either apocrine or eccrine in nature. On microscopy, we found small nests, cords, and

**Table 4: Malignant skin adnexal tumors with frequency**

Appendageal tumors	Malignant tumor types	Number of cases (%)
Hair follicle	Malignant proliferating trichilemmal cyst	1 (16.67)
	Malignant proliferating pilar tumor	1 (16.67)
Sebaceous Eccrine	Sebaceous carcinoma	2 (33.33)
	Eccrine	1 (16.67)
	spiradenocarcinoma	
	Malignant eccrine hidradenoma	1 (16.67)
Apocrine	-	0 (0)
Total		6 (100)



**Figure 2: Pilomatrixoma showing basaloid and ghost cells (H & E, ×10). Inset (H & E, ×40)**

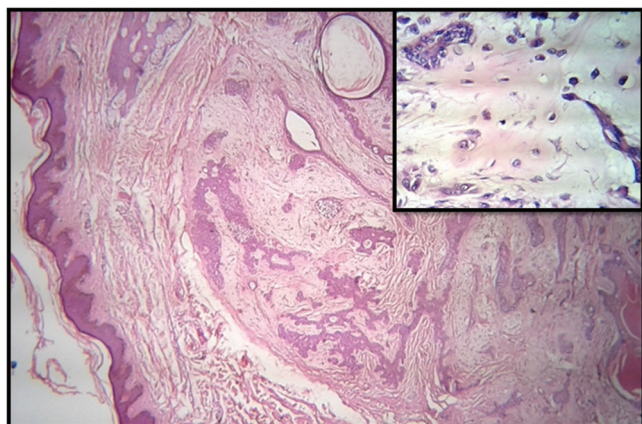


**Figure 3: Trichofolliculoma showing dilated hair follicle with numerous secondary follicles (H & E, ×10)**

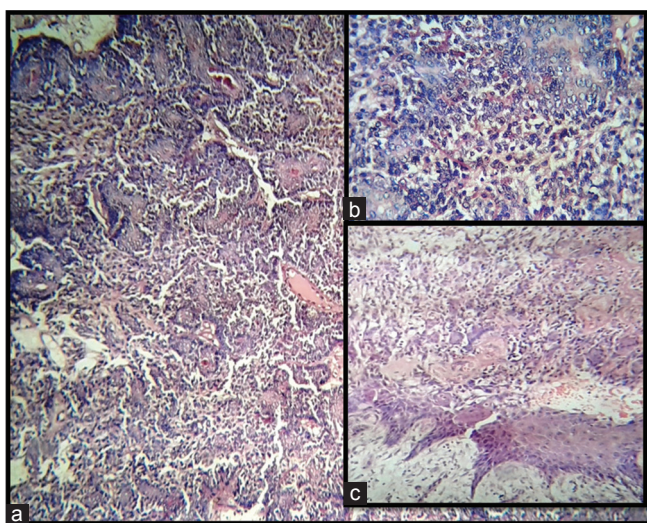
monolayered tubules of epithelial cells in a chondromyxoid stroma in the dermis which was used to classify it as eccrine neoplasm (Figure 4).

Malignant adnexal tumors are rare.<sup>2-4</sup> We found 6 malignant adnexal tumors in our study, of which sebaceous carcinoma

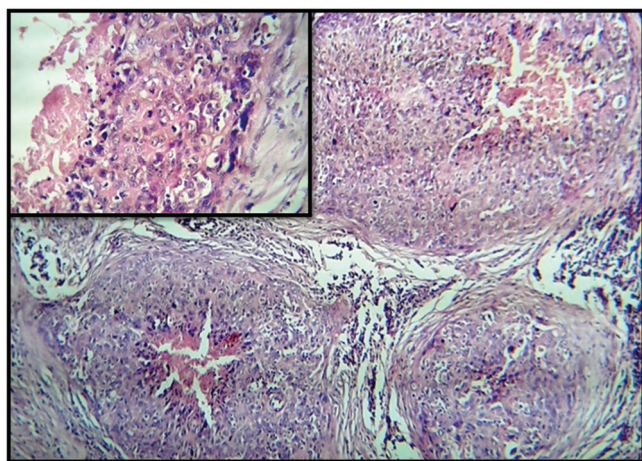




**Figure 4: Chondroid syringoma with epithelial cords and nest in dermis (H & E, x10). Inset (H & E, x40) showing chondromyxoid stroma**



**Figure 5: Eccrine spiradenocarcinoma. (a) Benign spiradenoma with dual population of cells (H & E, x10). (b) Areas of malignant transformation (H & E, x40). (c) Area of squamous differentiation (H & E, x10)**



**Figure 6: Malignant proliferating pilar tumor showing squamous lobules with abrupt keratinization (H & E, x10). Inset (H & E, x40) abnormal mitotic figures**

was found to be the most common. Sebaceous carcinoma has been divided into ocular and extraocular varieties.<sup>15</sup> The 2 cases we reported were both of the ocular variety, found as upper eyelid masses. One case was in a 86-year-old female and the other in a 68-year-old female.

Eccrine spiradenocarcinoma is a very rare tumor with few cases reported worldwide.<sup>16,17</sup> It usually arises from a benign spiradenoma. We reported a case of eccrine spiradenocarcinoma in a 45-year-old female who presented with ulceration and bleeding in a long-standing back swelling. On microscopy, we found benign spiradenoma component with well-defined nodules composed of small dark cells in periphery and large pale cells in the center along with areas of malignant change showing loss of dual cell population, hyperchromatic nuclei, pleomorphism, prominent nucleoli, and mitosis. There were also areas of malignant squamous and spindle cell differentiation (Figure 5).

Malignant proliferating pilar tumor is a rare tumor of hair follicle origin with 39 cases reported in English literature.<sup>18</sup> We diagnosed a case of malignant proliferating pilar tumor in a 45-year-old female presenting with a scalp lesion clinically diagnosed as a granuloma. On microscopy, we found lobules of squamous epithelium with abrupt pilar keratinization and foci of calcification. There was marked cytological atypia and stromal invasion with the presence of numerous abnormal mitotic figures (Figure 6).

## CONCLUSION

Skin adnexal tumors are rare neoplasms which are difficult to diagnose clinically. There is a dearth of literature concerning skin adnexal tumors. The incidence in our study is 0.25% which highlights the rarity of these tumors. The incidence of benign tumors is more compared to malignant ones. Skin adnexal tumors can occur anywhere in the body but head and neck region is found to be the most common location. The most common are benign tumors of hair follicle origin and sebaceous carcinoma is the most common of the malignant cases. Histopathology is the gold standard for diagnosis of these tumors.

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# Knowledge Regarding Antenatal Care Services in Mothers (15-49 Years) in Rural Areas of Aligarh

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## Abstract

**Introduction:** Antenatal care (ANC) is the care of a woman throughout her pregnancy. The World Health Organization recommends a minimum of four antenatal visits comprising interventions such as tetanus toxoid (TT) vaccination, screening, and treatment of infections and identification of warning signs during pregnancy. The reasons for high maternal mortality ratio in India are inadequate access and underutilization of health services.

**Materials and Methods:** A cross-sectional study was conducted during May-June 2013 in the rural areas of Jawan, Aligarh. The study population comprised married women (15-49 years) who had delivery in the last 5 years. Informed consent was taken from each participant. A total of 100 mothers were selected for the study. Questionnaires were prepared for the study. Data were collected and analyzed using SPSS software.

**Results:** Majority of the mothers responded that pregnant women need to go for ANC checkup (95%). However, only 60% knew correctly the minimum number of ANC visits during pregnancy. 99% of mothers knew that TT should be given during pregnancy, but only 50% knew the correct dose. Although 84% of mothers knew the importance of iron folic acid (IFA) tablet, only 40% knew the correct dose. 85% of mothers knew about birth spacing, and 90% said it to be a good practice. 100% mothers knew that blood pressure should be recorded, but adverse effects of high blood pressure on fetus growth were reported only by 50% of females. More than half of mothers (56%) knew that emotional disturbances affected fetal growth. Most of the mothers knew the importance of blood and urine investigations.

**Conclusion:** Awareness should be developed in the community about the importance of registration for ANC, educating women about the detection of complications during pregnancy, importance of TT injection, IFA tablet, extra nutrition, etc. There is also the need to encourage women to involve their male partners in birth spacing programs. Health workers need to identify the pregnant mother, and they should give reminder before a particular dose of ANC.

**Key words:** Antenatal care, Knowledge, Mothers, Rural areas

## INTRODUCTION

Antenatal care (ANC) is the care of a woman throughout her pregnancy. Almost 90% of maternal deaths occur in developing countries, and over half a million women die each year due to pregnancy and childbirth-related causes.<sup>1</sup> Many women in developing countries do not receive such

care.<sup>2</sup> According to the National Family Health Survey, only about 50% of women received folic acid/iron supplements during pregnancy in India and this percentage is still lower in Rajasthan, Uttar Pradesh, Bihar, and Nagaland.<sup>3</sup> The World Health Organization recommends a minimum of four antenatal visits comprising interventions such as tetanus toxoid (TT) vaccination, screening, and treatment of infections and identification of warning signs during pregnancy.<sup>4</sup> In India, it is heartening to note that maternal mortality ratio (MMR) has declined from 212 in 2007-2009 to 178 in 2010-2012.<sup>5</sup> The reasons for high MMR in India are inadequate access and underutilization of health services. Other common reasons are high illiteracy among females, early marriages, ignorance, malnutrition, social factors, etc. Hence, utilization of these services by

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the beneficiaries remains unsatisfactory.<sup>6-8</sup> Two of the most important indicators of health of a country are life expectancy and maternal mortality rates.<sup>9</sup> Nutrition during preconception as well as throughout pregnancy has a major impact on the outcome of pregnancy.<sup>10</sup> Utilization of ANC is associated with the level of education and family income of the respondents.<sup>11</sup>

The aim of this study was to assess the knowledge of mothers (15-49 years) regarding ANC services in rural areas of Aligarh.

## MATERIALS AND METHODS

A cross-sectional study was conducted during May-June 2013 in the rural areas of Jawan, Aligarh. The study population comprised married women (15-49 years) who had delivery in the last 5 years. Informed consent was taken from each participant. A total of 100 mothers were selected for the study. Questionnaires were prepared for the study. Data were collected and analyzed using SPSS software. Full ANC is defined as at least 3 visits for ANC checkup, at least one TT injection received, and 100 iron folic acid (IFA) tablets/syrup consumed.<sup>12</sup>

## RESULTS

As shown in Table 1, majority of them responded that pregnant women need to go for ANC checkup (95%). However, only 60% knew correctly the minimum number of ANC visits during pregnancy. 99% of mothers knew that TT should be given during pregnancy, but only 50% knew the correct dose. Although 84% of mothers knew the importance of IFA tablet, only 40% knew the correct doses. 96% of mothers knew that smoking or alcohol intake is harmful to the fetus. 85% of mothers said that extra nutrition is necessary for pregnancy. 80% of mothers reported that deliveries should be conducted in institutions.

83% of mothers said that breastfeeding should be started within 24 h. 75% of mothers knew the importance of post-natal care.

As shown in Table 2, 85% of mothers knew about birth spacing and 90% said it to be a good practice. 95% had knowledge of one or other methods of birth spacing.

As shown in Table 3, 100% mothers knew that blood pressure should be recorded, but adverse effects of high blood pressure on fetus growth were reported only by 50% of females. 78% of mothers knew that ultrasonography was safe for fetus. More than half of mothers (56%) knew that emotional disturbances affected fetal growth. Most of the mothers knew the importance of blood and urine investigations.

## DISCUSSION

As shown in Table 1, majority of them responded that pregnant women need to go for ANC checkup (95%). However, only 60% knew correctly the minimum number of ANC visits during pregnancy. This finding was similar to other study,<sup>13,14</sup> in which the respondents had adequate knowledge about ANC registration, IFA tablet supplementation, TT injection, and increase in food intake, but knowledge regarding the number of ANC visits was dismal. The reason of good knowledge in our mothers was might be because of health education given to them by social workers of our center or Accredited Social Health Activists or Anganwadi workers in the villages. In our study, we do not correlate impact of mothers' education on utilization of health services, but other studies found strong correlation between it.<sup>15,16</sup>

Javali *et al.* study<sup>17</sup> and Roy *et al.* study<sup>18</sup> revealed 100% ANC registration.

**Table 1: Knowledge of the respondents on ANC (n=100)**

Questions	Yes/correct	No/incorrect	Don't know
1. Do pregnant women need to go for ANC?	95	1	4
2. If yes, is it required to go for ANC even if there is no complication during pregnancy?	90	6	4
3. What should be the minimum number of ANC visits?	60	22	18
4. Is it necessary to give injection TT during pregnancy?	99	0	1
5. If yes, how many times injection TT should be given?	50	34	16
6. Is it necessary to give IFA during pregnancy?	84	1	15
7. If yes, how many IFA has to be given during pregnancy?	40	10	50
8. Is smoking or alcohol harmful for the fetus?	96	2	2
9. Do pregnant female require extra nutrition?	85	4	11
10. What is the ideal place of delivery?	80 (institutional)	11 (home)	9 (don't know)
11. Breastfeeding within 24 h	83	7	10
12. Postnatal care is important?	75	5	20

ANC: Antenatal care, IFA: Iron folic acid, TT: Tetanus toxoid

**Table 2: Knowledge of the respondents on birth spacing (n = 100)**

Variable	Yes	No
1. Ever heard of birth spacing	85	15
2. Is it a good practice	90	10
3. Knowledge of birth spacing methods	95	5

**Table 3: Knowledge of the mothers on various investigations done during pregnancy (n = 100)**

Knowledge	Correct answers
1. Blood screening for hemoglobin level, hepatitis B infection	89
2. Blood sugar level	80
3. Urine test for bacterial infection	85
4. Is USG safe for fetus	78
5. Blood pressure examination	100
6. Can emotional disturbances affect fetal growth?	56
7. Can high blood pressure affect the fetus growth?	50

USG: Ultrasonography

A study reported<sup>19</sup> results almost similar to our study, for example, 97.9% of mothers responded for ANC checkup although only 55.2% revealed the correct number of ANC visits. Similarly, 98.6% of mothers knew the importance of injection TT during pregnancy, but only 54.1% knew the correct number of times injection TT should be given.

In our study, 99% of mothers knew that TT should be given during pregnancy, but only 50% knew the correct dose. In another study also,<sup>20</sup> pregnant mothers were aware of injection TT and IFA supplementation.

In our study, 80% of mothers said that deliveries should be conducted in institutions. An association between the use of ANC services and health facility delivery was observed in India and in other developing countries.<sup>21-23</sup> Low level of knowledge of antenatal well-being and desire for hospital or assisted delivery was also observed in other studies.<sup>24</sup>

The reasons for knowledge of ANC were might be because of close proximity and therefore easier accessibility of health facilities as stated by Magadi *et al.*<sup>25</sup> that the frequency of ANC is also influenced by the accessibility of ANC service.

85% of mothers knew the importance of extra nutrition during pregnancy in our study. This is contrary to that revealed by Daba *et al.*,<sup>26,27</sup> where most of the respondents did not know the main food groups of the balanced diet and more than half did not know even the meaning of food. Despite the high level of respondents, some confusion and ignorance existed as regards maternal knowledge

of adequate nutrition practices during pregnancy and identification of harmful food items in pregnancy.<sup>28</sup>

As shown in Table 2, 85% of mothers knew about birth spacing and 90% said it to be a good practice. 95% had knowledge of one or other methods of birth spacing. These findings were similar to another study.<sup>29</sup> The reasons of good information were because of good sources of health information such as health facilities, mass media, and family.

As shown in Table 3, 100% mothers knew that blood pressure should be recorded, but adverse effects of high blood pressure on fetus growth were reported only by 50% of females. Another study also reported that about half of the women did not know the complications that might arise among hypertensive and diabetic mothers.<sup>30</sup>

## CONCLUSION

Awareness should be developed in the community about the importance of registration for ANC, educating women about the detection of complications during pregnancy, importance of TT injection, IFA tablet, extra nutrition, etc. There is also the need to encourage women to involve their male partners in birth spacing programs. Health workers need to identify the pregnant mother, and they should give reminder before a particular dose of ANC.

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# Pitfalls and Complications of Stapedectomy: A Prospective Study

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## Abstract

**Introduction:** Stapedectomy is now one of the most popular and common surgeries done worldwide. Otosclerosis remains the most common single cause of conducting hearing loss in adult population. Females are more frequently affected than males with an approximate 2:1 ratio.

**Materials and Methods:** This study consists of 94 patients who underwent stapedectomy for otosclerosis. This study was conducted at Government Theni Medical College Hospital, Theni, during the period of 3-year (2013-2016). Patients were evaluated and operated. The various anatomical variations, diagnostic dilemmas, intraoperative complications, its management and follow-up were done systematically.

**Results:** Age of patients included in this study ranged from 14 to 58 years. Youngest patient was a 14-year-old girl. Surgery was done commonly in the age group between 31 and 40 years. Out of 94 patients, 46 (48.9%) were males and 48 (51.1%) were females. The family history of otosclerosis was noted in 48 patients (51.1%). Positive family history in females was about 56.3%, and positive family history in males was 43.7%. The most common symptom was hard of hearing followed by *Paracusis willisi* and tinnitus. In this study, 50% of the patients initially had noticed onset of conductive hearing loss during 2<sup>nd</sup> pregnancy and also aggravation of hearing loss during subsequent pregnancies. Bilateral otosclerosis was commonly encountered than unilateral involvement. The ratio was found to be higher in females. In cases of bilateral equal conductive hearing loss weber test was done to select the ear for surgery. In this study, 52% of patients had air-bone gap between 41 and 60 dB.

**Conclusion:** The common problems encountered during stapedectomy are (1) excessive posterosuperior overhang, (2) narrow external auditory canal, and (3) narrow oval window niche. Surgical skills, tissue respect, experience, and aseptic surgical technique are essential to perform stapedectomy with least complications. Adequate postoperative care and proper instruction of the patient are mandatory for a good hearing result.

**Key words:** Floating footplate, Otosclerosis, Stapedectomy

## INTRODUCTION

The advent of microscope has revolutionized the treatment of the patients suffering from otosclerosis. Stapedectomy is now one of the most popular and common surgeries done worldwide. It is a rewarding surgery for both the patient and the surgeon. It gives relief for patients who are socially handicapped.<sup>1-6</sup>

Otosclerosis is a primary and exclusive disease of the otic capsule. Although a number of plausible causes of otosclerosis have been suggested, genetic, racial, hormonal, metabolic, viral, pregnancy, infection, vascular and traumatic and more recently autoimmune disorders, its etiology remains unknown. Otosclerosis remains the most common single cause of conducting hearing loss in adult population.

Females are more frequently affected than males with an approximate 2:1 ratio. Otosclerosis occurs far more commonly in persons of European origin and Indians than Africans. Family history is positive in 50% of cases. Pregnancy, puberty, menopause has been thought to stimulate the activity of otosclerosis.<sup>3,7-13</sup>

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Surgeons have recognized the mechanical impediment to sound transmission caused by otosclerosis since the last 19<sup>th</sup> century. John Shea in 1956, revived stapedectomy and also introduced prosthetic restoration of ossicular continuity from incus to tissue covering oval window. Other than stapedectomy, treatment options available are hearing aids and fluorides.

Although indications for stapedectomy and hearing aid are the same, stapedectomy is usually preferred by the patient because hearing aid is not acceptable socially and cosmetically. Today, the properly selected patient in the hands of an experienced otologic surgeon has a better than 95% chance of closure of the air-bone gap with a low incidence of complications. Stapedectomy usually results in restoration of normal hearing with air-bone gap closure to <10 dB.<sup>14-19</sup>

Complications commonly encountered during surgery include tympanic membrane perforation, injury to chorda tympani nerve, ossicular dislocation, floating footplate and perilymph gusher and sensorineural hearing loss. Hence, the proper selection of patients should be done very carefully. Although complications are rare, counseling of the patient should be done regarding the treatment modalities available and results of surgery.<sup>20-24</sup>

## MATERIALS AND METHODS

This study consists of 94 patients who underwent stapedectomy for otosclerosis. This study was conducted at Government Theni Medical College Hospital, Theni, during the period of 3-year (2013-2016).

In this study, all the selected patients were subjected to a thorough ear, nose and throat clinical examination including tuning fork tests. Pure tone audiogram and impedance audiometry were done for all the patients. Speech audiometry was done selected number of patients (30%). The intra- and post-operative complications encountered during surgery were recorded. Congenital anomalies and variations were also recorded.

### Patient Selection Criteria

1. Patients with otosclerosis with positive family history of otosclerosis with moderate to severe conductive hearing loss (air conduction level 45-65 dB at speech frequencies with bone conduction level 0-25 dB at speech frequencies)
2. Also patients with unilateral otosclerosis with good cochlear reserve
3. Age of the patients should be more than 12 years
4. Patients with mixed hearing loss with speech discrimination score of more than 90%.

### Exclusion Criteria

1. Patients with Meniere's disease were excluded from the study
2. Patients with chronic suppurative otitis media and otitis externa were also excluded from the study
3. Patients with only one hearing ear
4. Those patients with cochlear otosclerosis
5. Age more than 60 years
6. Patients with conductive hearing losses from other causes such as tympanosclerosis causing stapes fixation and secretory otitis media
7. Patients with active otosclerosis (Schwartz sign positive).

Those patients who are willing for surgery after proper counseling were selected (this includes those not willing for hearing aid and fluoride therapy). Patients with otosclerosis with conductive hearing loss with air-bone gap of more than 30 dB with good cochlear reserve were selected for stapedectomy.

### Surgical Technique

Stapedectomy was done in all cases as following.

#### Anesthesia

Stapedectomy was done under local anesthesia with 2% xylocaine with adrenaline. Before surgery, injection fortwin and injection phenergan, injection atropine given as premedication 45 minutes before surgery. Local anesthesia is safer and associated with less bleeding than general anesthesia. Intraoperative improvement in hearing can be tested under local anesthesia. Injury to facial nerve in case of prolapsing and bare facial nerve can be detected under local anesthesia intraoperatively. There is some belief that the patient's ability to report intraoperative vertigo may help the surgeon to avoid injury to the saccule.

Before starting the surgery, auricle and the external auditory canal are cleaned with betadine (povidone iodine).

The ear canal is washed with warm saline solution to remove the povidone iodine, and local infiltration is with 2% xylocaine with adrenaline (1 in 20,000). The initial injections are made with a 30-gauge needle around the periphery of the entrance to the ear canal (3 o'clock, 6 o'clock, 9 o'clock, 12 o'clock positions of the external auditory canal). Approximately, 2.5-3 ml of this solution is injected. Several sizes of ear speculums should be available on the tray, and the largest one that can be seated into the canal is used commonly. A fixed speculum holder is not used. The advantage of not using a fixed speculum holder is flexibility of the speculum for viewing purposes and for allowing the patient to move his or her head if desired.

## Procedure

Approach: Transcanal approach is used in stapedectomy.

Incision: A tympanomeatal flap is elevated by making a vertical incision in the 12 o' clock position and 6 o' clock position and connecting these two incisions by a curvilinear incision from the 6 o'-12 o' clock position. These incision join approximately 5-6 mm from tympanic annulus. A flap of this size should be adequate to cover any resultant defect but small enough to allow adequate exposure. The tympanic membrane is elevated with the annulus. The resulting tympanomeatal flap is turned anteriorly and usually remains in position without further fixation.

## Identification of Chorda Tympani Nerve

The chorda tympani nerve may lie close to the fibrocartilaginous annulus but it may also be hidden behind the bone of the posterior meatal wall or run free through the middle ear. It is easily identified by dissection with a sickle knife or a dissecting needle. It should be preserved if possible. Usually in 90% of cases, it is preserved. The importance of avoiding instrumental trauma (or) stretching of the chorda tympani nerve is helpful in preserving the taste sensation of anterior 2/3<sup>rd</sup> of the tongue.

## Curetting of the Posterosuperior Bony Meatal Wall

This is done with a sharp House curate to expose incudostapedial joint, stapes, pyramidal process, and horizontal portion of the facial nerve. This should be done from medial to lateral direction. Facial nerve is dehiscence in 10% of patients in this area, and caution should be exercised during this step.

## Inspection of the Ossicular Chain

The middle ear cleft is carefully inspected to identify any other possible causes for pre-operative conductive loss. The malleus is palpated to identify associated fixation that would limit post-operative success.

Fixation of stapes is confirmed by a slight lateral movement of the long process of the incus. This step also allows the mobility of the ossicular chain in the epitympanum to be checked and fixation of the head of the malleus to be excluded. The footplate is palpated to know the type of otosclerosis and also to know the extent of the otosclerotic focus.

## Incudostapedial Joint Disarticulation

Incudostapedial joint is disarticulated using a capsular knife.

## Division of the Stapedius Tendon

The tendon of the stapedius muscle is cut with microscissors (or) using sickle knife.

## Removal of the Stapes Suprastructure

Before fracturing the suprastructure, a control hole is made in the posterior half of the footplate with a perforator in some cases. Then, the next step is the fracture of the stapes suprastructure from the footplate of stapes. A fine incision knife is applied from the side of the facial nerve that is immediately above the footplate, to the base of the posterior crus of the stapes, and the stapedial crus is fractured by applying gentle pressure toward the promontory. This must be carried out carefully to prevent the footplate from being mobilized at this time.

Enlargement of the control hole made in the footplate is usually done with perforators of increasing size. In many cases, a fenestra is made in the footplate using perforator. Usually, a 0.6 mm fenestra is the ideal size for 0.5 mm diameter prosthesis. Small fenestra stapedectomy results in less post-operative vertigo and better high-frequency hearing than total footplate removal.

The distance from the inferior surface of the long process of incus and to the fenestra made in the footplate of stapes is measured using house measuring stick. The measurement is usually 4.5 mm but may vary from 3.5 mm to as much as 5.5 mm. One-half of a millimeter is added to this distance to determine the prosthesis length.

Usually, Teflon piston is used. Preoperatively autoclaving of the Teflon piston is done as a method of sterilization. Teflon piston of variable sizes (0.4 mm, 0.5 mm, and 0.6 mm) is usually kept in separate bottles.

The Teflon piston is spread open and gasped with alligator forceps; in such a way that the forceps and the long axis of prosthesis form an obtuse angle. The prosthesis is now introduced into the vestibule and snapped onto the incus. Because Teflon has memory, the ring tends to close without crimping. The prosthesis position can be adjusted easily. Gelfoam is placed around the prosthesis.

Hanging test and bending test are done to test the placement of the prosthesis. If hanging test is positive, then Teflon piston should be replaced by another piston of adequate length because the piston is not fitting properly into the fenestra made in the footplate.

Crimping of the piston is usually done if bending test is positive. It occurs because the piston is not fitting properly in the long process of incus.

Intraoperative hearing improvement is checked by asking the patient to repeat numbers, sentences and also by asking questions, in whispering voice and also in normal conversational voice.

The tympanomeatal flap is then gently returned to its normal position with a blunt instrument. The meatus is packed from the tympanic membrane to the junction of the inner and middle thirds of the meatus using pieces of gelfoam soaked in antibiotic solution. Medicated canal packing was done afterward. A cotton ball is placed in the ear, and the patient is awakened from surgery.

## RESULTS

The observation of 94 patients who underwent stapedectomy during the period of 3-year (2013-2016) is as follows.

### Age Incidence

Age of patients included in this study ranged from 14 to 58 years. Youngest patient was a 14 year-old-girl. Surgery was done commonly in the age group between 31 and 40 years (Table 1).

### Sex Incidence

Sex incidence of the patients is as follows.

Out of 94 patients, 46 (48.9%) were males and 48 (51.1%) were females (Table 2).

### Family History

Patients with the family history of otosclerosis are as follows.

The family history of otosclerosis was noted in 48 patients (51.1%). Positive family history in females was about 56.3% and positive family history in males was 43.7% (Table 3).

**Table 1: Age incidence**

Age group (years)	Total (%)
<21	14 (14.9)
21-30	22 (23.4)
31-40	42 (44.7)
41-50	15 (16)
51-60	1 (1.0)

**Table 2: Sex incidence**

Sex	Number of patients (%)
Males	46 (48.9)
Females	48 (51.1)

**Table 3: Family history**

Age group (years)	Males	Females	Total
<21	5	4	9
21-30	5	10	15
31-40	10	12	22
41-50	1	1	2
51-60	0	0	0
Total	21	27	48

### Pre-operative Symptomatology

The most common symptom was hard of hearing followed by *Paracusis willisi* and tinnitus (Table 4).

### Role of Pregnancy in Otosclerosis

In this study, 50% of the patients initially had noticed onset of conductive hearing loss during 2<sup>nd</sup> pregnancy and also aggravation of hearing loss during subsequent pregnancies (Table 5).

### Unilateral Versus Bilateral Involvement

Bilateral otosclerosis was commonly encountered than unilateral involvement. The ratio was found to be higher in females. In cases of bilateral equal conductive hearing loss weber test was done to select the ear for surgery (Table 6).

In this study, 52% of patients had air-bone gap between 41 and 60 Db (Table 7).

### Difficulties Encountered During Stapedectomy

During surgery, it was observed that 40.4% of patients had excessive posterosuperior bony overhang, 20.2% of patients had narrow external auditory canal, 10.6% of patients had narrow oval window niche. Obliterative otosclerosis was observed in 2.1% of patients (Table 8).

**Table 4: Pre-operative symptomatology**

Symptoms	Patients (%)
Hard of hearing	94 (100)
<i>Paracusis willisi</i>	60 (63.8)
Tinnitus	3 (3.2)
Vertigo	1 (1.1)

*P. willisi: Paracusis willisi*

**Table 5: Role of pregnancy in otosclerosis**

Age group	Number of patients
<21	1
21-30	10
31-40	13
Total	24

**Table 6: Unilateral versus bilateral involvement**

Sex	Unilateral (%)	Bilateral (%)
Male	16 (35)	30 (65)
Female	7 (15)	41

**Table 7: Preoperative pure tone audiogram**

Air bone gap	Patients (%)
20-30 dB	15 (16)
31-40 dB	28 (29.8)
41-60 dB	49 (52.1)
61-70 dB	2 (2.1)



### Microscopic Appearance of Footplate Types of Footplate

In this study, 80% of patients had thick chalky footplate and 10% had thin footplate with a milky opalescence (Table 9).

### Congenital Anomalies and Variations

During the study, it was observed that 5.3% of patients had bare facial nerve, 3.2% of patients had bare facial nerve hanging over the oval window, 2.1% of patients had persistent stapedia artery, and 1.1% of patients had congenital anomalies of the ossicular chain (Table 10).

### Intraoperative Complications

During surgery, it was observed that 4.25% of patients had an injury to chorda tympani nerve, 2.1% of patients had tear in the tympanic membrane, 1.1% of patients had perilymph gusher (Table 11).

### Post-operative Complications

During surgery, it was observed that 4.2% of patients had taste disturbance, 4.2% of patients had persistent conductive hearing loss, and 3.2% of patients had sensorineural hearing loss (Table 12).

**Table 8: Difficulties encountered during stapedectomy**

Difficulties encountered	Patients (%)
Excessive posterosuperior overhang	38 (40.4)
Narrow external auditory canal	19 (20.2)
Narrow oval window niche	10 (10.6)
Intra operative bleeding	3 (3.2)
Tympanomeatal flap elevation	2 (2.1)
Obliteration otosclerosis	2 (2.1)
Round window otosclerosis	1 (1.1)

**Table 9: Microscopic appearance of footplate types of footplate**

Types	Microscopic appearance	Patients (%)
Type 1	Minimally fixed in the oval window niche	6 (6.4)
Type 2	Thin footplate having a milky opalescence	9 (9.6)
Type 3	Thick chalky and opaque footplate	75 (79.8)
Type 4	Very thick and tightly fixed (obliterative otosclerosis)	4 (4.2)

**Table 10: Congenital anomalies and variations**

Anomalies and variations	Patients (%)
Bare facial nerve	5 (5.3)
Bare facial nerve hanging over the oval window	3 (3.2)
Persistent stapedia artery	2 (2.1)
Congenital anomalies of the ossicular chain	1 (1.1)
High jugular bulb	1 (1.1)
The facial nerve bulge down and obscures the foot plate	1 (1.1)
The facial nerve takes an anomalous course splitting to surround the stapes	1 (1.1)

## DISCUSSION

This study consists of 94 patients from 2000-2002, included 46 males and 48 females. A maximum number of patients belonged to the age group of 31-40 years.

Stapedectomy was done under local anesthesia. Surgery done under local anesthesia was useful to prevent general anesthetic complications and to know hearing improvement intraoperatively. Intraoperative vertigo was detected during surgery under local anesthesia.

In this study, the most common difficulty encountered during surgery was excessive posterosuperior bony overhang in 40.4% of patients. House curette was used carefully to curette excessive posterosuperior bony overhang. Curetting should be done from medial to lateral direction and also from superior to inferior direction.<sup>25-27</sup>

It was done carefully to avoid dislocation of incus and injury to the horizontal portion of the facial nerve. Excessive curetting of the overhang can cause problems in reposition of the tympanomeatal flap. It was not reported in our study.

This was followed by narrow external auditory canal in 20.2% of patients, narrow oval window niche in 10.6% of patients. The surgeon should always look for prominent or bare facial nerve in these cases. Hoard P. House in his

**Table 11: Intraoperative complications**

Complications	Patients (%)
Injury to chorda tympani nerve	4 (4.2)
Bleeding	
a. During elevation of tympanomeatal flap	2 (2.1)
b. Due to persistent stapedia artery	1 (1.1)
Tear in tympanic artery	2 (2.1)
Intraoperative vertigo	2 (2.1)
Fracture of the lenticular process of the incus	1 (1.1)
Floating footplate	1 (1.1)
Perilymph gusher	1 (1.1)

**Table 12: Postoperative complications**

Postoperative complications	Patients	Percentage
Taste disturbances	4	4.2
Persistent conductive loss		4.2
Sensorineural hearing loss		3.2
a) Intraoperative	1	
b) Early	1	
c) late	1	
Otitis media	2	2.1
Persistent vertigo	1	1.1
Tinnitus	1	1.1
Perilymph fistula	1	1.1
External canal granulation	1	1.1

study reported few cases of narrow oval window niche. They used cutting burr to enlarge the control hole made in the oval window region instead of perforator.<sup>28-31</sup>

In our study, obliterative otosclerosis was reported in 2.1% of patients. Obliterative otosclerosis was managed as follows.

After removal of the suprastructure of the stapes, hand burrs were used to define the footplate region (preferably in posteroinferior portion of the footplate). It was identified by a blue area and seepage of perilymph. Prosthesis introduced after obtaining an adequate opening (twice the width of the 0.6 mm Teflon piston) in the oval window region using perforators. The piston in these cases must extend about 0.5 mm beyond the inner edge of the footplate opening. Gelfoam placed around the prosthesis. Hand burring should be done very slowly and meticulously to avoid perilymph fistula.

Amedee and Miles L. Lewis, during a 25 year period study in 3000 patients reported obliterative otosclerosis in 4% of patients. The technique followed by them was as follows. After drilling to convert the obliterative footplate to a blue footplate from one-third to half of the entire footplate, it was removed by hook. Gelfoam was used to cover the open oval window. In their study, they reported 20 patients with obliterative otosclerosis had a progressive sensorineural hearing loss and 10 had a progressive mixed (or) conductive hearing loss. 7 patients had complete sensorineural hearing loss.<sup>32-35</sup>

In one of the studies reported diffuse obliterative otosclerosis in 2.1% of patients. Ugo Fisch, in his study reported obliterative otosclerosis in 13.7% of patients.

In our study round, window otosclerosis was reported in 1.1% of patients. The patient had partial obliteration of the round window niche. Surgery was done in the usual way (burring of the round window otosclerosis may result in sensorineural hearing loss). In a study conducted by Peter S. Ronald and William L. Meyerhoff reported about 30% of patients had round window otosclerosis, but complete closure of the niche is very uncommon. The study conducted 1989 reported closure of round window in 9 patients out of 1040 patients (0.87%).

In our study, bleeding during elevation of the tympanomeatal flap was controlled using cotton ball soaked in 4% xylocaine with adrenaline. It has both analgesic and vasoconstriction effect. Shea in his study reported 6.3% of patients had excessive bleeding during surgery, which can cause further cochlear hearing loss after 1 year of surgery. In one study has reported mucosal trauma with disruption of the capillary of the footplate as the cause of bleeding.

In our study, the most common congenital anomaly encountered was bare facial nerve in 5.3% of patients. This was followed by bare facial nerve overhanging the oval window in 3.2% of patients. The facial nerve taking an anomalous course was reported in 1.1% of patients. In those cases were bare facial nerve hanging over the oval window, perforator was used to make control hole in the posteroinferior quadrant to avoid injury to the facial nerve. This was done meticulously. In our study, facial paralysis was not reported. In these cases, surgery was not abandoned.

In our study, persistent stapedia artery was reported in 2.1% of patients. Bleeding from persistent stapedia artery was managed conservatively. Surgery was done without any difficulty.

Congenital anomalies of the ossicular were reported in our study to be 1.1%. The patient had malformed incus. The Teflon piston was placed in between the handle of malleus and footplate of stapes. Wiet *et al.* reported about 1% incidence of incus malleus fixation and malformed or short long process of incus was reported in 14% of patients.

In our study, fixed malleus was reported. Wiet *et al.* in his study reported about the incidence of malleus fixation as 1%. Causse and Causse in their study reported about 10.6% of patients had malleus fixation. Manubrium of the malleus was palpated during surgery to identify malleus fixation.

High jugular bulb was reported in 1.1% patients in our study. In our study, stapedectomy was done in the usual way without causing injury to the high jugular bulb. Mas Takashima in his study reported jugular bulb as rare.

In our study, the most common intraoperative complication was an injury to chorda tympani nerve in 4.2% of cases. In our study, routinely chorda tympani nerve was preserved to avoid taste disturbances postoperatively. In a few cases, chorda tympani nerve was kept as a support for Teflon piston. Chorda tympani nerve was cut deliberately in two cases to visualize the footplate of stapes.

In our study, we used curette to remove bony overhang. Careful delineation of the nerve was also done to avoid injury. A network of Florida Otolaryngologists reported loss of taste sensation in 5-10% of patients. Zoran Becvarovski reported injury to chorda tympani nerve in 5-10% of patients.

In our study, tear in the tympanic membrane was encountered during the elevation of the tympanomeatal flap in 2.1% of patients. To prevent tear, the tympanomeatal

flap should be carefully elevated en masse with periosteum down to annular ligament. In these cases, small tear was encountered and the edges were approximated and gel foam placed around the tear. Enfolding the margins of the tear should be avoided to prevent perforation of the tympanic membrane. Zoran Becvarovski reported tympanic membrane perforation in <1% of patients.

In our study, bleeding during elevation of the tympanomeatal flap was encountered in 2.1% of patients. It was controlled by keeping small cotton balls soaked in 4% xylocaine with adrenaline. This should avoid because Shea in his study reported as the association between profuse intraoperative bleeding and post-operative development of cochlear hearing loss.

In our study, intraoperative vertigo was reported in 2.1% patients. This was mainly due to manipulation of the footplate. It may occur due to frequent suctioning in the middle ear. This was treated by reassurance of the patients and antivertiginous drugs.

In our study, perilymph gusher was reported in 1.1% of patients. It was encountered usually while drilling through the thick footplate, piston placed over the graft and inadvertent injury of the perilymphatic membrane in patients having wide cochlear aqueduct. It was treated by elevating the head end of the table. Gelfoam was placed in the middle ear. The endomeatal flap was replaced, and external was packed with medications. Daily fluid intake was restricted postoperatively. Patients were instructed to take steroids and tab, acetazolamide.

In our study, floating footplate was encountered in 1.1 patients. During the surgery, safety control hole helped in the extraction of the footplate with minimal trauma to the vestibule. Surgery was not abandoned in our study due to floating footplate.

In our study, fracture of the lenticular process of the incus was reported in 1.1 patients. This was due to improper separation of the incudostapedial joint. In this case, Teflon piston was crimped carefully above the site of the fracture of the lenticular process. Chorda tympani nerve was kept around the piston to secure it in place. Gelfoam was also kept around the piston.

Incus dislocation was not reported in our study. This was due to careful separation of the incudostapedial joint and curetting of the posterosuperior bony overhang. Medialization of the incus can occur due to prolonged duration of surgery.<sup>36-39</sup> In our study, we did not encounter medialization of the incus. Duration of the surgery plays a vital role in stapedectomy.

In our study, the most common post-operative complication reported was taste disturbance due to chorda tympani nerve injury in 4.2% of patients. Permanent taste disturbances occurred in 5% of patients in a study conducted by Wiet *et al.* In our study, taste disturbances following stapedectomy was reduced because of careful separation of the chorda tympani nerve. It was usually pushed anteriorly to avoid injury to chorda tympani nerve. It was usually pushed anteriorly to avoid injury to chorda tympani and also to visualize the footplate.

A network of Florida Otolaryngologists, in their study, reported 5-10% patients of loss of taste sensation. The study conducted by Zoran Becvarovski reported prolonged taste disturbances in 5% of patients. Wiet *et al.* in his study reported taste disturbance due to complete sectioning of the chorda tympani nerve in 20-30% of patients. In most of the cases, the symptoms subsided in 3-4 months.

In our study, the persistent conductive hearing loss was reported in 4.2% of patients. In four patients, one patient developed fracture of the long process of incus. In our study, it was reduced because of proper selection of patients, correct technique, and crimping the prosthesis. Kacker *et al.* reported few patients of persistent conductive hearing loss. It was commonly encountered due to adhesions in the middle ear. The necrosis of the long process of incus was also mentioned as a cause of persistent conductive hearing loss in their study. Hildmann, Steinbach in 1989 reported about 11% patients of persistent conductive hearing loss in their study. It was reported due to adhesions in the middle ear.

Otitis media was reported in 2.1% of patients. These patients were treated aggressively with higher antibiotics because to avoid the risk of developing sensorineural hearing loss, labyrinthitis, and meningitis. John W. House in his study reported middle ear infections very rarely. Victor Goodhill, Irwin Harris in their study reported few patients of otitis media due to concomitant upper respiratory tract infections. These patients were treated with decongestants and intravenous antibiotics.

About 87% of hearing improvement was reported in a study conducted by Mathews and Rasgon in 1994. Shea Jr. reported 95% of hearing improvement in his study. David M. Vernick reported 78% of hearing improvement in 1984. Coker and Duncan reported hearing impairment in 75% of patients. Peter S. Roland, William L. Meyerhoff reported hearing impairment in about 90% of cases. Hough, Michael McGee reported closure of the air-bone gap to within 10 dB in 90-95% of patients. Paparella in his study reported hearing improvement in 90% of cases. In our study, about 90% of cases showed improvement in hearing.

In our study, the sensorineural hearing loss was reported in 3.2% of patients. One patient had obliterative otosclerosis. He developed dead ear intraoperatively due to injury to vestibule during hand burring. One patient developed sensorineural hearing loss about 6 months after surgery. The one patient developed perilymph gusher and fistula postoperatively. Goodhill and Harris in their study reported 1-2% of severe sensorineural hearing loss. Causse in his series reported 2% patients of sensorineural hearing loss following surgery.

Austin in his study reported 1% of the sensorineural hearing loss. The factors proposed by him was bone chips in the vestibule, irrigation with an open oval window, trauma with instruments to the vestibular contents, too violent or rapid aspiration of perilymph, middle ear infections.

Hughes in 1987 in his study of 75 patients reported severe sensorineural hearing loss in 1 patient. Pederson and Felding have reported in their study of 1111 patients, about 2 patients of partial sensorineural hearing loss. Jean Marquet in his 30 years study of 2919 patients reported sensorineural loss in 0.91% of patients. Kacker *et al.* reported 1-2% of sensorineural hearing loss. Mathews and Rasgon, in 1994, in their study of 71 patients reported high severe sensorineural hearing loss in 3 patients. Wiet *et al.* in his study of stapedectomy reported 1-3% of patients had sensorineural loss following surgery.

The duration of surgery is very important in stapedectomy because the results of surgery vary depending on the duration of surgery. Duration of surgery is always proportional to the post-operative sensorineural hearing loss. The time taken for surgery after making control hole in the footplate is very important because of continuous perilymph leak and also exposure of the vestibule which causes sensorineural hearing loss postoperatively. Continuous suctioning of the blood in the vestibule should not be done because of the risk of post-operative sensorineural hearing loss. The incidence of post-operative tinnitus also depends on the duration of surgery, so it is very important for the surgeon to finish the surgery as quickly as possible.

In our study, persistent tympanic membrane perforation was not reported. 2.1% of patients had small perforation of the tympanic membrane during surgery. They healed very well because of the proper approximation of the edges of the tympanic membrane and also due to sterile aseptic technique. Cause and Causse reported tympanic membrane perforation as 1.9% in their study. Myringoplasty was done to repair the defect after 2-3 months of surgery.

In our study, perilymph fistula was reported in 1 patient. The patient developed total sensorineural hearing loss postoperatively.

In our study, external canal granulation was reported in 1.1% of patients and it was managed conservatively.

In our study, facial palsy and suppurative labyrinthitis were not reported. Shambaugh in his study reported 1 patient of partial facial paralysis. Shea in his study reported five and one-half day post-operative facial palsy after stapedectomy and reported an incidence of 0.1%. Smith *et al.* reported an incidence of 0.5% of facial palsy.

## CONCLUSION

Surgical skills, tissue respect, experience, and aseptic surgical technique are essential to perform stapedectomy with least complications. Adequate postoperative care and proper instruction of the patient are mandatory for a good hearing result.

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# Management of Polycystic Ovarian Disease in Karur: A Prospective Study

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## Abstract

**Introduction:** Polycystic ovary disease (PCOD) a condition in which a woman has an imbalance of female sex hormones. This may lead to menstrual cycle changes, cysts in the ovaries, trouble in getting pregnant and other health changes. The main causes are genetic and hormonal imbalance.

**Aim:** To study the clinical presentation of PCOD, the general management and the relation with hormonal changes, effects on pregnancy, and its complications.

**Materials and Methods:** Prospective observational study, 20 patients with irregular menses were included in the study. Hormonal assays, blood, and urine investigations and USG studies were performed. General, physical, clinical, systemic, gynecological examinations and special investigations such as endometrial biopsy and radiology were also done.

**Results:** A majority of the patients fall under the age group 21-25 (35%) from their teenage itself. 30% of patients came under 31-35 and 70% represent 26-30 years. In 20 patients, 60% represented fertility and 40% represented infertility. Among 20 patients, 25% showed mild improvement, 55% showed moderate improvement after treatment.

**Conclusion:** Hormonal dysfunctions in PCOD manifested together or independently. PCOD women can be sub-grouped based on clinical features suggestive of endocrinological malfunctions and can be investigated accordingly for selection of appropriate treatment modalities.

**Key words:** Adolescents, Clinical features, Polycystic ovary disease, Women health

## INTRODUCTION

The polycystic ovarian disease is the most common endocrine disorder in women worldwide. The syndrome is characterized by ovulatory dysfunction, hyperandrogenism, and polycystic ovaries (PCO). These features can lead to multiple symptoms with systemic as well as organ-specific aberrations. As PCO disease (PCOD) is associated with several other diseases/morbidity-related factors such as obesity and other cardiovascular disease risk factors

which are becoming more prevalent among females today, further research on the pathophysiology and the long-term effects of PCOD is of the utmost importance to prevent future health problems in the large group of PCOD women.<sup>1</sup>

PCOD is a heterogeneous disorder of uncertain cause. There is some evidence that it is a genetic disease. Such evidence includes the familial clustering of cases, greater concordance in monozygotic compared with dizygotic twins and heritability of endocrine and metabolic features of PCOD.<sup>2,3</sup>

The severity of PCOD symptoms appears to be largely determined by factors such as obesity.<sup>4</sup> PCOD has some aspects of a metabolic disorder, since its symptoms are partly reversible. Even though considered as a gynecological problem, PCOD consists of 28 clinical symptoms.

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The clinical presentation of PCOD varies widely. Women with PCOD often seek care for menstrual disturbances, clinical manifestations of hyperandrogenism, and infertility. Menstrual disturbances commonly observed in PCOD include oligomenorrhea, amenorrhea, and prolonged erratic menstrual bleeding.<sup>5</sup>

The choice of treatment for women with PCOD depends on the symptoms with which a patient presents. Symptoms typically fit into three categories: Menstruation related disorders, androgen-related symptoms, and infertility.<sup>6</sup>

### Aim

To study the clinical presentation of polycystic ovarian disease, the general management and the relation with hormonal changes, effects on pregnancy and its complications.

## MATERIALS AND METHODS

This is a prospective observational study conducted in Poongothai Hospital in karur town. Hospital approval and informed consent from the patients were obtained. 20 patients were included in the study. Age group between 15 and 35 years, obese patients with metabolic syndrome, patients with the history of menstrual irregularities, women with the history of infertility, women with the findings of acne, and hirsutism and alopecia, patients with the positive genetic history and hormonal imbalance were included in the study. Age group above 35 years, obese patients with fertile and regular menstrual history, patients with ovarian cysts but no history of menstrual irregularities and infertility, infertile women with no history of obesity and with the history of regular menses, obese women with fertile and hormonal balance and with no history of acne, hirsutism, and alopecia, patients with no genetic history were excluded from the study.

## RESULTS

Figure 1 shows the frequency distribution among the age groups. There were 20 patients in this study and 30% come under the age group 15-20 years, 35% came under the age group 21-25 years, 30% come under the age group 26-30 years, and 5% came under the age group 31-35 years.

Figure 2 shows the frequency distribution of occupation among the patients. There were 20 patients in this study and 35% come under private job, 10% come under government job, 10% under self-employee, 30% are students, and 15% are housewives of the total respondents.

Figure 3 shows the distribution of socioeconomic status among 20 patients out of 20 patients 5% belong to poor economic status and 95% belong to middle income group.

Figure 4 shows the frequency distribution of the age at menarche. There were 20 patients in this study. Among these, those who attained the menarche at the age of 12 years represent 15%, at the age of 13 years represent

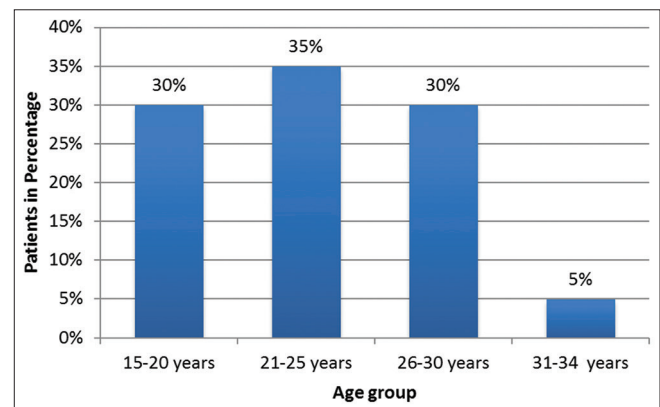


Figure 1: Distribution of patients in age groups

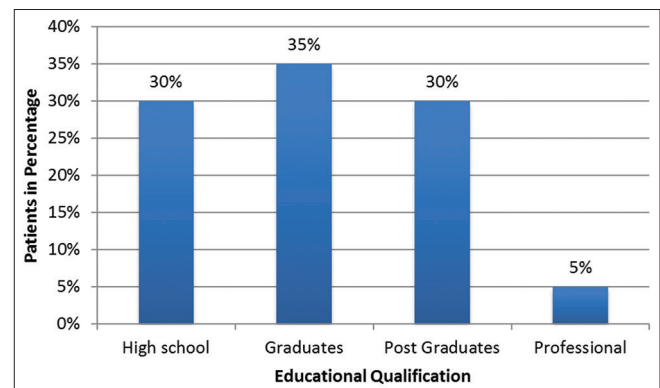


Figure 2: Distribution of patients in educational qualifications

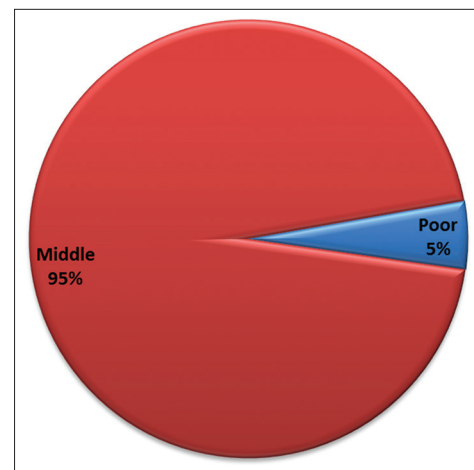


Figure 3: Distribution of patients in socioeconomic status

45%, at the age of 14 years represent 30%, and at the age of 15 years represent 10%.

Figure 5 shows the distribution of body mass index (BMI) of 20 patients. 30% of patients came under 31-35 and 70% represent 26-30.

Figure 6 shows the frequency distribution of the result of the treatment among 20 patients. Among 20 patients, 25% showed mild improvement, 55% showed moderate improvement and 20% shows marked improvement.

Figure 7 shows the distribution of infertility among the patients. Out of these 60% represented fertility and 40% represented infertility.

Figure 8 shows the frequency of fertility at the end of the treatment among 4 patients. Out of these 50% become fertile and 50% become infertile.

## DISCUSSION

The prevalence of PCOS depends on the choice of diagnostic criteria. The World Health Organization

estimates that it affects 116 million women worldwide as of 2010 (3.4% of women).<sup>7</sup>

In our study, 30% of cases were reported in 15-20 years which is second higher, first is 21-25 years. Bronstein *et al.* studied the incidence were 26% (15/58) preadolescent girls (9-12 years) versus 74% (43/58) adolescents (13-18 years).

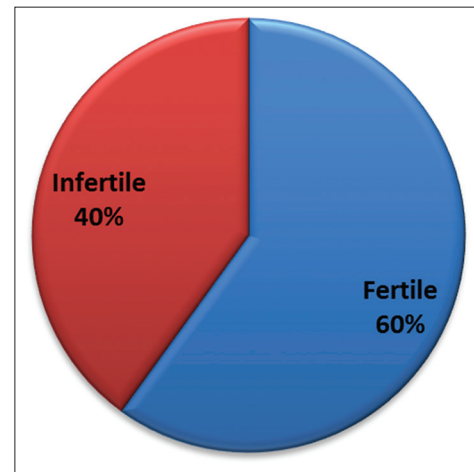


Figure 6: Distribution Infertility among the married people

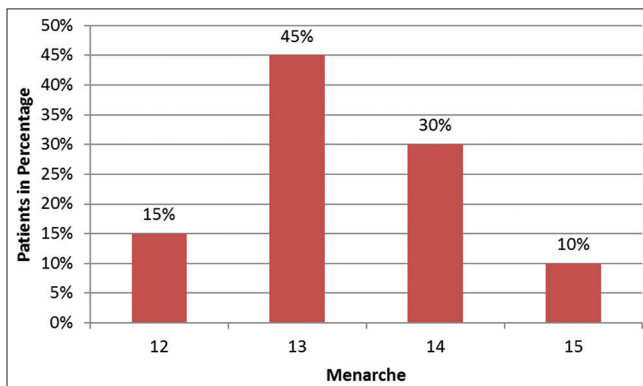


Figure 4: Distribution of age at menarche

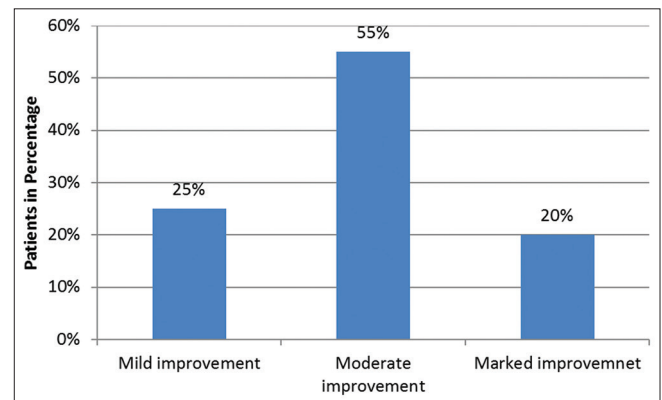


Figure 7: Distribution of the result of treatment

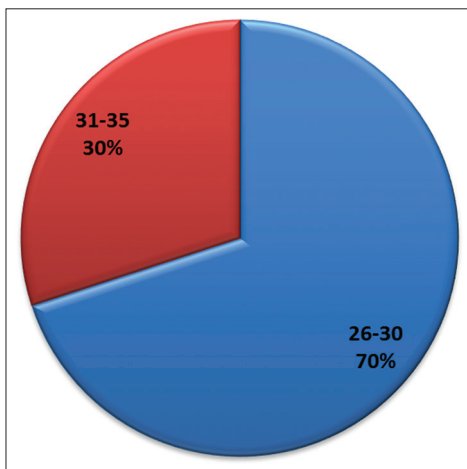


Figure 5: Distribution of patient's body mass index

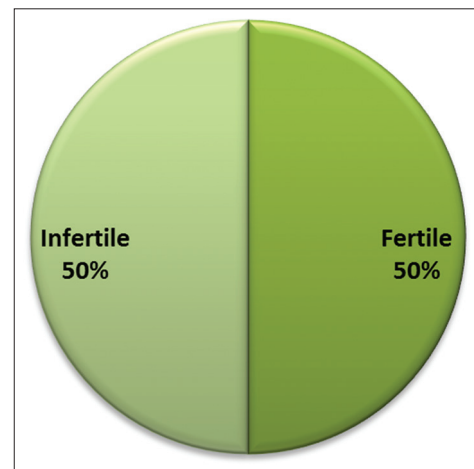


Figure 8: Distribution of fertility at the end of the treatment



PCOD may occur at a younger age in girls who develop early pubarche and thelarche. Therefore, the diagnosis and workup should be considered in young girls with risk factors suggestive of PCOD.<sup>8</sup>

95% patients in our study are in middle socioeconomic status where Joshi *et al.* study reported the majority of the participants (73.2%) were adolescents (15-19 years) from lower socioeconomic strata. Venkatarao *et al.* reported 54.2% in lower economic status where there is no middle economic status in both the studies.<sup>9,10</sup>

In our study, 70% were in 26-30 and 30% in 31-35 BMI. Obesity is a common finding in PCOS and aggravates many of its reproductive and metabolic features. The relationship between PCOS and obesity is complex, not well understood, and most likely involves interaction of genetic and environmental factors.<sup>11</sup>

4 patients in 10 married, reported infertility. The prevalence of PCO among ovulatory women with infertility is higher than that in the normal population, suggesting that PCO may, perhaps by virtue of an effect of hyperandrogenemia, contribute to the causes of subfertility in women with regular menses.<sup>12</sup>

## CONCLUSION

Polycystic ovarian disease may be one of the most complex female health issues of our time. It is the most common endocrine disorder in women of reproductive age. PCOD

is accompanied by a variety of different health issues, many of which directly impact fertility. If permanent diet and lifestyle changes are implemented, risks, and health issues may become obsolete.

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# Treatment of Refractory Lateral Epicondylitis of Humerus with Local Autologous Plasma Injection

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## Abstract

**Introduction:** Elbow lateral epicondylitis is a common problem that usually resolves with conservative treatment modalities such as local infiltration with steroids, ultrasonic therapy, manipulation, and finally operative procedures are tried. An alternative to surgical intervention is sought for when the conservative measures fail.

**Purpose:** The hypothesis of this study is to establish the role of local autologous plasma injection to bring along biological cure in these cases.

**Materials and Methods:** A total of 40 patients (40 elbows) with persisting pain for approximately 6 months, despite another conservative mode of intervention, were treated. The patients were injected with 2cc autologous plasma locally at the site of epicondylitis aseptically after preparation by centrifugation of 5cc blood. A post procedure physiotherapy program with an active range of exercises was followed in every patient. The outcome was rated by post procedure visual analog pain scores (VAS) and Mayo elbow performance scores (MEPSs). Informed consent had been obtained from the subjects, and the study protocol was approved by the institutional ethics committee.

**Results:** All patients in this study noted improvement in their VAS and MEPS. Minimal complication occurred in some patients. Mean VAS improved from 74.9 to start with to 41.5 at 4 weeks, 29.8 at 8, and 18.5 at 6 months follow-up. Mean MEPS improved from 50.3 to start with to 71.8 at 4 weeks, 79.7 at 8 weeks, and 84 at 6 months follow-up.

**Conclusion:** The treatment of patients with refractory lateral epicondylitis with local autologous plasma reduced pain significantly. Hence, local autologous plasma injection is a viable option to be considered before contemplating surgical intervention in refractory lateral epicondylitis of humerus.

**Key words:** Autologous plasma, Refractory lateral epicondylitis, Tennis elbow, Tendinitis, Tendinosis

## INTRODUCTION

The lateral epicondylitis (tennis elbow) is a familiar term used to describe myriad symptoms along with activity-related pain around the lateral aspect of the elbow, with a common age of onset of 35-50 years and affecting around four adults/1000 annually. Activities requiring supination and pronation movements in near full elbow extended position leads to lateral epicondylitis of humerus.<sup>1</sup>

Lateral epicondylitis is initiated by micro tear, most often, in the origin of the extensor carpi radialis brevis. The chronic overuse injuries following multiple micro traumatic events cause disruption of the internal structure of the tendon and degeneration of the cells and matrix. These fail to mature into normal tendon, at times, leading to tendinosis.<sup>2</sup> The term tendinitis is used frequently to describe these conditions, but histopathological studies have shown that specimens of tendon obtained from areas of chronic overuse do not contain large numbers of macrophages, lymphocytes, or neutrophils.<sup>3,4</sup> The histopathologically tendinosis has been found to be a population of fibroblasts, vascular hyperplasia, and disorganized collagen which is termed as angiofibroblastic hyperplasia.<sup>5</sup> Tendinitis, on the contrary, is characterized by the presence of an increased number of lymphocytes or neutrophils.

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The cause of tendinosis to be painful is unclear, and the cause of failure of collagen maturation is unknown. Tendons that are susceptible to injury are those that are involved in locomotion and ballistic performance, transmitting loads under elastic, and eccentric conditions.<sup>2,3,6</sup> Tendons, wrapping around a convex surface or the apex of a concavity, those crossing two joints, those with areas of scanty vascular supply, and those that are subjected to repetitive tension and are susceptible to overuse injuries.<sup>4,7-10</sup>

The cyriax noted in his study that the origin of the extensor carpi radialis brevis was the primary site of this injury, and histopathological changes have been documented at this location.<sup>4,10-12</sup> Involvement of the origin of the extensor digitorum communis is also found in one-third of patients.<sup>4,12,13</sup> If it is assumed that tendinoses have basically the same pathogenesis, then the biologic methods of the treatment of patients with tennis elbow can serve as a method for the treatment of pain in other regions in which tendinoses have been reported, such as the patellar ligament, the rotator cuff, the flexors and extensors of the elbow, the adductors of the hip, the triceps, the plantar fascia, and the achilles tendon. The plasma probably helps recruit bone marrow-derived stem cells to the site of injection and plasma-derived growth factors moderate the microvascular environment leading to the healing process. Further study into the mechanism of action of local autologous plasma is needed.

We chose to study lateral epicondylitis because it is clinically a very common entity and greatly hampers activities of daily living. Our hypothesis is that local autologous plasma injection in the treatment of cases of refractory lateral epicondylitis of humerus promotes biological healing and yield better functional results.

## MATERIALS AND METHODS

The study was conducted in the Department of Orthopaedics, Medical College and Hospitals, Kolkata on a prospective basis from February 2014 to July 2015. Out of the patients attending the outpatient Department of Orthopaedics, Medical College and Hospitals, Kolkata and diagnosed as suffering from lateral epicondylitis of humerus, 40 patients were selected who fitted our criteria for the study. A written consent was obtained from all the patients. Inclusion criteria included adult patients (age group 20-60 years) suffering from lateral epicondylitis of humerus (after confirmation of diagnosis), pain persisting for at least 6 months and failure of conservative therapy including rest, activity modification, bracing, physiotherapy, steroid injection, and non-steroidal anti-inflammatory medication.

Exclusion criteria included pregnancy, presence or history of carpal tunnel syndrome, cervical radiculopathy, significant intra-articular pathology, lateral collateral ligament injuries, and systemic disorders such as diabetes, rheumatoid arthritis, and hepatitis. In all cases, patients complained of significant persistent pain that interfered with normal activities of daily living including combing hair, wrenching clothes and toileting, etc.

Every patient was assessed thoroughly and a detailed history of the patient was taken, noting the duration of pain, the mode and severity of injury, if any, and detailed examination of the affected part. A case included for the study was then again thoroughly examined. The case is again evaluated to confirm the diagnosis using the several tests for tennis elbow, such as extending the fully pronated and flexed elbow, Thompson's test, Mill's Maneuver and Cozen's test. The elbow tendinosis is diagnosed by physical examination and diagnostic imaging. Anteroposterior and lateral projection of radiographs of the affected elbow were checked in all cases to exclude obvious pathology of trauma or cubital tunnel osteophytes. Collateral ligament injury and neuritis were excluded by clinical or imaging studies. Sonographic scanning was used for the evaluation of tendon and ligament condition. All the patients were evaluated by visual analog pain scale (VAS) and Mayo elbow performance scores (MEPSs). The plasma for injection was prepared in the Institute of Haematology and Transfusion Medicine, Medical College and Hospitals, Kolkata.

After proper counseling and following aseptic precautions, about 5cc of blood was drawn in a syringe containing 0.5 cc of heparin from the patient's contralateral forearm vein. The drawn blood was then transferred to a pre-sterilized centrifuge tube. The blood was centrifuged at 1300 rpm for approximately 20-25 min to generate the plasma. Of the centrifuged plasma, only the clear upper layer and the buffy coat layer that contained mononuclear cell were used for injection. The duration from drawing of blood and injecting the plasma was between 30 and 45 min.

The patients were placed in the supine posture with the arm fully adducted at the patient's side, and the elbow flexed to 45° with the wrist dorsiflexed passively using a sand bag to relax the affected tendons in pronation. In this position, the lateral epicondyle and the most tender point is identified. The local area is then painted and draped adequately. The disposable syringe with 22-gauge needle was advanced perpendicular to the lateral epicondyle through the skin till it touches the bone. The needle is then slightly withdrawn by 1-2 mm and approximately 2.5 mL of autologous plasma was injected directly into the area of maximum tenderness and into the common extensor tendon origin and undersurface of extensor carpi radialis brevis. The technique involved a single skin entry and then

5 penetrations of the tendon.

Immediately after the injection, the patient was kept in a supine position without moving the arm for 15 min. The patients were sent home with a compression bandage and instructions to limit their use of the arm for approximately 24 h and use oral nonsteroidal anti-inflammatory drugs for 3 days for pain and local ice pack if required. After 24 h, patients were given a standardized stretching protocol to follow for 2 weeks. The patients were told to continue activities of normal daily living but to avoid any activities that were likely to aggravate symptoms. A formal strengthening program was initiated after this stretching. At 4 weeks after the procedure, patients were allowed to proceed with normal activities as tolerated. The patients were examined at 4 weeks, 8 weeks, and 6 months after the procedure. On every follow-up visit, the patients were examined thoroughly.

MEPS system is the most widely used scoring system in cases of analysis of elbow pathology. It provides a good analysis of the functional outcome of procedures done around the elbow. Hence, we used the MEPS for analyzing our results. A 100 mm VAS (0=no pain; 100 worst pain possible) with color coding is used to evaluate the subjective interpretation of pain.

The changes in the mean values of the MEPS and the VAS from the pre procedure to each follow-up level were assessed by analysis of variance (ANOVA). Statistical analysis is performed using Student's *t*-test, Chi-square test, and standardized statistical package.

## RESULTS

The patients ranged from 26 to 56 years (average 41.4 years). The most frequent age group affected was 30-39 years. They all underwent injection procedure and were followed up in this hospital on outpatient basis for a period ranging from 6 to 14 months (average 8 months). 18 among the 40 patients were males and 22 among them were females. Sex distribution can be stated to be equal in incidence. Among the 40 patients, 21 were housewives, 9 were farmers, 9 were daily laborers, and 4 were desktop workers. Among the 40 patients selected, in 28 the dominant upper limb was affected and in 12 the non-dominant side was affected.

The presence of pain was graded as none, mild, moderate, and severe; 33 out of the total 40 cases (82.5%) had moderate pain and 7 out of 40 (17.5%) had severe pain at the pre procedure level. At 6 months follow-up, 8 out of 40 (20%) had "none" pain, 30 out of 40 (75%) had mild pain, and 2 out of 40 cases (5%) had moderate pain. The function to comb hair improved from 10 out of 40 cases (25%) pre procedure to 36 out of 40 cases (90%) at

6 months follow-up; feed self-function improved from 31 out of 40 cases (77.5%) pre procedure to 39 out of 40 cases (97.5%) at 6 months follow-up; hygiene function improved from 19 cases (47.5%) pre procedure to 38 cases (95%) at 6 months follow-up; dressing function improved from 1 case (2.5%) pre procedure to 33 cases (82.5%) at 6 months follow-up; finally, shoe function improved from 2 cases (5%) pre procedure to 23 cases (57.5%) at 6 months follow-up. Initially, the patients selected for the study had a mean Mayo elbow score of 50.25; which at 4 weeks follow-up showed a mean of 71.75; at 8 weeks follow-up showed a mean of 79.75 and at 6 months follow-up improved to 84. Result interpretation based on MEPS showed improvements as excellent in 7, good in 29, fair in 3, and poor in 1.

Initially, the patients selected for the study had a mean VAS of 74.9; which at 4 weeks follow-up showed a mean of 41.5; at 8 weeks follow-up showed a mean of 29.8 and at 6 months follow-up improved to 18.5.

A graphical representation of the mean VAS and mean MEPS respectively from pre procedure status to 6 months post procedure follow up is given in Graphs 1 and 2.

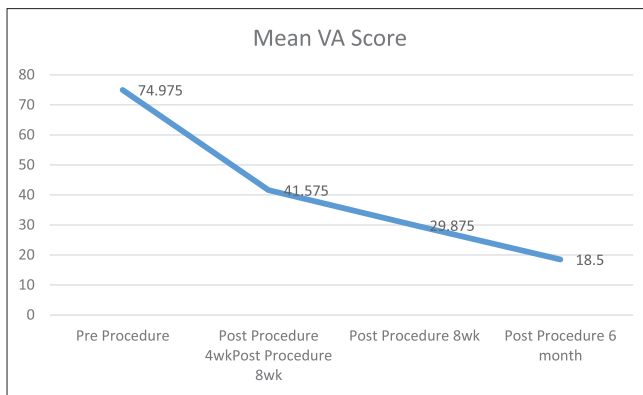
The changes in the mean values of the MEPS and the VAS from the pre procedure to each follow-up level were assessed by ANOVA. Based on the results of the above-mentioned statistical analyses, we concluded that the difference we obtained between the modalities of evaluation was statistically significant ( $P < 0.0001$ ).

Pain (moderate) with associated functional difficulties persisted in 2 (5%) cases. Severe pain was not the present in any cases at 6 months follow-up. No other cases had any other complications of infection, local skin condition changes, and neurovascular deficit distally. 24 patients complained of increased pain following injection procedure, which was relieved with analgesics and local ice pack application within 5 days.

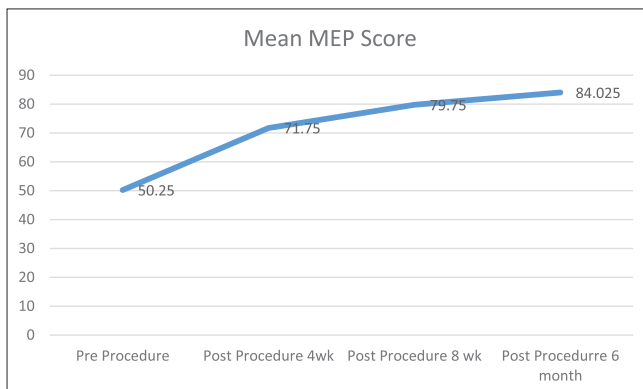
## DISCUSSION

The lateral epicondylitis of humerus is a common problem usually controlled by conservative modalities. If conservative methods do not provide satisfactory remedy, other options are tried. A meta-analysis of physical therapy, recently, failed to provide evidence to establish it as a treatment modality providing long-term relief.<sup>14</sup> The physical therapy, though, is also used in our study in the post procedure stretching and strengthening exercises. Corticosteroid injections have been used most popularly and extensively for treatment, but studies have raised certain doubts about their efficacy.<sup>15,16</sup> The superficial injection of corticosteroid may result in





Graph 1: Mean visual analog score



Graph 2: Mean Mayo elbow performance score

subcutaneous atrophy and sometimes leading to permanent ultrastructural changes following intratendinous injection, as observed by Jobe and Ciccotti.<sup>17</sup> In our study, this sort of complication did not occur as this is a biologic form of treatment. Extracorporeal shock wave therapy was shown to be no better than placebo in a recent study.<sup>18</sup> In this day, orthopedics biological treatment modalities are gaining popularity. Bone morphogenic proteins and other growth factors have been studied *in vitro* and presently are being tested *in vivo* also.<sup>19</sup> Autologous plasma may also be helpful for wound healing. The study by Edwards and Calandruccio<sup>20</sup> showed that 22/28 patients responded to autologous blood injections, with average MEPS decreasing from 6.5 to 2.0 after a mean follow-up of 9.5 months. They, using whole blood, noted a 79% success rate when treating lateral epicondylitis. We used autologous plasma instead of blood to decrease the volume of injection and also to avoid the deposition of iron locally following breakdown of red blood cells if any. Mishra *et al.*<sup>21</sup> introduced buffered platelet rich plasma technique in the treatment of chronic elbow tendinosis. Moon *et al.*<sup>22</sup> concluded that the injection of iliac bone marrow plasma after arthroscopic debridement in severe elbow tendinosis demonstrated early recovery of daily activities and clear improvement. Klein *et al.*<sup>23</sup> reported in their study that transforming growth factor

beta increases Type I collagen production in tendon sheath fibroblasts. These mechanisms may be at work in our study also. Further study into the mechanisms by which plasma works is needed. We chose to study lateral epicondylitis of humerus because it is clinically very common and hampers activities of daily living. In this study, the patients treated with plasma did significantly better at 4 weeks and 8 weeks. At 6 months after treatment, however, the autologous plasma injected patients improved from a mean VAS of 74.9 at pre procedure level to 18.5 at 6 months follow-up and a mean Mayo elbow pain score of 50.25 at pre procedure level improved to 84 at 6 months follow-up. Of importance, no plasma treated patient was worse after treatment. Two out of 40 cases (5%) had residual moderate pain, and there were no significant complications in this study. Although, there were some problems with some patients in explaining the methodology and post procedure protocol. The limitations of this study include lack of a randomized control group and the small number of patients. Further study of autologous plasma versus whole blood or cortisone should also be performed in the future.

## CONCLUSION

The data suggest autologous plasma may be an alternative to surgery in patients with this disorder or of its kind. Hence, to conclude, the use of autologous plasma injection method provides biologic healing and is an effective solution for refractory lateral epicondylitis of humerus and similar disorders.

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# Practical Knowledge and Perception about Antibiotic Usage and Resistance: A Questionnaire-based Study

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## Abstract

**Introduction:** Nowadays antibiotic resistance is an important global issue of health-care problem which needs urgent attention. Indiscriminate use of antibiotics unnecessarily probably the foremost cause of this problem. Awareness of this fact among under graduate MBBS students and Nursing trainee students who become the health-care provider of future generation is extremely important.

**Materials and Methods:** A format of questionnaire which covers the different aspects of knowledge about proper antibiotic usage was distributed among all students and to assess their knowledge, attitude, and practices regarding antibiotic use and resistance by a five-point Likert scale.

**Results:** Among total 352 participants, 96% of medical students and 82% of nursing students considered that antibiotic resistance is a global issue whereas 96% of medical students and 73% of nursing students agreed with the matter that in India it is also a serious issue. This study also observe the various false practices and belief which include tendency to take a large dose of antibiotics for quicker action, have tendency to skipping of drugs after become well without taking full course of medicines, indiscriminate and injudicious use of antibiotics, that also complicated the scenario. As per their suggestion, measures should be taken to reduce the antibiotic resistance are institutional specific guideline and conduct frequent educational programs, easy access to local and this antibiogram, require regular antibiotic surveillance programs.

**Conclusion:** This study revealed many important clues regarding some improper knowledge, attitude, perception and practices regarding antibiotic resistance and usage among the future doctors, and nurses. The results can be considered, to plan for an effective undergraduate curriculum. The medical education strategies should aim, not only to increase the knowledge but also to change behavior and practices among medical students.

**Key words:** Antibiotic resistance, Indiscriminate antibiotic use, Knowledge questions

## INTRODUCTION

Antibiotics are not only commonly used but also indiscriminately practiced in India. Irrational use of antibiotics without any proper guideline and law against its use make the drugs ineffective very soon which is a

serious health-care problem in many developing countries. In 2011, WHO introduced a six-point policy package to fight against the spread of antibiotic resistance.<sup>1</sup> Many people seek care in different medical stores for their clinical problems, and thus different antibiotics are easily made available and distributed to population neglecting its rational use.<sup>2</sup> However, concern has been raised about the low-quality practices; profit aspirations, poor application of legislation and also about the improper knowledge of general population about this problem.<sup>3</sup>

In India, there is no such strong law against male practitioners and drug sellers. In developing countries,

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more than 50% of antibiotics are purchased without prescription.<sup>4,5</sup> The containment of this problem requires changes in the behavior of practitioners and health workers. In the hospitals, we need to change the behaviors of medical students and nurses, who will be the future health-care provider in our society, which is extremely vital.<sup>6-8</sup>

Young doctors should be given more education during their undergraduate training regarding antibiotic resistance and their appropriate use. This is a crucial time period during which the importance of these issues should be emphasized, because once the doctors become qualified, it is difficult to change their views and habits. The interventions which are undertaken to prevent and control antimicrobial resistance, usually aim to bring about behavioral changes in the target group, and the outcome of these interventions is affected by the previous beliefs and motivations which are held by this group. Hence, for any educational intervention to be successful and for the changes to be sustained, it should change the knowledge, attitudes, and practices of the target group.<sup>8,9</sup> A better understanding of what the students know and believe about the issues of antimicrobial use and resistance can assist us in planning an effective educational intervention for them.

In this regards, this study was conducted among 2<sup>nd</sup> year undergraduate medical students and nursing students to assess their knowledge and attitude concerning antibiotic resistance, as well as their self-reported practices which are related to antibiotic usage.

## MATERIALS AND METHODS

### Study Design

A questionnaire-based study was conducted among two batches of MBBS and nursing students in BSMC, Bankura a Government Medical College in India, each has strength of 150 and 50 in number. A sample size of total 352 was calculated. Before data collection the format of questionnaire was distributed to every student. The questionnaire was prepared after consultation with a group of experts and was submitted for prior test to faculty doctors of various disciplines to check comprehension and clarity of the questions. A total 35-item of questions were placed in each sets based on their knowledge of the local and national prevalence of antibiotic resistance, their perception of the importance of this problem, their attitude about antibiotic prescribing, their beliefs about the causes of antibiotic resistance and what is the knowledge about current and ideal intervention designed to improve antibiotic stewardship. Most questions about perceptions and attitude used five-point Likert scale response options.

### Study Procedure

Each participant was allotted 30 min to answer the questionnaire in the form of options, which they feel appropriate to answer. Informed consent was obtained from the participants, to utilize their data for research purposes.

### Ethical Consideration

All participants gave written informed consents to participate in this study.

## RESULTS

The results are tabulated as percentages in Tables 1-4. Regarding contributory factors (Table 1) behind antibiotic resistance, most of them have improper knowledge and practice. Considering the contributing factor to antibiotic resistance, 35% of the medical students and 51% of the nursing student thought that for quicker relief larger dose of antibiotics will be appropriate. Although larger study group agree with the fact that inappropriate antibiotics selection lately contributes to the antibiotic resistance but at least 15% of study population strongly disagree this truth. 76% of medical students and 49% of nursing student used to believe that irrespective of the etiology of fever, antibiotics help to get relieved from fever. 76% of nursing students and 57% of medical students believe broad spectrum antibiotics are better than targeted antibiotics. In contrast to confident appropriate knowledge various responses also found regarding skipping doses, incomplete courses, and antibiotics safety. 49% of medical students and 35% of nursing students believe that simultaneous use of two or more antibiotics is better to control infections than monotherapy.

Regarding medical practices (Table 2) most of the questions have mixed response, *viz.*, completion of the course of antibiotics, prior consultation with physician before starting antibiotics and usage of antibiotics in common ailments such as common cold, diarrhea, skin infection though 64% of nursing students and 66% of medical students used to check expiry date of antibiotics before consumption.

The self-medication behavior was identified in 24% of the students, but the majority of the participants always consulted a doctor before starting on an antibiotic and most of them always completed the course of the prescribed treatment.

About 82% of nursing students and 96% of medical students consider antibiotic resistance is a global issue, whereas 73% of nursing students and 96% of medical students agrees with the matter that in India it is also a serious issue (Table 3).



**Table 1: Rating by the medical personnel of the factor contributing to antibiotic resistance**

Factors	n (%)				
	Strongly agree	Somewhat agree	Undecided	Somewhat disagree	Strongly disagree
1. Large doses of antibiotics are better to use for quick action					
a. Nursing student (88)	5 (5.7)	40 (45.4)	8 (9.1)	10 (11.3)	25 (28.4)
b. MBBS student (264)	4 (1.5)	91 (34.4)	14 (5.3)	63 (23.8)	92 (34.8)
2. I belief inappropriate empiric choices can be a cause of antibiotic resistance					
a. Nursing student (88)	13 (14.7)	48 (54.54)	2 (2.2)	11 (12.5)	14 (15.9)
b. MBBS student (264)	59 (22.3)	123 (46.6)	7 (2.6)	34 (12.9)	41 (15.5)
3. Use of short course of antibiotics in case of any diarrheal or flu like symptoms					
a. Nursing student (88)	4 (4.5)	51 (57.9)	6 (6.8)	13 (14.7)	15 (17)
b. MBBS student (264)	18 (6.8)	113 (42.8)	37 (14)	58 (22)	38 (14.4)
4. Use of 2 or more type of antibiotics at a time is better choice to control infections					
a. Nursing student (88)	5 (5.7)	27 (30.7)	6 (6.8)	15 (17)	35 (39.7)
b. MBBS student (264)	26 (9.8)	104 (39.4)	11 (4.1)	41 (15.5)	82 (31)
5. Broad spectrum antibiotics is better choice than use highly selective antibiotics					
a. Nursing student (88)	26 (29.5)	41 (46.6)	1 (1.1)	2 (2.2)	18 (20.4)
b. MBBS student (264)	74 (28)	76 (28.7)	18 (6.8)	38 (14.4)	58 (22)
6. When I get fever, antibiotics help me to get better more quickly					
a. Nursing student (88)	26 (29.5)	41 (46.6)	-	9 (10.2)	12 (13.6)
b. MBBS student (264)	34 (12.8)	97 (36.7)	17 (6.4)	60 (22.7)	56 (21.2)
7. When I have a cold, I should take antibiotics to prevent getting a more serious illness					
a. Nursing student (88)	17 (19.3)	13 (14.7)	4 (4.5)	37 (42)	17 (19.3)
b. MBBS student (264)	28 (10.6)	60 (22.7)	13 (4.9)	76 (28.7)	87 (32.9)
8. Whenever I take antibiotics, I contribute to the development of antibiotic resistance					
a. Nursing student (88)	14 (15.9)	10 (11.3)	15 (17)	27 (30.7)	22 (25)
b. MBBS student (264)	32 (12.12)	52 (19.7)	12 (4.5)	101 (38.2)	67 (25.4)
9. Skipping of 1 or 2 doses does not contribute to development of antibiotic resistance					
a. Nursing student (88)	34 (38.6)	19 (21.6)	10 (11.3)	20 (22.7)	5 (5.7)
b. MBBS student (264)	60 (22.7)	82 (31)	21 (7.9)	46 (17.4)	55 (20.8)
10. Antibiotics are safe drugs, hence they can be commonly used					
a. Nursing student (88)	7 (7.9)	12 (13.6)	5 (5.7)	26 (29.5)	38 (43.1)
b. MBBS student (264)	28 (10.6)	30 (11.3)	16 (6)	78 (29.5)	116 (43.9)

As per their suggestion measures should be taken to reduce antibiotic resistance are institutional specific guideline and conduct frequent educational programs, requirement of easy access to the local and current antibiogram, require regular antibiotic surveillance programs. Their knowledge of proper health and hygiene and hand washing is absolutely correct to reduce the use of antibiotics (Table 4).

## DISCUSSION

Antibiotic resistance is an emerging public health problem, and everyday different drug resistant microorganisms are isolated in our hospitals against which many of the first line and second line antibiotics are ineffective. It is impossible to invent new drugs frequently to compete this bacterial resistance.

This study revealed many important misconceptions about antibiotics. Some belief of participant's needs rectification, as large proportion of the respondents thought that antibiotics better worked on all fever cases, common cold, and diarrhea cases. Many of them thought that for quicker relief larger doses may be considered. More than half of the students prefer broad spectrum antibiotics than single targeted antibiotics, but they strictly disagree about the tendency of skipping doses.

Our results showed that a majority of the students were well known of the global as well as national problems of antibiotic resistance, but in many condition they use antibiotics irresponsibly. Most of the participants are well aware about the clinical effectiveness of antibiotics depends partially on various factors such as proper use including

**Table 2: Medication practice questions rated response**

Intervention	Strongly agree Nursing student (88) MBBS student (264)	Somewhat agree Nursing student (88) MBBS student (264)	Undecided Nursing student (88) MBBS student (264)	Somewhat disagree Nursing student (88) MBBS student (264)	Strongly disagree Nursing student (88) MBBS student (264)
1. Doctor prescribe a course of antibiotic for you, after taking 2-3 doses you start feeling better and stop taking medicine					
a. Nursing student (88)	7 (7.9)	8 (9)	3 (3.4)	19 (21.6)	51 (58)
b. MBBS student (264)	11 (4.1)	38 (14.3)	2 (0.75)	62 (23.5)	151 (57.1)
2. Do you consult a doctor before starting an antibiotic or buy a antibiotics previously given by doctor					
a. Nursing student (88)	58 (66)	17 (19.3)	2 (2.3)	6 (6.8)	5 (5.7)
b. MBBS student (264)	104 (39)	116 (43.9)	-	28 (10.6)	14 (5.3)
3. Do you check expiry date of the antibiotic before using					
a. Nursing student (88)	57 (64.7)	21 (23.8)	-	10 (11.3)	-
b. MBBS student (264)	176 (66)	75 (28.4)	-	13 (4.9)	-
4. Do you prefer to take an antibiotic when you have any cough and cold					
a. Nursing student (88)	21 (23.8)	25 (28.4)	7 (7.9)	24 (27.2)	9 (10.2)
b. MBBS student (264)	57 (21.6)	93 (35.2)	11 (4.1)	47 (12.8)	57 (21.6)
5. In case of any diarrhea, skin ulcer antibiotics have a role					
a. Nursing student (88)	5 (5.7)	17 (19.3)	3 (3.4)	35 (40)	28 (31.8)
b. MBBS student (264)	27 (10.2)	34 (12.9)	12 (4.5)	102 (38.6)	89 (33.7)

**Table 3: Beliefs**

Beliefs	Strongly agree Nursing student (88) MBBS student (264)	Somewhat agree Nursing student (88) MBBS student (264)	Undecided Nursing student (88) MBBS student (264)	Somewhat disagree Nursing student (88) MBBS student (264)	Strongly disagree Nursing student (88) MBBS student (264)
1. I belief widespread use of antibiotics is a contributing cause of resistance					
a. Nursing student (88)	21 (23.8)	29 (32.9)	3 (3.4)	19 (21.6)	16 (18.2)
b. MBBS student (264)	157 (59.5)	62 (23.5)	2 (.75)	26 (9.8)	17 (6.4)
2. Antibiotics can prevent any illnesses from becoming worse					
a. Nursing student (88)	15 (17)	14 (15.9)	7 (7.9)	28 (31.8)	24 (27.3)
b. MBBS student (264)	42 (15.9)	34 (12.8)	9 (3.4)	66 (25)	113 (42.8)
3. I belief Indiscriminate and injudicious use of antibiotics can lead to exacerbation of prolongation of illness					
a. Nursing student (88)	38 (43.2)	12 (13.6)	3 (3.4)	25 (28.4)	10 (11.36)
b. MBBS student (264)	58 (22)	51 (19.3)	10 (3.7)	80 (30.3)	65 (24.6)
4. I belief Indiscriminate and injudicious use of antibiotics can lead to emergence of bacterial resistance					
a. Nursing student (88)	36 (41)	42 (47.7)	3 (3.4)	4 (4.54)	3 (3.4)
b. MBBS student (264)	111 (42)	98 (37.1)	6 (2.2)	35 (13.2)	13 (4.9)
5. I belief genetic mutation is one of the cause of antibiotic resistance					
a. Nursing student (88)	17 (19.3)	20 (22.7)	12 (13.6)	23 (26.1)	16 (18.2)
b. MBBS student (264)	149 (56.4)	87 (32.9)	5 (2)	10 (3.78)	13 (4.9)
6. I belief inappropriate duration of course a contributing cause of resistance					
a. Nursing student (88)	28 (31.8)	31 (35.2)	2 (2.7)	17 (19.3)	10 (11.36)
b. MBBS student (264)	87 (32.9)	90 (34)	8 (3)	44 (16.6)	35 (13.2)

(Contd...)

**Table 3: (Continued)**

Beliefs	Strongly agree Nursing student (88) MBBS student (264)	Somewhat agree Nursing student (88) MBBS student (264)	Undecided Nursing student (88) MBBS student (264)	Somewhat disagree Nursing student (88) MBBS student (264)	Strongly disagree Nursing student (88) MBBS student (264)
7. I belief antibiotic resistance is an important and serious public health issue worldwide					
a. Nursing student (88)	33 (37.5)	40 (45.4)	3 (3.4)	9 (10.2)	3 (3.4)
b. MBBS student (264)	164 (62.1)	92 (34.8)	3 (1.1)	2 (0.75)	3 (1.1)
8. I belief antibiotic resistance is an important and serious public health issue in our country					
a. Nursing student (88)	29 (32.95)	36 (40.9)	2 (2.27)	13 (14.7)	8 (9)
b. MBBS student (264)	166 (62.87)	91 (34.4)	-	3 (1.13)	3 (1.1)
9. Patients demand and expectation leads to use frequent wrong antibiotics					
a. Nursing student (88)	29 (32.9)	14 (15.9)	4 (4.5)	26 (29.5)	19 (21.6)
b. MBBS student (264)	78 (29.5)	87 (32.9)	5 (1.9)	59 (22.3)	35 (13.2)
10. I belief Indiscriminate and injudicious use of antibiotics can lead to additional burden of medical cost					
a. Nursing student (88)	45 (51.1)	26 (29.5)	5 (5.6)	7 (8)	5 (5.7)
b. MBBS student (264)	186 (70.4)	71 (26.9)	4 (1.1)	3 (1.1)	-

self-medication, proper doses, and taking incomplete course. Their knowledge of proper health and hygiene and hand washing is absolutely correct to reduce the use of antibiotics.

The most optimistic fact is that most of these participants are well aware of the situation about the increasing drug resistance, and this self-motivated awareness is a great opportunity to win the battle against antibiotic resistance. Many similar studies has reported that insufficient public knowledge regarding antibiotics is one of the most common cause of antibiotic resistance of various countries.<sup>9-12</sup>

Last but not the least is strict government policy for antibiotic use is utmost important to control the whole situation of indiscriminate use of these precious drugs as early as possible.

There was statistically significant difference between medical and nursing students regarding knowledge of the antibiotic uses. Apart from teaching about antibiotic prescribing, the principle protocols for antibiotic use in health-care providers should form an integral part of the undergraduate teaching.<sup>13</sup> In this study, the four leading causes of antibiotic resistance were (1) overuse or misuse of antibiotics, (2) unnecessary use of broad-spectrum antibiotics, (3) poor adherence to prescribed antibiotics, and (4) lack of access to antibiotic susceptibility testing.<sup>8,14</sup>

Regarding interventions to prevent antibiotic resistance, their knowledge and attitude is satisfactory and majority of participants believed in that most appropriate measures were as follows: (1) Establishing rational antibiotic surveillance program, (2) easy availability of clinical

microbiology laboratory, (3) local guidelines for rational use of antibiotics, and (4) habits of proper hand hygiene.<sup>5,15</sup> This requires proper counseling of patients by physicians and also require honesty of medical retailers when any patient seeking treatment or medicine, respectively. It is also true that current antibiogram for the most hospitals is not readily available or not strictly followed by the physicians. There also have no strict policy regarding interventions that can restrict physician's behavior strictly. When the risk factors for bacterial resistance are identified, effective measures should be undertaken, then only to reduce the risk of future resistant infections. The adoption of certain guidelines and polices regarding more appropriate use of antibiotics can improve patient outcomes and minimized the resistance microorganisms.

## CONCLUSION

This study revealed an important insight regarding the knowledge, attitude, perception and practices regarding antibiotic resistance, and usage among the future doctor and nurses. The medical education strategies should aim, not only to increase the knowledge but also to change the behavior and practices among medical and nursing students which can be considered, to plan for an effective undergraduate curriculum.

## LIMITATION

The main limitation of this study is that the data provided is of local interest. It is also true that the knowledge of common people about antibiotic resistance is far different from health-care providers. Sometime there is a possibility

**Table 4: Physicians rating to interventions to reduce antibiotic resistance**

Intervention	Strongly agree Nursing student (88) MBBS student (264)	Somewhat agree Nursing student (88) MBBS student (264)	Undecided Nursing student (88) MBBS student (264)	Somewhat disagree Nursing student (88) MBBS student (264)	Strongly disagree Nursing student (88) MBBS student (264)
1. Institutional-specific antibiotic guideline					
a. Nursing student (88)	44 (50)	21 (23)	23 (26)	-	-
b. MBBS student (264)	179 (67.8)	58 (21.9)	22 (8.3)	3 (1.1)	2 (0.75)
2. Conduct frequent educational					
a. Nursing student (88)	64 (72.7)	16 (18.1)	6 (6.8)	2 (2.2)	-
b. MBBS student (264)	178 (67.4)	72 (27.2)	5 (1.9)	5 (1.9)	4 (1.5)
3. Easy access to local and current antibiogram					
a. Nursing student (88)	30 (34.1)	28 (31.8)	13 (14.7)	7 (7.9)	10 (11.3)
b. MBBS student (264)	137 (51.9)	88 (33.3)	20 (7.5)	12 (4.5)	7 (2.6)
4. Updating about local antibiotic resistance pattern					
a. Nursing student (88)	41 (46.6)	20 (22.7)	12 (13.6)	12 (13.6)	3 (3.4)
b. MBBS student (264)	147 (55.7)	90 (34.1)	9 (3.4)	12 (4.5)	6 (2.2)
5. Regular antibiotic surveillance programs as infection control tool					
a. Nursing student (88)	35 (39.7)	29 (32.9)	10 (11.3)	9 (10.2)	5 (5.6)
b. MBBS student (264)	162 (61.3)	71 (26.9)	14 (5.3)	6 (2.2)	11 (4.1)
6. Regular updating about the situation of antibiotic resistance pattern in my institution					
a. Nursing student (88)	43 (48.8)	32 (36.3)	11 (12.5)	2 (2.27)	-
b. MBBS student (264)	156 (59.1)	77 (29.1)	13 (4.9)	13 (4.9)	5 (1.9)
7. Proper isolation of the patient in hospitals can leads to reduce the use of antibiotics					
a. Nursing student (88)	50 (56.8)	29 (32.9)	4 (4.5)	5 (5.6)	-
b. MBBS student (264)	149 (56.4)	62 (23.4)	10 (3.7)	19 (7.2)	24 (9)
8. Proper hand washing can reduce of use of antibiotics					
a. Nursing student (88)	47 (53.4)	29 (32.9)	3 (3.4)	6 (6.8)	3 (3.4)
b. MBBS student (264)	191 (72.3)	66 (25)	2 (0.75)	5 (1.9)	-
9. Knowledge of proper health and hygiene is absolutely require to reduce use of antibiotics					
a. Nursing student (88)	44 (50)	24 (27.2)	8 (9)	12 (13.6)	-
b. MBBS student (264)	152 (57.5)	91 (34.4)	11 (4.1)	5 (1.9)	5 (1.9)
10. Strict government policy for antibiotics restriction and empiric antibiotic use					
a. Nursing student (88)	39 (44.3)	29 (32.9)	12 (13.6)	4 (4.5)	4 (4.5)
b. MBBS student (264)	176 (66.6)	64 (24.2)	14 (5.3)	6 (2.7)	4 (1.5)

that some participants may give socially acceptable answer that may not be reflecting their usual habits.

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# Comparative Study of Placental Morphometry and Histomorphology in Normal and Pre-eclamptic Pregnancies

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## Abstract

**Background:** Placental examination forms an integral part of prenatal or fetal autopsy and helps in adding important or conclusive information. A glance at the literature reveals that the preeclampsia-eclampsia syndrome exerts its deleterious effects on the placenta.

**Aims and Objectives:** To record and compare the morphometry, histomorphology of normal and pre-eclamptic placentae.

**Materials and Methods:** A total of 200 placentae were examined - 100 pre-eclamptic placentae and 100 normal placentae. The morphometric measurements were taken and histologic features noted.

**Observation and Results:** The pre-eclamptic placentae showed decrease in the morphometry and an increase in histomorphological features such as syncytial knot formation, villous stromal fibrosis, and trophoblastic basement membrane thickening when compared to normal placentae.

**Conclusion:** We conclude that preeclampsia adversely influences the placental morphometry and histomorphology.

**Key words:** Placenta, Placental histomorphology, Placental morphometry, Pre-eclampsia, Syncytial knot.

## INTRODUCTION

Placental pathology has undoubtedly received very little attention by both the obstetricians and pathologist. The various indications for placental examination are essentially any maternal disease or disorders of the infant or any other clinically accepted placental abnormality.<sup>1</sup> Placental examination forms an integral part of prenatal or fetal autopsy and helps in adding important or conclusive information.<sup>2</sup> Toxemia of pregnancy is one of the known leading causes of maternal mortality and stands to be an important factor in terms of fetal wastage as well.<sup>3</sup>

The placenta stays to be the best record of the prenatal experience of every infant. A glance at the literature reveals that the pre-eclampsia-eclampsia syndrome does exert its deleterious effects on the placenta.<sup>3</sup> Grossly, the pre-eclamptic placentae are lesser in weight, diameter, and thickness, with an increase in the incidence of abnormal shape and cord insertion, and diminished fetoplacental ratio. Furthermore, there seems to be a higher incidence of infarction and retroplacental hematoma, in pre-eclamptic placentae. The numerous placental changes bear a direct relation to severity and duration of the disease process. The fetal outcome is adversely influenced by the pathological changes in the placenta. Thus, there is a need for a thorough examination of placenta which may help in revealing the various abnormalities that contribute to the disorder of pregnancy, toxemia, in this study. This study is an attempt to observe and to compare the morphometric and the histomorphological features, in pre-eclamptic and normal placentae.

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### Aims and Objectives

1. To record the data on morphometry, histomorphology of normal and pre-eclamptic placentae, respectively
2. To compare and analyze the placental morphometry and placental histomorphology in normal and hypertensive pregnancies.

### MATERIALS AND METHODS

This prospective study was conducted from April 2015 to September 2015 at Institute of Obstetrics and Gynaecology, Madras Medical College, Chennai. A total of 200 placentae were examined. The study group comprised 100 pre-eclamptic placentae from singleton pregnancies and the control group comprised 100 placentae from normotensive singleton pregnancies. All placentas were collected immediately after delivery and washed in tap water which removed the blood clots. The placenta was examined in fresh state, disc weight obtained after removal of the membranes, cord, and extraneous clot. Measurements of the disc were taken and using standard mathematical formulae, the values for placental surface area and placental volume were derived.

Placental surface area (cm<sup>2</sup>) = ( $\pi \times \text{largest diameter} \times \text{shortest diameter}$ )/4.

Placental volume (cm<sup>3</sup>) = surface area  $\times$  thickness at center.

The placenta along with cord and membranes fixed in 10% formalin, sections were taken and subjected to routine histopathological examination with hematoxylin and eosin staining. All statistical analyses were done with IBM SPSS software version 20.

### RESULTS

The comparison of placental morphometry is shown in Table 1. The mean placental weight is reduced in pre-eclampsia. This is statistically significant. The mean placental surface area is reduced in the pre-eclamptic group and is statistically significant. The mean placental volume is again decreased in the pre-eclamptic group when compared with the control group. This is also statistically very significant.

Table 2 shows the comparison of placental histomorphology. In the pre-eclamptic group, there is an increase in the mean number of areas/low power field of syncytial knot formation (Figure 1), cytotrophoblastic cellular proliferation, villous fibrinoid degeneration (Figure 1), and villous stromal fibrosis (Figure 2). This difference is statistically significant.

The comparison of trophoblastic basement thickening is shown in Table 3. The incidence of irregular thickening of trophoblastic basement membrane (TBM) (Figure 3) is increased in the study group. This is statistically significant.

### DISCUSSION

Pre-eclampsia is one of the leading causes of maternal as well as perinatal mortality and morbidity. The etiopathogenesis of pre-eclampsia still remains a subject of controversy. The classical view in this regard focuses on the placenta and uteroplacental circulation. Pregnancy-induced hypertension (PIH) clinically presents with hypertension,

**Table 1: Comparison of placental morphometry**

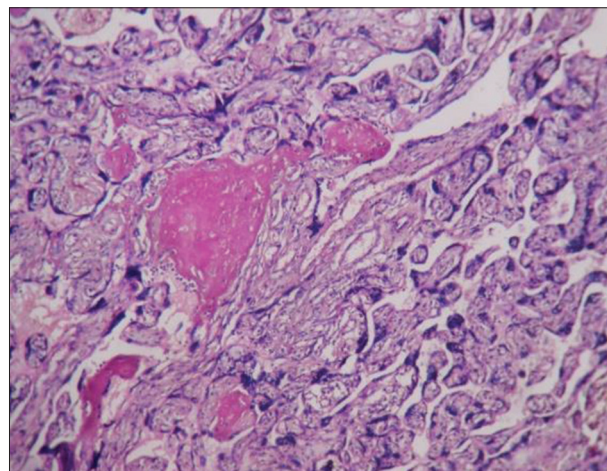
Placental morphometry	Mean $\pm$ SD		P value
	Case	Control	
Placental weight (g)	421.8 $\pm$ 120.09	461.75 $\pm$ 99.08	0.011
Placental surface area (cm <sup>2</sup> )	172.77 $\pm$ 60.82	195.25 $\pm$ 58.82	0.009
Placental volume (cm <sup>3</sup> )	270.8 $\pm$ 132	385.01 $\pm$ 142.66	0.001

SD: Standard deviation

**Table 2: Comparison of placental histomorphology**

Placental histomorphology	Group		P value
	Mean±SD		
	Case	Control	
Mean no of areas of syncytial knot formation/lpf	23.15±4.84	9.75±3.18	<0.001
Mean no of areas of cytotrophoblastic cellular proliferation/lpf	17.72±2.63	5.78±1.31	<0.001
Mean no of areas of villous fibrinoid degeneration/lpf	7.05±2.87	3.04±1.24	<0.001
Mean no of areas of villous stromal fibrosis/lpf	9.22±2.19	2.47±1.01	<0.001

SD: Standard deviation



**Figure 1: Syncytial knot formation and fibrinoid degeneration**

proteinuria, and edema. Typically once the uterus is emptied of the fetus and the placenta, the disease process ceases. In fact immediate postpartum curettage of the placental bed brings down the maternal blood pressure at a faster pace than in places where curettage is not done. The fact that PIH occurs even in the absence of the fetus, for e.g., in hydatidiform moles, shows clearly that PIH is ultimately dependent on the presence of placental tissue. It is difficult to define the normal placental findings and differentiate it from the abnormal, because of the structural complexity and rapid evolution of the placenta.

### Placental Morphometry

Normally, a placenta weighs from 400 to 800 g. In this study, we observed the reduction of placental weight in the pre-eclamptic group. Similar findings were reported by

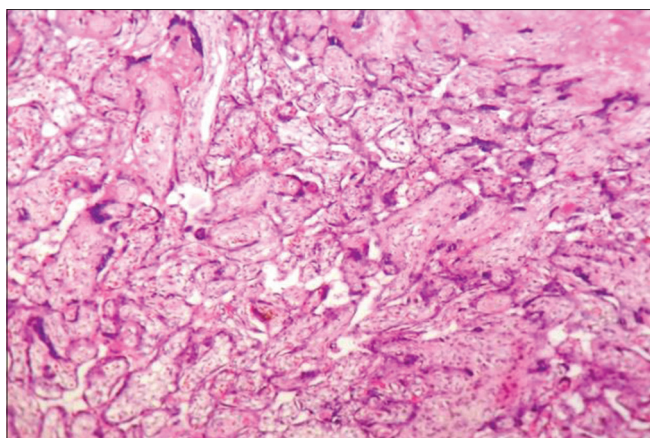


Figure 2: Villous stromal fibrosis

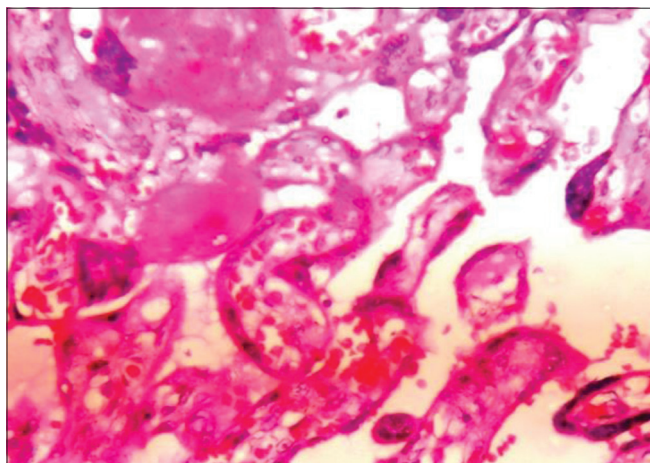


Figure 3: Trophoblastic basement membrane thickening

Table 3: Comparison of TBM thickening

TBM thickening (%)	Case (%)	Control (%)	P value
<3	38.10	61.90	<0.001
>3	70.30	29.70	

TBM: Trophoblastic basement membrane

Das *et al.* (1996), Dutta and Dutta (1989), and Nobis and Das (1991), Londhe and Mane (2011).<sup>4,7</sup> The mean placental volume is decreased in the pre-eclamptic placentae. The mean placental surface area is significantly decreased in pre-eclamptic placentae. This is in concordance with the study of Londhe and Mane and Majumdar and Dasgupta *et al.*<sup>4,8</sup>

### Placental Histomorphology

The histology of placenta from pre-eclamptic pregnancies shows a significant increase in villous cytotrophoblastic proliferation, villous syncytial knot formation, irregular thickening of TBM, patchy villous fibrinoid degeneration, and villous stromal fibrosis, in the study group when compared to the control group. This is very much in accordance with previous studies conducted by Jones and Fox (1980). Genest (1992) reported that stromal fibrosis and excessive syncytial knot formation are seen in generalized form occurring due to overall reduction of fetal perfusion of placenta.<sup>9,10</sup>

Teasdale (1980) and Udainia *et al.* (2004) quoted that localized villous fibrinoid degeneration could be the aftermath of hypertension.<sup>11,12</sup> Tenny and Parker (1940) quoted that the influence of maternal factors is best shown in pre-eclampsia where the decreased intervillous blood flow finally leads to increased syncytial knotting, so-called the Tenny-Parker changes. He emphasized that the increased bridging of placental syncytium producing knots is very much characteristic of pre-eclampsia. Syncytial knots are also seen normally in term and preterm placentae, but their number is much increased in toxemia.<sup>13</sup>

### CONCLUSION

From this study, it can be concluded that although placenta readily adapts to hypoxia due to uteroplacental insufficiency, the compensatory changes are insufficient and result in a primary failure to develop and form an adequate placental mass, thereby adversely influencing the placental morphometry and histomorphology. Although there are various combinations of histologic and gross changes which are characteristic of placenta in pre-eclampsia, the abnormalities are specific to pre-eclamptic placentae.

There are numerous cases where the pre-eclamptic placenta is virtually normal, mainly if the disease was mild and of a shorter duration. In severe pre-eclampsia, the lesions are, however, more prominent and accentuated, and at the same time, the duration of the disease is of importance.

This study greatly emphasizes the importance of placental morphometry and its variation in pre-eclampsia. Currently, with the help of three dimensional ultrasonography and



virtual organ computer-aided analysis, the placental volume can be ascertained in utero and a correlation with the fetal growth can be obtained.

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# Amebic Liver Abscess: Varied Presentation and Management Update

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## Abstract

**Introduction:** Amebic liver abscess (ALA) is the most common extraintestinal manifestation of *Entamoeba histolytica*. Because of highly varied presentations, accurate diagnosis of ALA is difficult. Hence, early and correct diagnosis of ALA is essential to avoid serious complications.

**Materials and Methods:** The study was carried out in 64 cases of ALA admitted to the Surgery Department of MGM Medical College and Hospital, Jamshedpur, between March 2012 and April 2016. All the cases with confirmed diagnosis of ALA were included in this study.

**Results:** Sixty-four cases of ALA were studied over a 4-year period with a male to female ratio of 9.6:1. The age ranged from 15 to 65 years (mean age 35 years). There were 58 males (90.63%) and 6 females (9.37%). Age group of 31 to 40 years showed the highest incidence of ALA consisting of 43.75% cases. Pain was located most commonly in the right hypochondrium in 44 (68.75%) patients, fever observed in 50 cases (90.63%), and coincident diarrhea in 40.62% patients. Solitary abscess cavity was found in 59 (92.18%) cases. The right lobe of the liver was involved in 55 (85.93%) patients. In this study, 40 patients (62.5%) were chronic alcoholics. Pleuropulmonary complications such as right atelectasis and pleural effusion due to ALA were the most common complications found in 22 patients (34.37%). This was followed by intraperitoneal rupture of abscess in 15 patients (23.43%). Other complications were jaundice in 12 cases, ascites in 10 cases, subphrenic abscess in 3, and intrapleural rupture in 2 patients.

**Conclusion:** ALA has highly varied clinical presentation. The typical features of ALA which include pain, fever, and tender hepatomegaly are non-specific. A high index of clinical suspicion in patients from an endemic area and low socioeconomic class combined with ultrasonography, ultrasound-guided aspiration, and computerized tomography scan will improve the diagnostic accuracy to reduce catastrophic complication as a result of delayed diagnosis.

**Key words:** Amebic liver abscess, Management update, Varied presentation

## INTRODUCTION

Amebic liver abscess (ALA) is the most common inflammatory space-occupying extraintestinal manifestation of protozoa *Entamoeba histolytica*. 10% of the world population harbors *E. histolytica* in their colon, 10% of them may develop invasive amoebiasis,<sup>1</sup> and 1-10% of these patients develop amebic abscess in their liver.<sup>2,3</sup> ALA

is common in tropical countries and is due to overcrowding and poor sanitation.<sup>4</sup> The colon is the initial site of infection. The protozoa reach the liver through the portal vein.<sup>5,6</sup> Amebiasis may involve any other site, but liver is the most common site for extraintestinal infection.<sup>2,3,7</sup> ALA has a highly variable presentation causing diagnostic difficulties. As described by Berne,<sup>8</sup> ALA may mimic acute cholecystitis, perforated peptic ulcer, acute hepatitis, malignancy of biliary tree, liver, colon, or stomach, cirrhosis, hydatid cysts, pancreatic pseudocysts, pneumonia, acute pleurisy with effusion, empyema, chronic lung disease, tuberculosis, and pyrexia of unknown origin. Early and correct diagnosis of ALA is imperative because delayed diagnosis and treatment leads to complications.<sup>9,10</sup> Despite tremendous improvements in the diagnostic accuracy, delayed diagnosis continues to occur.

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The aim of this study is to find out varied clinical presentation and accurate management of this disease to treat this case early to avoid complications.

## MATERIALS AND METHODS

The study was carried out in 64 cases of ALA admitted to the Surgery Department of MGM Medical College and Hospital, Jamshedpur between March 2012 and April 2016. All the cases with confirmed diagnosis of ALA were included in this study. The diagnosis of ALA was based on clinical symptoms and signs such as weight loss, fever, abdominal pain, tenderness, ultrasound results, radiology, aspiration of characteristic anchovy sauce pus on needle aspiration, and absence of bacteria and neutrophil on microscopy, by serological tests and a good response to therapy with specific amebicidal drugs as shown by the disappearance of clinical symptoms.

Data of patients such as age, sex, and clinical features including duration, vital signs, physical findings and laboratory data, ultrasound, chest x-rays, aspiration study of the lesion if greater than 5 cm, computerized tomography (CT) scan, and outcomes of treatment and complications were recorded in a pre-prepared questionnaire.

## RESULTS

Sixty-four cases of ALA were included in this study. All the patients were from low socioeconomic group. The age ranged from 15 to 65 years (mean age 35 years). The 31-40 years age group showed the highest incidence constituting to 28 (43.75%) of the cases. Age and sex distribution is shown in Table 1.

There were 58 males and 6 females (male to female ratio = 9.6:1).

The duration of symptoms ranged from 10 to 110 days. Seventeen patients (26.56%) presented within 15 days, 41 patients (64.06%) within 30 days, and 6 patients (9.37%) after 6 weeks of onset of symptoms.

Most of the patients presented with abdominal pain and tenderness (Tables 2 and 3). The pain was located most commonly in right hypochondrium in 44 (68.75%) patients, in the whole abdomen in 7 (10.93%), lower chest in 4 (6.25%), and in the left hypochondrium in 4 (6.25%) patients. Intercostal tenderness was seen in 48 patients (75%). Fever was present in 58 (90.63%) cases. New onset of diarrhea noticed in 26 (40.62%) patients.

**Table 1: Age and sex distribution of patients with ALA**

Age (in years)	n (%)		
	Males	Females	Total
<20	1 (1.56)	1 (1.56)	02 (03.13)
21-30	4 (6.25)	1 (1.56)	05 (07.81)
31-40	25 (39.06)	03 (4.68)	28 (43.75)
41-50	16 (25.00)	01 (1.56)	17 (26.56)
51-60	10 (15.62)	00 (0.00)	10 (15.62)
>60	02 (03.13)	00 (0.00)	02 (03.13)
Total	58 (90.63)	06 (9.37)	64 (100)

ALA: Amebic liver abscess

**Table 2: Presenting symptoms with ALA**

Symptoms	Number of patients (%)
Abdominal pain	59 (92.18)
Fever	58 (90.63)
Anorexia	59 (92.18)
Nausea	58 (90.63)
Diarrhea	26 (40.62)
Jaundice	10 (15.62)
Cough	06 (09.37)

ALA: Amebic liver abscess

**Table 3: Signs of patients at the time of admission**

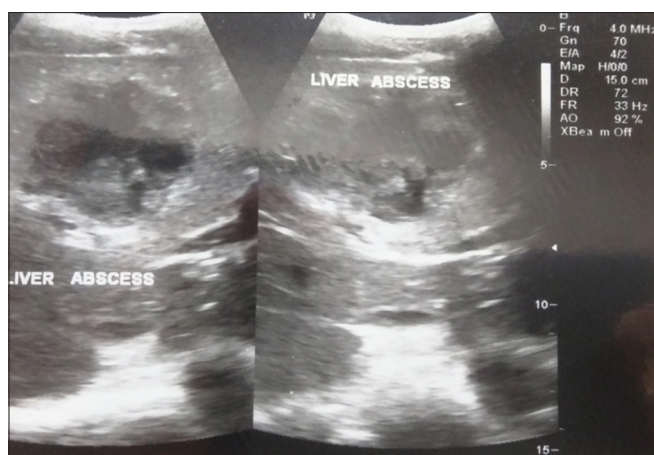
Signs	Number of patients (%)
Right hypochondrium tenderness	44 (68.75)
Acute abdomen	06 (09.37)
Icterus	10 (15.62)
Ascites	02 (03.13)

Solitary abscess cavity was found in 59 (92.18%) cases. The right lobe of the liver was involved in 55 (85.93%) patients.

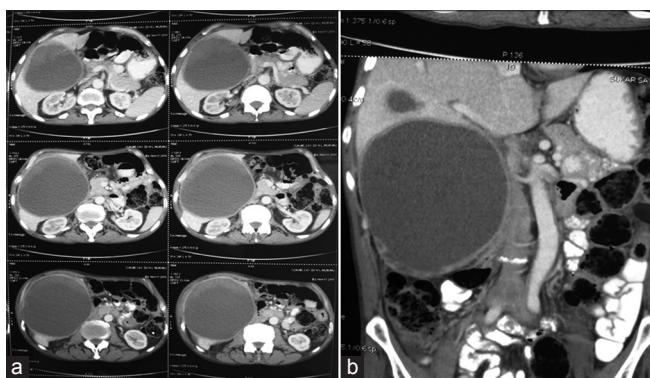
Pleuropulmonary complications such as right atelectasis and pleural effusion due to ALA were the most common complications found in 22 patients (34.37%). This was followed by intraperitoneal rupture of abscess in 15 patients (23.43%). Other complications were jaundice in 12 cases, ascites in 10 cases, subphrenic abscess in 3, and intrapleural rupture in 2 patients.

In our study, 4.68% (3 patients) mortality was observed due to intraperitoneal rupture of abscess leading to delayed diagnosis.

Ultrasonography (Figure 1) was performed in all the cases, but ALA was diagnostic in 46 patients (71.87%) only. All the patients underwent routine blood examination, stool examination, liver function test, renal function test, and X-ray Chest. CT-scan was required in some difficult cases and in those patients who had intraperitoneal rupture of ALA leading to difficulty in ultrasonographic diagnosis. Laparotomy was done in 16 (25%) cases for ruptured ALA.



**Figure 1: Amebic liver abscess as shown by ultrasound**



**Figure 2: (a and b) Amebic liver abscess as shown in computerized tomography scan**

and failed aspiration. Patients with smaller ALA (<5 cm) responded pretty well with a higher dose (800 mg thrice daily) of metronidazole for ten days. Those who had ALA more than 6 cm size were treated with ultrasound-guided aspiration and metronidazole course. Intrapleural rupture of ALA was treated with water-sealed intercostal drainage. Most of the patients were followed up for more than 6 months, but in 14 (21.87%) cases, residual ALA cavity was seen on ultrasonography. There were 3 (4.68%) deaths in this group.

## DISCUSSION

ALA is widely prevalent in the Indian subcontinent.<sup>11-13</sup> As ALA has varied presentations, it complicates the asymptomatic colonic infection more often than its symptomatic counterpart and this is the main reason why the disease may be overlooked or misdiagnosed.<sup>14</sup> This study has shown the patterns of ALA similar with other studies in terms of age, sex, number, size, location, and ultrasonographic pattern.<sup>15</sup> Although the disease occurs in any age group, in this study, the most common age group was 31-40 year. Male to female ratio was 9.6:1. Pain and fever were the most prevailing features in this study. Hence,

pain and fever in an adult patient from low socio-economic status should raise the suspicion of ALA.<sup>16</sup> In this study, right lobe of the liver was involved most frequently in 85.93% of cases which is consistent with the other studies.<sup>17</sup> Diarrhea was present in 40.62% of patients; however, it is reported in other studies in 12-33% of cases.<sup>18-20</sup>

In this study, 40 patients (62.5%) were chronic alcoholics. Ocshner and De Bakey<sup>21</sup> attribute higher incidence in males to alcoholism, which predisposes to hepatitis and trauma. It is observed that alcoholics had larger abscesses, greater frequency of complications, and poor response to treatment.

Pleuropulmonary complication consisted of atelectasis and right pleural effusion accounted for highest incidence of complication (34.37%). This is in confirmation with the reported 25-42%.<sup>19,22</sup> Intrapertitoneal rupture of ALA is considered the second most common complication amounting to 23.43%. This may be due to lower socioeconomic condition and their delayed reporting to the hospital. Icterus developed in 12 cases (18.75%) and ascites in 10 cases (15.62%). In this study as well as those of others suggests that both jaundice and ascites tend to occur most commonly in the presence of multifocal abscesses, especially when these are associated with impingement of hepatic hilar tubular structures.<sup>23-26</sup>

Like the clinical features, investigations too are neither sensitive nor specific. According to some literature, indirect hemagglutination test is positive in >90% of cases,<sup>19</sup> but may be of limited value in endemic areas.<sup>21,27</sup> Isolation of ameba is specific but very difficult. These investigations are neither helpful in the early diagnosis nor available at the time of making decision.<sup>16,28</sup> Thus, ALA is difficult to diagnose and may be missed on initial clinical examination.

Ultrasonography, cheap and safe observer-dependent, is widely accepted as a first-line investigation for imaging focal hepatic lesions as well as liver abscesses.<sup>14,29</sup> This is attributable to its low cost, greater availability, and high accuracy. It is useful not only in diagnosis and intervention but also in the follow-up of the condition and to assess resolution. The sensitivity of ultrasound is nearly 92-97%.<sup>7,19</sup> However, ultrasonographic features of ALA and other space-occupying lesions of the liver, for example, hepatoma, pyogenic liver abscess may overlap.<sup>30</sup> The combination of ultrasonographic findings with clinical features and aspirate analysis increases the sensitivity.<sup>7,19,30</sup> Nowadays, availability of CT scan (Figure 2a and b) also has a pivotal role but may not be available in the remote area where clinical suspicion, laboratory investigations have only use. Hence, in these settings, other differential diagnoses also have to be kept in mind.



## CONCLUSION

ALA has highly varied clinical presentation. The typical features of ALA which include pain, fever, and tender hepatomegaly are non-specific. A high index of clinical suspicion in patients from an endemic area and low socioeconomic class combined with ultrasonography, ultrasound-guided aspiration, and CT-scan will improve the diagnostic accuracy to reduce catastrophic complication as a result of delayed diagnosis. High dose of metronidazole (800 mg) thrice daily for 10 days with frequent ultrasound-guided aspiration is found most curative.

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# Comparative Evaluation of Oral Stereognosis in Epileptic and Nonepileptic Patients: An Original Research

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## Abstract

**Introduction:** Oral stereognosis basically is the ability of our sensory mechanism to recognize the shape of objects placed in oral cavity. The science of stereognosis is very important for the dentist as well as technician so that to understand the expectation level of the patients and predict the prognosis of the prosthesis.

**Subjects and Methods:** This study was carried out on 60 selected patients. The patients were divided into two groups, one being epileptic group and another control group. Five types of different test samples were cured in heat cured resin and a hole was drilled in the center of the test samples using freemium relieving bur and a floss of 10 cm length was tied to the test sample avoiding the risk of engulfment. Dimensions of all different test samples were multiplied by 5 and the geometric designs were drawn on the chart paper and marked as 1-5. A time period of 1 min was provided to each patient for the identification on the chart followed by gap of 30 s for the next test sample to be placed in the mouth. A score of 2 was given for each correct identification, score of 1 for no identification, and score of 0 for wrong identification of sample.

**Results:** The oral stereognostic scores were statistically analyzed using analysis of variance and *t*-test. In intergroup comparison between two groups, epileptic group patients ( $7.52 \pm 3.02$ ) recorded less value than control group ( $12.65 \pm 3.65$ ) which was statistically significant ( $P < 0.001$ ). In intragroup comparison of control group, partially edentulous group ( $11.5 \pm 3.57$ ) had higher mean values than completely edentulous group ( $9.01 \pm 4.09$ ) which was statistically significant ( $P < 0.001$ ).

**Conclusion:** Oral stereognosis predicts the prognosis of the treatment provided. Epileptic patients have decreased stereognostic activity both in dentulous as well as edentulous patients against the physiologically healthy patients.

**Key words:** Dentulous, Epileptic, Physiologic, Stereognosis

## INTRODUCTION

Prediction of a dental prosthesis to be successful not only depends on the clinical proficiency and accuracy level of the clinician but also on the ability of the patient to adapt to his prosthesis. As aging occurs, several changes such as

decreased masticatory efficacy, loss of taste, and alterations in proprioceptive responses take place.

Human brain is equipped with certain sensory feedback mechanisms that are important in motor control and learning.<sup>1</sup> During the oral phase of deglutination, somatic sensation is only feedback source in oral cavity. Size and shape of an intraoral bolus of food provides oral sensory information important for oropharyngeal swallowing and tongue is responsible for stereognosis.<sup>2-4</sup>

Oral stereognosis also called as haptic perception or tactile gnosis is the ability of the oral mucous membrane to perceive and recognize the forms of objects placed in

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oral cavity.<sup>5</sup> Rossetti *et al.*<sup>6</sup> classified stereognosis in four different types:

- General stereognosis: Overall capacity to recognize the shape of objects
- Homo stereognosis: Self body recognizing capacity, e.g., palate, tongue
- Organ stereognosis: Capacity to recognize muscular units as target areas, e.g., position of limbs to execute routine tasks
- Hetero stereognosis: Capacity to recognize foreign body inside oral cavity, e.g., glass particles, wood stick.

Several investigators<sup>7,8</sup> have conducted researches to study the diagnostic effect in dentulous as well as edentulous patients using both removable as well as fixed type of prosthesis<sup>9</sup> and concluded to undergo oral stereognostic tests before fabrication of prosthesis for better prognosis of treatment. However, to our knowledge, no study has been published which reflected the stereognostic effect in epileptic patients.

Epilepsies are a group of disorders of the central nervous system characterized by a paroxysmal cerebral dysrhythmia, manifesting as brief episodes of loss or disturbance of consciousness, with or without characteristic body movements, sensory or psychiatric phenomena.<sup>10</sup> Epilepsy has a focal origin in the brain; manifestations depend on site of focus and regions into which discharges spread. (Table 1).

This study aims to compare the oral stereognosis in dentulous as well as completely edentulous patients having epilepsy against the physiologically healthy patients. Null hypothesis states that no difference exists between the epileptic group and the control group in terms of stereognostic activity both in dentulous and completely edentulous patients.

## SUBJECTS AND METHODS

This study was carried out on 60 selected patients that reported to the Indira Gandhi Government Dental College, Jammu. The study was approved by the college Ethical Committee, and the patients were divided into two groups, each having 30 patients. Patients were informed of the objective of the study and verbal consent was taken by the patients (Tables 2 and 3).

Oral stereognosis test was performed on the patients using five types of different test samples. 60 test samples of each shape were prepared in modeling wax (Hiflex) and were cured in heat cured resin using compression molding technique (Table 4).

**Table 1: Types of epilepsy**

Generalized seizures	Partial seizures
Generalized tonic-clonic seizures	Simple partial seizures
Absence seizures	Complex partial seizures
Atonic seizures	Simple partial or complex partial seizures secondarily generalized
Myoclonic seizures	






**Table 2: Distribution of samples**

Group	Type of patients	Total number of patients	Subgroups (presence of teeth)	
			(a) Edentulous	(b) Dentulous
I	Epileptic	30	15	15
II	Normal	30	15	15

**Table 3: Inclusion criteria**

Age group >30 years
Absence of any other systemic disease except epilepsy
All teeth up to second molars present in both the arches in dentulous group

**Table 4: Different shapes used with dimensions**

Shape of the test sample	Dimension of the test sample	Diagram
Circle	1 cm radius	
Square	2×2 cm	
Rectangle	3×2 cm	
Triangle	2×2×2 cm	
Star		

Heat cured samples were sand papered and polished to high finish. A hole was drilled in the center of the test sample using frenum relieving bur and a floss of 10 cm length was tied to the test sample. Dimensions of all different test samples were multiplied by 5 and the geometric designs were drawn on the chart paper and marked as 1-5. A time period of 1 min was provided to each patient for the identification on the chart followed by gap of 30 s for the next test sample to be placed in the mouth. A score of 2 was given for each correct identification, score of 1 for no identification, and score of 0 for wrong identification of sample.

## RESULTS

The oral stereognostic scores were recorded, mean values were calculated, and statistically analyzed using analysis of variance and *t*-test. In intergroup comparison between two groups, Group I ( $7.52 \pm 3.02$ ) recorded less value than

Group II ( $12.65 \pm 3.65$ ) which was statistically significant ( $P < 0.001$ ).

In intragroup comparison of Group I (epileptic group), sub group Ia ( $7.43 \pm 2.24$ ) had less mean values than sub group Ib ( $7.71 \pm 2.51$ ), which was not significant statistically ( $P < 0.001$ ).

In intragroup comparison of Group II (control group), sub group IIb ( $11.5 \pm 3.57$ ) had higher mean values than sub group IIa ( $9.01 \pm 4.09$ ) which was statistically significant ( $P < 0.001$ ).

## DISCUSSION

Oral stereognosis basically is the ability of our sensory mechanism to recognize the shape of objects placed in oral cavity. The science of stereognosis is very important for the dentist as well as technician so that to understand the expectation level of the patients and predict the prognosis of the prosthesis. A defect or nonintegration of the proprioceptive changes can result in poor function or pathologic changes in the system.<sup>5</sup> Various authors<sup>7-9</sup> have conducted studies to compare the dentulous and edentulous state in terms of stereognosis and found varying results. However, none of the author has compared the epileptic patient with normal patient in terms of oral stereognosis. In this study, both dentulous and completely edentulous patients were tested so that to note whether the presence of teeth has any influence on the stereognostic score of epileptic patients. No attempt was made to evaluate the stereognostic score with the complete dentures in the mouth as it has been reported that stereognostic ability is not affected by the presence or absence of dentures.<sup>11,12</sup>

Furthermore, no differentiation was made in males and females in this study as a previous study by Chauvin and Bessette<sup>13</sup> reported that no difference exists in oral stereognosis between males and females. Five different forms ranging from simple circle to complex star with edges was used as test sample with floss attached to center to avoid any risk of engulfment of the test sample. Null hypothesis that no difference exists between epileptic group and control group in terms of stereognostic capability stands rejected as a statistically significant difference exists between the two groups. During intergroup comparison, it is found that the epileptic group patients were having less mean values than the control group. This may be explained as most of the patients reported to us were on antiepileptic therapy. They were consuming drugs such as phenobarbitone, carbamazepine, and phenytoin which may have caused adverse reactions such as diminution

of intelligence, impairment of learning, and memory and mental confusions.<sup>10</sup> Furthermore, in intragroup comparison in epileptic group both dentulous as well as edentulous patients showed poor stereognostic score indicating sensory feedback mechanism is impaired in epileptic patients. In intragroup comparison in control group completely edentulous patients showed less mean score than the dentulous patients. This can be explained as aging reduces the perceptive responses. This is in agreement with the study by Landt and Fransson<sup>14</sup> which stated that elder people has less stereognostic capability than the younger adults due to weakening of sensory feedback mechanism. It can be suggested that stereognostic score should be recorded during initial appointment only and the treatment plan should be directed keeping in mind the score obtained. In compromised patients or patients with severely less score, a training program and proper counseling before fabrication of prosthesis should be carried out.

## CONCLUSION

1. Oral stereognosis predicts the prognosis of the treatment provided
2. Epileptic patients have decreased stereognostic capability than the control group
3. In epileptic patients, proper counseling and training program should be carried out before fabrication of prosthesis.

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# Febrile Jaundice in a Tertiary Care Center: A Prospective Study

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## Abstract

**Background:** Acute febrile jaundice is a common entity in clinical practice. A variety of causes have been observed including noninfectious causes.

**Aim and Objectives:** The aim of this study was to identify the causes of fever with jaundice and to analyze their clinical and laboratory profiles.

**Methods:** The study included 86 patients (70 males and 16 females) admitted in Sri Ramachandra Medical College Hospital from the year 2007 to 2009. All routine laboratory parameters, chest X-ray, electrocardiogram, and two-dimensional echo were carried out for all patients. Serology for specific bacterial pathogen and virus was performed along with cultures. Computed tomography scan was done when required.

**Results:** Viral hepatitis was noted in 35 patients (16 patients each with Hepatitis A and B and three patients had Hepatitis E). Nine patients had clinical malaria, seven had leptospirosis, and 32 patients had no definite etiology. 47 patients were found to be alcoholic, and four had history of blood transfusion. 50 patients had clinical hepatomegaly and 62 had splenomegaly. Seven patients had leukocytosis, 47 had thrombocytopenia, 21 had elevated blood urea nitrogen, 7 had elevated creatinine, 19 had elevated alkaline phosphatase, 83 had elevated serum glutamic pyruvic transaminase, and 50 had proteinuria.

**Conclusion:** Febrile jaundice is a distinct clinical entity. Elevated liver enzymes, thrombocytopenia along with proteinuria, were frequently observed, and leukocytosis is uncommon.

**Key words:** Hepatitis, Jaundice, Liver enzymes, Proteinuria, Thrombocytopenia

## INTRODUCTION

Fever with Jaundice is one of the common presentations among patients. Some of the common causes include malaria, leptospirosis, and viral hepatitis. Various noninfectious conditions including connective tissue disorders, drugs, and malignancies are all known to contribute to febrile jaundice. Coinfection with two organisms worsens the outcome.

The approaches to a febrile patient with jaundice/deranged liver functions start with a careful history and physical examination. This is aimed at ruling out other features such as pain and other systemic manifestations which often give clues to alternative diagnosis. In general, patients present with a short febrile illness, and the jaundice appears or is noted by the relatives or the clinician. Patients may be completely unaware of jaundice. If the patients present with ongoing fever with jaundice, one must rule out alternative causes. In endemic countries, tropical infections are important, but one must never forget that fever with jaundice, vomiting, and abdominal pain could be a clinical manifestation of acute onset cholangitis. Jaundice can mask anemia in patients with hemolysis due to infections. Coagulation parameters are usually preserved in patients with tropical jaundice.<sup>1-3</sup>

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While clinically approaching such patients, one must rule out surgical causes of jaundice. Multiorgan dysfunction is rare in acute viral hepatitis unless it is complicated by fulminant hepatic failure. The presence of a normal-sized liver or hepatomegaly along with splenomegaly would indicate a tropical infection.<sup>4</sup> When in doubt, hepatic enzymes and serum bilirubin can help. The clinical picture mimicking acute hepatic failure with preserved coagulation parameters points toward a diagnosis of tropical infections.

The management strategy in patients having tropical jaundice is aimed at treating the underlying causes and supporting the liver till recovery occurs.<sup>5</sup> Since the febrile patient may be vomiting with minimal intake the management starts by assessing the hydration status and hydrate using isotonic fluids. Although malarial infection is the most common cause of tropical hepatopathy, empiric use of antimalarial is not indicated.<sup>5-8</sup>

Antibiotic therapy is indicated for enteric fever, leptospirosis, and scrub typhus, which are the most common causes of tropical infections. Patients should be observed for the development of multiorgan dysfunction, with careful observation on urine output, blood pressure, seizures, encephalopathy, and bleeding. Blood and blood products should be liberally transfused if there is high risk of bleeding. One must use local guidelines for transfusing platelets in patients with thrombocytopenia at high risk of bleeding. Dengue is an important infection which affects liver which can at times be fatal. Prophylactic platelet transfusion in dengue is not indicated even if the platelet count is  $<10,000$ .<sup>8-11</sup> Enteric fever can rarely produce moderate to severe hepatitis.<sup>12,13</sup>

This study was conducted to identify the various clinical spectrum of febrile jaundice.

## MATERIALS AND METHODS

This study was conducted in Sri Ramachandra University between August 2007 and August 2009. This was a prospective study done on 86 patients who presented with fever and jaundice. All patients who met the inclusion criteria (patients  $>18$  years of age presenting with fever and jaundice or serum bilirubin  $>2$  mg/dl at presentation) were subjected to laboratory and imaging studies.

A questionnaire for detailed history was taken from all patients, and a thorough physical examination was done. Abdomen examination was done to demonstrate hepatomegaly, splenomegaly, free fluid, or cirrhosis of liver. Complete blood count, blood urea, sugar, serum creatinine,

liver function tests including coagulation profile, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and urine analysis were done for all patients. Based on their clinical and laboratory profiles, certain special studies were done the collected data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows software. Data were expressed as the mean  $\pm$  standard deviation.  $P < 0.05$  was considered statistically significant.

## RESULTS

In this study, we analyzed a group of 86 patients with acute febrile jaundice. Of these 86 patients, 81.4% were males and 18.6% were females. Alcohol consumption was seen in 55.8% patients, sexual promiscuity in 19.8%, blood transfusion history in 4.7%, and respiratory symptoms in 3.5%. History of drug intake was seen in 3.5%. Clinically, liver was palpable in 60.5% and spleen in 73.3% patients. Urine protein was present in 57.65% patients, blood urea nitrogen (BUN) was abnormal in 24.4%, and creatinine was abnormal in 7%. Malarial parasite was positive for 10.5% patients using quantitative buffy coat method. HBsAg was positive for 20.9% patients, anti-hepatitis A virus in 18.6%, and anti-hepatitis E virus in 7%. IgM leptospirosis was positive in 8.1%. In ultrasonography, abdomen hepatomegaly was present in 44.2% patients, splenomegaly in 11.6%, and hepatosplenomegaly in 20.9%. Chest X-ray was abnormal in 5.8% patients. 2.3% patients had dengue and hepatitis C. The platelets were low ( $<150,000$ ) in 54.85% patients and normal in 45.35%. About 37.2% patients had mild icterus fever, and myalgia predominated rather than jaundice. Almost 37.2% of people were treated for both malaria and leptospirosis and all of them became symptomatically better. One patient presented with respiratory symptoms and suspected to have atypical pneumonia.

## DISCUSSION

In our study, of 86 patients, 8 (11.4%) patients of males were malaria positive and 1 (6.3%) of females was malaria positive. *Plasmodium falciparum* was positive for 5 patients and *Plasmodium vivax* was positive for 4 patients.

In a study conducted by Shah *et al.*,<sup>14</sup> 19 malarial hepatopathy in falciparum malaria who had jaundice was studied. Hepatomegaly was present in 30.6% patients. Splenomegaly was seen in 70.9% patients. About 51.6% had bilirubin more than 3 mg. Nearly 45% had alanine transaminase (ALT) levels more than 65. ALT levels were increased in 67.6% patients, of which 11.4% had ALT  $>3$  times normal. Bilirubin was elevated in 81% patients.

About 23% had bilirubin >3 mg/dl. Thrombocytopenia was present in 91.6% patients.

Leptospirosis was positive in 7 patients (6 males and 1 female). Three patients were in age group in this study ranging from 40 to 50 years, 2 patients in 30-40 years, and 2 patients in 18-30 years. Clinically, splenomegaly was present in all 7 patients and hepatomegaly in 6 patients. All patients had normal total white blood cell count. Thrombocytopenia was present in all 7 patients; thrombocytopenia was also present in the study by Berman *et al.*<sup>15</sup>

None had change in mental status. In the study conducted by Edwards *et al.*,<sup>16</sup> altered sensorium was the predominant manifestation. Altered mental status was the strongest predictor of death in Salvador study group.<sup>17</sup>

BUN and creatinine were elevated in 3 patients; all patients had mild proteinuria similar to a study conducted by Lin *et al.*<sup>18</sup>

No patients expired in our study, and in other study conducted by Salvador *et al.*, case fatalities were 15% and 24.1%.

No patients had skin manifestation where skin manifestation was present in 2% in a study conducted by Edwards *et al.*

Liver enzymes, i.e., aspartate transaminase (AST)/alanine transaminase (ALT), was elevated in all patients, but none had elevation above 3-fold from normal, i.e., 8.3% among patients who had elevation >65 units. All patients had a elevated bilirubin with a direct bilirubin elevated >30% of total bilirubin. In hepatitis group, hepatitis A was diagnosed in 16 (18.6%) patients; hepatitis B was diagnosed in 17 (19.8%) patients; and hepatitis E was diagnosed in 3 (3.5%) patients. The maximum number of patients in hepatitis A group was between 18 and 30. The maximum number of patients in hepatitis B group was between 30 and 40. Promiscuity history was present in 13 patients of hepatitis B (76.5%). Three patients in hepatitis B group had history of prior blood transfusion.

Clinically, hepatomegaly was present in 11 (21.2%) patients in hepatitis A group, and 4 patients in hepatitis B group (7.7%). Two patients of hepatitis E had hepatomegaly. Clinically, splenomegaly was present in 1 patient of hepatitis A group and 3 patients of hepatitis B group.

BUN was abnormal in 5 patients of hepatitis group. Creatinine was abnormal in 4 patients. AST and ALT enzymes were elevated >3-fold in all patients of viral hepatitis group. Direct bilirubin was elevated above 30% of total bilirubin in all patients of viral hepatitis group. No patients were positive for HCV.

## CONCLUSION

Febrile jaundice is an increasingly common entity in clinical practice. Early evaluation and empirical treatment has a definite role in final outcome.

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# Comparison of Bone Biomarkers in Postmenopausal Women

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## Abstract

**Introduction:** Osteoporosis is a skeletal disorder characterized by reduced bone strength and increased susceptibility to fractures secondary to minor trauma. Major sequelae include fragility of bone and increased predisposition to fractures such as vertebral crush fracture, femoral neck fracture, and colles' fracture.

**Aims and Objectives:** The present study aims to understand the bone markers in postmenopausal women. In this study, we measured N-telopeptide, calcium, phosphorus, and alkaline phosphatase (ALP) levels in postmenopausal women and compared it with premenopausal women.

**Materials and Methods:** Study group included postmenopausal women aged 50-70 years who had bone mineral density (BMD) T-score  $\geq -2.5$  and T-score between  $-1.0$  and  $-2.5$  and they were recruited from orthopedics outpatient department. Control group includes premenopausal women aged 25-35 years without any specific illness. Serum N-telopeptide was measured by ELISA method. Calcium, phosphorus and total ALP were measured in fully automated analyzer by chemical methods. BMD was assessed by ultrasonography taken in heel and the T-scores were recorded.

**Statistical Analysis:** Results were expressed as mean  $\pm$  standard deviation and were statistically analyzed using SPSS software version 16 and MS Excel. Student's *t*-test was used to analyze the difference between the two groups. The relationship between the variables was evaluated using Pearson's correlation coefficient. A  $P < 0.05$  was considered to be statistically significant. The mean range of serum N-telopeptide in the study group (101.47 nmol BCE/L) is significantly higher than the control group mean (17.35 nmol BCE/L), and the *P* value is statistically significant. Pearson's correlation studies showed a positive correlation between N-telopeptide and total alkaline phosphatase, which is statistically significant.

**Conclusion:** Our findings show that there is a significant increase in serum N-telopeptide level in postmenopausal women when compared to other bone biomarkers and it correlates well with the degree of osteoporosis.

**Key words:** Bone mineral density, Calcium, N-telopeptide, Phosphorus, Postmenopausal osteoporosis, Total alkaline phosphatase

## INTRODUCTION

Osteoporosis is a metabolic disorder characterized by decreased bone mass and increased susceptibility to fractures secondary to trivial trauma.<sup>1</sup> In osteoporosis, there is a disturbed balance between bone resorption and

bone formation with a decrease in the amount of normal mineralized bone. The World Health Organization (WHO) operationally defines osteoporosis as a bone density that falls 2.5 standard deviations (SDs) below the mean for young healthy adults of the same gender - also referred to as a T-score of  $-2.5$ .<sup>2</sup>

As our society is "aging" there is a considerable shift in the epidemiology of osteoporosis. WHO Technical Report Series-843-predicts a significant increase in fracture neck of femur among Asian population over a period. By 2050, osteoporosis will be a major demographic factor due to changes in lifestyle and the increase in survival rate of elderly. In most western countries, the peak incidence of

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osteoporosis occurs at about 70-80 years of age, whereas in India it may afflict those 10-20 years younger at the age of 50-60 years.

Why females are at risk of osteoporosis than male? The skeletal architecture in male has a different morphology than female that set them at lower risk for developing osteoporosis. The increased diameter of bone and greater muscle mass in men gives them more agility and padding in case of fall.<sup>3</sup>

In postmenopausal women, following ovarian failure, there is an absolute acceleration in the rate of bone resorption due to increased osteoclast recruitment leading to an exaggerated form of physiological bone depletion.<sup>4,5</sup> In women, the decrease in sex steroids at menopause accelerates the bone loss to about 2% per year for the first 5 years and then declines to 1% loss per year.<sup>6,7</sup> Although the principle cause of age-related osteoporosis is the continuing effects of estrogen deficiency; a further contribution is also provided by “calcium deficiency.”<sup>8,9</sup>

The cause of calcium deficiency is complex and is related to age-related decrease in calcium absorption in the gut and also due to reduced effectiveness of vitamin D on stimulating calcium absorption in the intestine.<sup>10</sup> Further, menopause related acceleration in renal calcium excretion is also noted. This is due to decreased resorption of calcium in the distal convoluted tubule associated with the loss of estrogen stimulation of  $\text{Ca}^{++}$  ATPase.<sup>11</sup>

Most of the cases of osteoporosis are not diagnosed until a fracture occurs. A routine spinal radiograph in a symptomatic patient will not detect osteoporosis until 30% of bone is lost. Hence, a radiograph is not useful in the follow-up of progression of bone loss in osteoporotic patients.

National osteoporosis foundation recommends that the diagnosis of osteoporosis is to be made clinically by quantifying the bone mineral density (BMD).<sup>12</sup> Recently, new bone turnover markers have been used to get a better idea on bone microarchitecture.<sup>13,14</sup> One such bone resorption marker is N-telopeptide, a stable degradation end product from Type 1 collagen present in bone (Figure 1).<sup>15</sup>

In view of the above facts, the present study was done to understand the bone markers in postmenopausal women. In this study, we have investigated N-telopeptide, calcium, phosphorus, and alkaline phosphatase (ALP) levels in postmenopausal women and compared it with premenopausal women.

## MATERIALS AND METHODS

The study was conducted at Thanjavur Medical College Hospital after getting approval from the Ethical Committee. Written informed consent was obtained from the participants before enrollment into the study.

The study group included postmenopausal women aged 50-70 years who had BMD T-score  $\geq -2.5$  and T-score between  $-1.0$  and  $-2.5$  and they were recruited from orthopedics outpatient department. Control group includes premenopausal women aged 25-35 years without any specific illness.

Under aseptic conditions, 5 ml of venous blood was collected from each subject. The vacutainers containing the blood samples were kept at room temperature for 30 min and then centrifuged at 2000 g for 15 min for a clear separation of serum. The following parameters were estimated immediately after the serum was separated in fully automated analyzer.

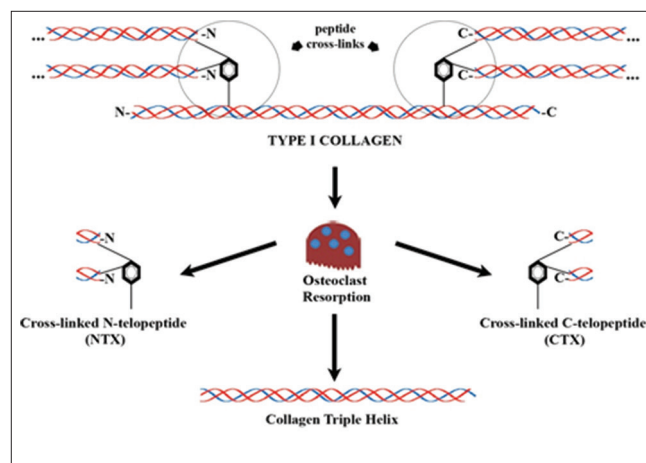
1. Calcium
2. Phosphorus
3. Total alkaline phosphatase.

The remaining aliquot of serum was stored at  $-20^{\circ}\text{C}$  in the deep freezer for estimation of serum N-telopeptide.

BMD was assessed by ultrasonography taken in heel and the T-scores were recorded.

## Statistical Analysis

Results were expressed as mean  $\pm$  SD and were statistically analyzed using SPSS software version 16 and MS Excel. Student's *t*-test was used to analyze the difference between the two groups. Relationship between the variables was evaluated using Pearson's correlation coefficient. A  $P < 0.05$  was considered to be statistically significant.



**Figure 1: Formation of cross-linked N-telopeptide during osteoclast resorption**

## RESULTS

Table 1 and Figure 2 show mean N-telopeptide level between control and study group.

Mean serum N-telopeptide in the study group is  $101.47 \pm 18.39$  nmol BCE/L which is higher than the control group mean  $17.35 \pm 3.2$  nmol BCE/L which is statistically significant ( $P 0.0001 < 0.05$ ).

Table 2 and Figure 3 show Student's *t*-test analysis of serum calcium, serum phosphorus, and the ionic product of calcium and phosphorus between control and study group.

In Table 2, there is a statistical decrease in mean serum calcium level in a study group of  $9.30 \pm 0.504$  mg/dl when compared with mean serum calcium level in control group of  $9.76 \pm 0.529$  mg/dl which is statistically significant.

Further, there is a statistical increase in mean serum phosphorus level in a study group of  $3.976 \pm 0.375$  mg/dl when compared with mean serum phosphorus level in control group of  $3.5728 \pm 0.4855$  mg/dl which is statistically significant.

Table 2 shows mean value of ionic product of calcium and phosphorus in the study group of  $36.9 \pm 3.27$  which is higher when compared to study group of  $34.72 \pm 3.89$  and it is statistically significant.

Table 3 and Figure 4 show a comparison of mean serum total ALP level between control and study group. Mean serum total ALP in study group is  $105.62 \pm 25.03$  U/L which is higher than the control group mean serum total ALP  $66.28 \pm 12.02$  U/L which is statistically significant.

Table 4 show Pearson's correlation between N-telopeptide and other study parameters.

Table 4 shows a positive correlation between N-telopeptide and total alkaline phosphatase, which is statistically significant.

## DISCUSSION

Osteoporosis is a complex, multifactorial, polygenic disease in which genetic determinants are modulated by hormonal, nutritional, and environmental factors.

The present concept is that osteoporosis represents the continuum, in which multiple pathogenic mechanisms converge to cause loss of bone mass and microarchitectural deterioration of skeletal structure. These factors coupled

**Table 1: Mean N-telopeptide level between control and study group**

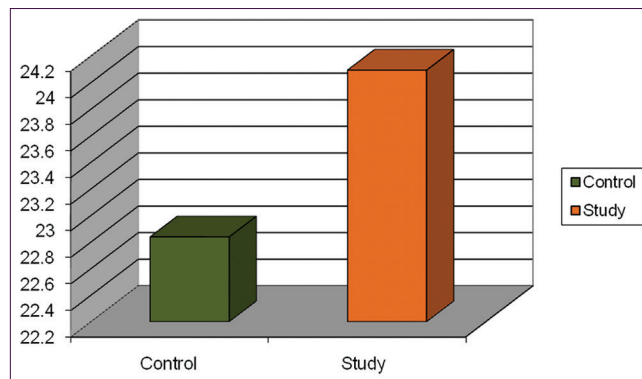
N-telopeptide	Mean $\pm$ SD	Statistical inference
Control (n=50)	17.3504 $\pm$ 3.23883	T=-31.840
Study (n=50)	101.4728 $\pm$ 18.39896	0.0001<0.05
		Significant

SD: Standard deviation

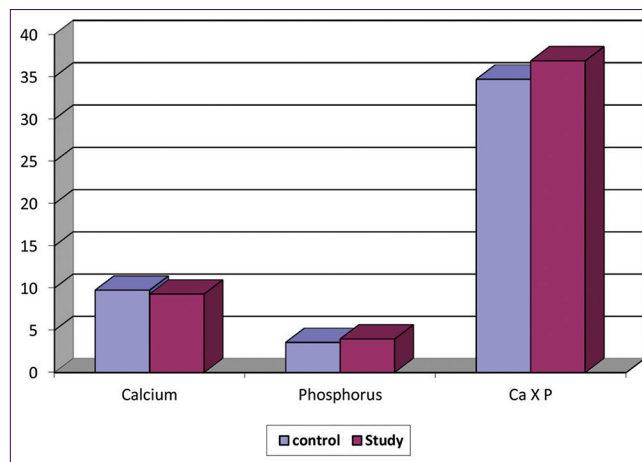
**Table 2: Student's *t*-test analysis of serum calcium, serum phosphorus and the ionic product of calcium and phosphorus between control and study group**

Analyte	Mean $\pm$ SD	Statistical significance
Calcium		T=4.451
Control (n=50)	9.7620 $\pm$ 0.52911	0.0001>0.05
Study (n=50)	9.3020 $\pm$ 0.50406	Significant
Phosphorus		T=-1.176
Control (n=50)	3.5728 $\pm$ 0.48556	0.0001>0.05
Study (n=50)	3.9760 $\pm$ 0.37502	Significant
Ca X P ratio		T=-3.040
Control (n=50)	34.72 $\pm$ 3.893	0.03>0.05
Study (n=50)	36.90 $\pm$ 3.279	Significant

SD: Standard deviation



**Figure 2: Mean N-telopeptide level between control and study group**



**Figure 3: Student's *t*-test analysis of serum calcium, serum phosphorus, and the ionic product of calcium and phosphorus between control and study group**

**Table 3: Comparison of mean serum total ALP level between control and study group**

ALP	Mean±SD	Statistical inference
Control (n=50)	66.28±12.026	T=-10.015
Study (n=50)	105.62±25.036	0.001<0.05
		Significant

ALP: Alkaline phosphatase, SD: Standard deviation

**Table 4: Pearson's correlation between N-telopeptide and other study parameters**

Study N-telopeptide	Correlation value	Statistical inference
BMD	-0.746 (**)	P<0.01 significant
Calcium	-0.238	P>0.05 not significant
Phosphorus	-0.015	P>0.05 not significant
Ca X P	-0.168	P>0.05 not significant
ALP	0.288 (*)	P<0.05 significant

\*P&lt;0.05, \*\*P&lt;0.01. ALP: Alkaline phosphatase, BMD: Bone mineral density

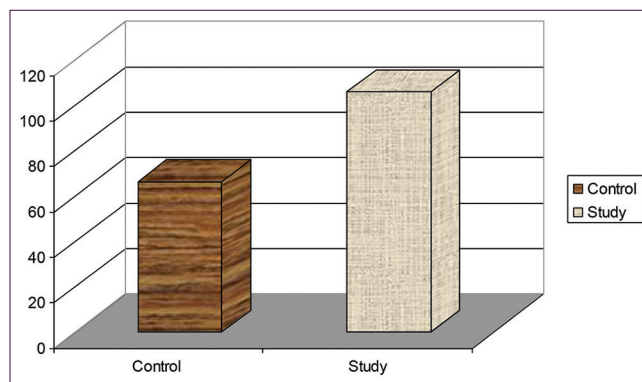
with increased incidence of falls contribute to a high incidence of fragility fractures in osteoporotic patients.

Due to increased longevity of Indian population, now it is realized as in the west, the osteoporotic fractures are the major cause of morbidity and mortality in the elderly. The commonly used technique to diagnose osteoporosis and predict future fracture risk is an assessment of BMD by bone densitometry which is principally a measure of mineral content of bone. BMD measurements strongly correlate with load bearing capacity of hip and spine and also with the risk of fracture.<sup>16</sup>

However, the densitometric scan does not reflect the dynamic nature of bone tissue. In contrast, biochemical markers of bone turnover provide a better insight of bone growth, bone remodeling, and their measurement is useful in the assessment of metabolic bone diseases like osteoporosis and they provide an integrated evaluation of global disease activity rather than assessing a regional activity as with densitometric scan.<sup>17,18</sup>

In this present study, we have studied the bone resorption marker N-telopeptide along with other markers namely calcium, phosphorus, and total ALP in association with BMD in postmenopausal women and compared it with the premenopausal women.

Comparison of mean value of serum N-telopeptide of the study group ( $101.47 \pm 18.39$ ) with that of control group ( $17.35 \pm 3.23$ ) showed a significant rise in the study group. This shows that there is increased rate of bone resorption the following menopause. This study also correlates with the previous studies done by Jayaram *et al.*<sup>19</sup>

**Figure 4: Comparison of mean serum total alkaline phosphatase level between control and study group**

In this study, serum calcium, serum phosphorus, and serum total ALP shows no significant correlation with serum N-telopeptide, which in turn suggests that these parameters do not reflect the same aspects of bone metabolism as that of serum N-telopeptide.

With regard to serum calcium, the blood level is tightly regulated within normal limits by Parathyroid hormone otherwise, alterations in the homeostasis of serum calcium may lead on to life-threatening complications.

Although there is a significant increase in the mean level of serum total ALP in the study group ( $105.62 \pm 25.03$ ) when compared to that of control group ( $66.28 \pm 12.02$ ) it cannot be considered as a reliable marker for osteoporosis because it is not specific for bone. The blood level of serum total ALP is contributed by various tissues such as liver, placenta, intestine in addition to osteoblasts of bone.<sup>20</sup>

In the Pearson's correlation analysis, the serum N-telopeptide shows significant negative correlation with BMD and a positive correlation with serum total alkaline phosphatase.

These observations finally suggest that the level of serum N-telopeptide, the cross-linked collagen peptides increases with bone resorption and can be used as a reliable marker in primary postmenopausal osteoporosis. They appear as a promising tool for defining the skeletal status of postmenopausal women.

## CONCLUSION

Our findings show that there is a significant increase in serum N-telopeptide level in postmenopausal women when compared to other bone biomarkers and it correlates well with the degree of osteoporosis. Further, measurement of serum N-telopeptide also helps to identify the high-risk individuals for fracture.



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# Pleomorphic Adenoma: An Observational Study

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## Abstract

**Background:** Pleomorphic adenoma is the most common salivary gland tumor. The most common gland involved is parotid gland. It is more common in females. It is uncommon in submandibular and sublingual glands.

**Objectives:** Although pleomorphic adenoma is more common in parotid gland, it should be a part of differential diagnosis in submandibular swellings.

**Materials and Methods:** This was an observational study carried out in the Department of Otorhinolaryngology at our institute from February 2014 to June 2015. A total of 6 patients out of 3432 outpatients were included in the study. In the same period, 20 cases of pleomorphic adenoma were diagnosed in various departments of our institution.

**Results:** In our study, the age of patients varied between 20 and 60 years. They were no patients who were above 61 years. In this series, there were 50 female patients and 10 male patients. The odds ratio is 5.5, that is, females have 5.5 times more chances of getting pleomorphic adenoma as compared to males. Moreover, the Chi-square is statistically significant at  $P < 0.0001$ .

**Conclusion:** Pleomorphic adenomas are more common in parotid gland. Even though they are rare in submandibular gland, they should be considered as differential diagnosis in case of submandibular mass lesions. Pleomorphic adenomas are treated by complete surgical excision. Improper removal can result in recurrences.

**Key words:** Parotid, Pleomorphic Adenoma, Submandibular

## INTRODUCTION

Salivary gland neoplasms account for 3% of all head and neck neoplasms. The overall incidence of salivary gland neoplasms is 4/100000/year, with the gender ratio being 1:1. Parotid gland is most commonly affected, followed by submandibular and minor salivary glands.<sup>1</sup> Neoplasms are more common in parotid and minor salivary glands, whereas non-neoplastic lesions are more common in submandibular salivary gland. Malignant neoplasms are more common in minor salivary glands, whereas benign neoplasms are more common in major salivary glands.<sup>2</sup>

The most common benign salivary gland tumor is pleomorphic adenoma. It is more common in parotid

(57%), followed by minor (20%) and submandibular salivary glands (18%). The most frequent tumors of submandibular salivary gland are pleomorphic adenoma (36%), followed by adenoid cystic carcinoma (25%), mucoepidermoid carcinoma (12%), and malignant mixed tumors (10%).<sup>1</sup>

In this study, we present a series of pleomorphic adenomas who presented to our institution over a period of 1-year.

## MATERIALS AND METHODS

This was an observational study carried out in the Department of Otorhinolaryngology at our institute from February 2014 to June 2015. A total of 6 patients out of 3432 outpatients were included in the study. In the same period, 20 cases of pleomorphic adenoma were diagnosed in various departments of our institution.

Patients aged >16 years who presented with longstanding swelling in the head and neck region which was proven as pleomorphic adenoma by histopathological examination were included in the study.

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The selected patients were subjected to detailed history, followed by complete clinical examination. All patients underwent either ultrasonography or computed tomography (CT) over the region of the swelling. They also underwent fine needle aspiration cytology of the swelling, and the diagnosis of pleomorphic adenoma was made. Patients later underwent surgical excision, and the diagnosis was confirmed by histopathology.

### Procedures

All patients underwent surgical excision under general anesthesia. Patients with pleomorphic adenoma in the parotid gland underwent superficial parotidectomy through standard parotidectomy approach. In case of submandibular gland, standard submandibular approach was followed.

## RESULTS

In our study, the age of patients varied between 20 and 60 years. There were no patients who were above 61 years (Table 1).

In this series, three groups had 20 patients each. There was no patient belonging to the age group of 21-30 years.

The age group of outpatients during that period is given in Table 2.

The Chi-square test done shows the difference between the age group prevalence being not significant.

### Sex Distribution

In this series, there were 50 female patients and 10 male patients (Table 3).

Sex distribution among our outpatients is described in Table 4.

**Table 1: Age group of Pleomorphic adenoma patients**

Age group	No of cases	Percentage
21-30	Nil	0
31-40	20	33
41-50	20	33
51-60	20	33

**Table 2: Age group of out patients**

Age group	No. of out patients	Percentage	No of cases	Percentage
21-30	549	16	Nil	0
31-40	755	22	20	2.6
41-50	961	28	20	2.1
51-60	412	12	20	4.8
61<	755	22	Nil	0

The odds ratio is 5.5, that is, females have 5.5 times more chances of getting pleomorphic adenoma as compared to males. Moreover, the Chi-square is statistically significant at  $P < 0.0001$ .

### Site Distribution

In this series, there were 55 patients with pleomorphic adenoma in the parotid gland and 5 in the submandibular salivary gland (Table 5) (Figures 1-5).

## DISCUSSION

Salivary gland tumors are complex neoplasms which account for 3% of all head and neck tumours.<sup>1</sup> Benign/malignant ratio among major salivary glands is 2.1:1. Parotid gland is the most commonly affected among major salivary glands. Minor salivary glands are involved in 21.5% of the cases. Palate is the most common site affected.<sup>3</sup> Most common benign tumor is pleomorphic adenoma, followed by Warthin's tumor.<sup>4</sup> Most common malignant tumor is mucoepidermoid carcinoma, followed by adenoid cystic carcinoma.<sup>5</sup>

Pleomorphic adenoma is the most common neoplasm of salivary glands. It most commonly occurs in the fifth or sixth decade. It has female preponderance. It typically arises as a slow growing, firm mass that is slightly compressible. Almost all are asymptomatic and they are usually brought to the attention of the physician when routine physical examination is performed or when the patient feels or sees a lump. Imaging studies alone can provide a presumptive diagnosis. CT scan findings are tumors which are smooth and have well-defined margins. The attenuation values of the mass are usually

**Table 3: Sex distribution of Pleomorphic adenoma patients**

Sex	No of cases	Percentage
Males	10	16.7
Females	50	83.3

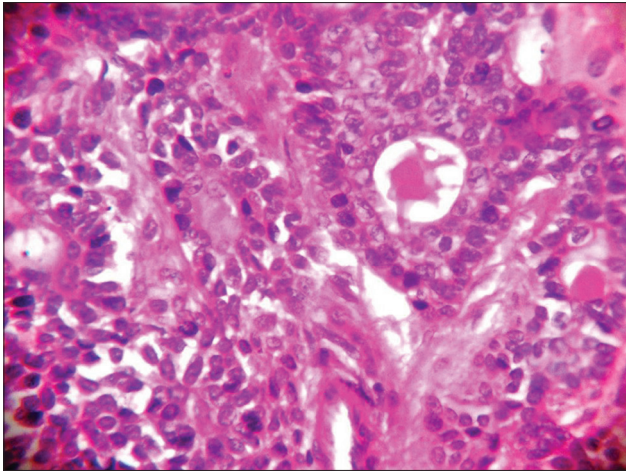
**Table 4: Sex distribution of out patients**

Sex	No of out patients	Percentage	No of cases	Percentage
Males	1842	53.7	10	0.54
Females	1590	46.3	50	3.1

**Table 5: Site distribution**

Site	No of cases	Percentage
Parotid	55	91.7
Submandibular	5	8.3

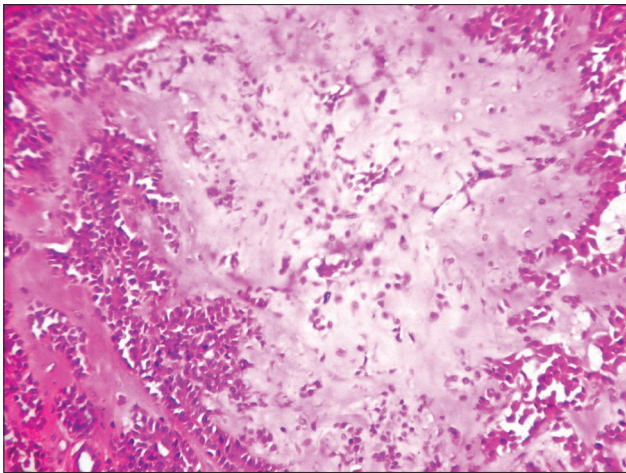




**Figure 1: Myoepithelial cells (40x)**



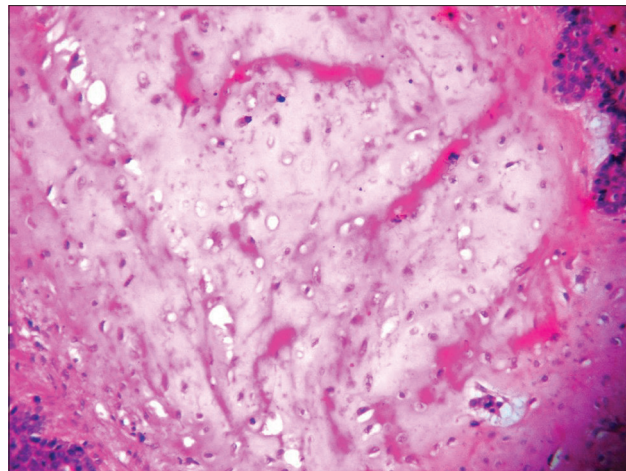
**Figure 4: Submandibular swelling**



**Figure 2: Myxoid matrix (40x)**



**Figure 5: Gross specimen**



**Figure 3: Pseudo cartilage (40x)**

homogeneous and higher than that of the surrounding gland. They typically show delayed contrast enhancement. When very large, they may develop a heterogeneous appearance with areas of necrosis, hemorrhage, cysts,

and calcification. They are typically well demarcated from the surrounding tissue by a fibrous capsule, which varies both in thickness and completeness. This capsule is a result of fibrosis of surrounding salivary parenchyma, which is compressed by the tumor and is referred to as “false capsule.” If the fibrous capsule can be completely removed, these tumors can be cured with surgery. The tumor also has small protrusions (pseudopodia) that extend beyond the central mass, caused by variability in the growth rates of the various cell types. This factor contributes to recurrence rates as high as 50%, depending on the type of surgical intervention. Microscopically, it is characterized by a myriad of morphological diversity. Epithelial cells are arranged in sheets and islands showing typical ductal structures and various epithelial and myoepithelial characteristics as spindle, clear, squamous, basaloid, plasmacytoid, oncocytic and sebaceous. The stroma characteristically is mixed with fibrous, chondroid, myxoid, or hyaline aspects. The incidence of malignant transformation in pleomorphic adenoma ranges from 1.9% to 23.3%.<sup>6</sup>



Ramirez *et al.* conducted a 10 year retrospective review of submandibular salivary gland tumors. They studied 22 cases of submandibular salivary gland neoplasms, out of which 19 cases were benign and 18 cases were pleomorphic adenoma. They concluded that pleomorphic adenoma was the most common submandibular salivary gland tumour.<sup>1</sup> Although it is the most common tumor of the submandibular salivary gland, 22 cases in 10-year period suggest that it is uncommon compared to other salivary glands. In our institution, we have reported the first case in this study.

Lawal *et al.* in their retrospective review of 413 cases of salivary gland neoplasms found only 49 neoplasms in submandibular salivary gland. Although pleomorphic adenoma was found to be the most common submandibular salivary gland neoplasm, it shows that neoplasms in submandibular glands are relatively uncommon.<sup>2</sup> The same message is conveyed through our study.

Sirohietal reported more common occurrence of pleomorphic adenoma in submandibular salivary gland than other tumors. However, neoplasms in submandibular salivary glands were relatively uncommon.<sup>5</sup>

Gupta *et al.* reported a giant pleomorphic adenoma of submandibular salivary gland which was 2.24 kg in weight. They concluded that it is very rare to find such a neoplasm in submandibular salivary gland.<sup>6</sup>

Rai *et al.* have reported an occurrence of pleomorphic adenoma of submandibular salivary gland. They also concluded that occurrence of pleomorphic adenoma in the submandibular salivary gland was uncommon.<sup>7</sup>

## CONCLUSION

Majority of submandibular salivary gland swellings are either inflammatory or lithiasis. In such cases, there will be the presence of inflammatory signs such as tenderness, local rise of temperature, and redness over the skin. Absence of these signs points the diagnosis toward neoplasms. Pleomorphic adenomas are more common in parotid gland. Even though they are rare in submandibular gland, they should be considered as differential diagnosis in case of submandibular mass lesions. Pleomorphic adenomas are treated by complete surgical excision. Improper removal can result in recurrences.

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# Outcome of Vaginal Birth after Cesarean Section: A Prospective Study

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## Abstract

**Introduction:** Cesarean section has been a part of human culture since ancient times, and there are tales in both Western and Eastern cultures of this procedure resulting in live mothers and off springs.

**Objectives:** The study, conducted in Katihar Medical College Hospital, Katihar, Bihar, describes the outcome of vaginal birth after cesarean section (VBAC).

**Materials and Methods:** (1) A prospective study was carried out from 1<sup>st</sup> January 2015 to 31<sup>st</sup> December 2015 on 100 women with one prior lower segment cesarean section (LSCS) for a nonrecurrent cause. (2) Exclusion criteria: All unbooked women and those with estimated fetal weight >3.5 kg, history of postoperative wound infection in previous LSCS, or any medical illness complicating pregnancy, cephalopelvic disproportion, abnormal presentation, and placenta praevia. (3) Spontaneous onset of labor was awaited up to 40 weeks. Induction of labor - only in highly selected cases.

**Results:** Out of the 100 women, 72 underwent elective repeat cesarean section (C/S), 28 patients (28%) underwent a trial of labor, among them, 15 had successful vaginal delivery (53.57), but 13 patients failed the attempt and had to undergo emergency C/S. To assist in the 2<sup>nd</sup> stage of labor, 6 had ventouse application. In total, 85 cases needed repeat C/S. Among the vaginal delivered cases, one had scar dehiscence (6.6%), one cervical tear (6.6%), two cases of manual removal of placenta (13.3%), one postpartum hemorrhage (6.6), and one case of puerperal pyrexia (6.6). Perinatal morbidity was comparable with the elective repeat C/S group.

**Conclusion:** VBAC should be considered in cases of previous one cesarean delivery for nonrecurrent indication.

**Key words:** Previous cesarean delivery, Vaginal birth after cesarean delivery, Post cesarean normal delivery

## INTRODUCTION

Cesarean section has been a part of human culture since ancient times, and there are tales in both western and eastern cultures of this procedure resulting in live mothers and off springs. Numerous references to cesarean section appear in ancient Hindu Egyptians, Grecians, Romans, and other European folklore.<sup>1-3</sup> In past 20 years, the rate of C/S has steadily increased from about 5% to more than

20%. The policy once a cesarean always a cesarean is no longer tenable. A planned vaginal birth after a previous C/S should be recommended for women whose first C/S was by lower segment transverse incision and who have no other indication for C/S in the present pregnancy.<sup>4-8</sup> There is a definite risk of uterine rupture in vaginal birth after cesarean delivery (VBAC) often leading to catastrophes which can be avoided by rapid diagnosis and prompt intervention. Evidence confirming the safety of VBAC within proper guidelines has been available for more than 10 years. However, wide variations in VBAC rates still exist between hospitals and physicians.<sup>9-14</sup> The present study was undertaken to reascertain these facts with the hope that more women will be encouraged to avoid an unnecessary repeat cesarean section by opting for vaginal delivery (VD). VBAC offers distinct advantages over a repeat cesarean section since the operative morbidity, and mortality are

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completely eliminated, the hospital stay is much shorter, and expenses involved are much less. The rate of cesarean section needs to be reduced, and this can be achieved to a small extent by avoiding primary cesarean sections done without explicit indications and more importantly by resorting to a trial of VD after previous cesarean section which is safe for the fetus.<sup>15-18</sup> The purpose of this study was to evaluate the efficacy and safety of VBAC.

## MATERIALS AND METHODS

A prospective study was carried out on 100 women with one previous lower segment cesarean section (LSCS) for a nonrecurrent cause, from 1<sup>st</sup> January 2015 to 31<sup>st</sup> December 2015. All the cases were booked in the antenatal clinic and were regularly reporting for check-up. The following cases were excluded from the study:

1. Associated medical disorder such as anemia (hemoglobin <10 g %), pregnancy-induced hypertension, diabetes, heart disease, and renal disease
2. Estimated fetal weight >3.5 kg
3. Breech presentation
4. History of postoperative wound infection following the previous LSCS
5. Details of the previous cesarean operation not available
6. Contraindications to VD such as cephalopelvic disproportion, major degree placenta praevia, and transverse lie
7. Postdated pregnancy with an unfavorable cervix.

All women were admitted if they went into spontaneous labor. Those who failed to go into labor on their own were induced after completion of 40 weeks. Induction was started in the morning with 5 units of oxytocin in 500 ml of ringer lactate and increased gradually from 6 mIU/min to a maximum of 20 mIU/min with the aim of getting 3-4 uterine contractions every 10 min each lasting 40-45 s. Whether the labor was spontaneous or induced, it was monitored with,

1. Hourly recording of vital parameters - temperature, pulse, respiration, and blood pressure,
2. Continuous electronic fetal monitoring by cardiotocography,
3. Monitoring of uterine contractions,
4. Partograph,
5. A close watch for the early recognition of scar dehiscence by identifying maternal tachycardia in the absence of fever, vaginal bleeding, scar tenderness, and fetal heart rate alterations.

An attempt at VD was abandoned if there was any suspicion of scar dehiscence or sign of fetal distress or unsatisfactory progress of labor. Vacuum extraction was used to cut short the second stage.

## RESULTS

Out of the total of 100 women, 5 went into preterm labor, 20 went into spontaneous labor between 37 and 39 weeks. Three women had to be induced since they did not go into spontaneous labor till 40 weeks. The demographic profile of the women is given in Table 1. It has been observed that women belonging to 20-30 age groups had maximum successful VD as shown in Table 2, indication for the previous cesarean section, fetal distress was the most common cause.

Table 3 shows the mode of delivery among the 28 patients who underwent a trial of labor. 13 amongst 28 needed emergency repeat C/S, 9 patients had spontaneous, unassisted VD, 6 patients needed vacuum extraction to cut short the second stage of labor.

Table 4 shows the indications of emergency repeat cesarean section after failed trial. It shows that scar tenderness was the most common cause followed by fetal distress.

Table 5 shows the comparison of maternal complications in vaginally delivered group and repeat cesarean group. It can be seen that postnatal complications such as puerperal pyrexia, blood transfusion, operative bladder injury, and pulmonary edema were more common in repeat cesarean group. One case of cervical tear occurred with ventouse extraction. Scar dehiscence was noticed in a case taken up for emergency LSCS due to scar tenderness. One case of primary atonic postpartum hemorrhage was managed with

**Table 1: Demographic profile (n=100)**

Maternal age	Number of cases	Successful VD	Emergency repeat C/S	Elective repeat C/S
<20	8	2	2	7
20-30	67	10	9	50
30-35	16	2	1	10
35-40	9	1	1	5
Total	100	15	13	72

VD: Vaginal delivery

**Table 2: Indication for previous cesarean section, fetal distress was the most common cause**

Indication for previous cesarean delivery	Number (%)
Fetal distress	64 (64)
Dystocia	20 (20)
Breech	4 (4)
Transverse lie	1 (1)
Placenta praevia	3 (3)
Abruptio placenta	1 (1)
Elderly primi	2 (2)
Severe PIH	4 (4)
Cord prolapse	1 (1)

PIH: Pregnancy-induced hypertension

**Table 3: Mode of delivery in patients who underwent trial of labor (n=28)**

Mode of delivery	Number (%)
Spontaneous and unassisted	9 (32.14)
Vacuum extraction	6 (21.42)
Forceps delivery	0 (0)
Emergency repeat C/S	13 (46.43)

**Table 4: Indications for emergency repeat cesarean section after failed trial (n=13)**

Parameter	Number (%)
In vaginally delivered group (n=15)	
Scar dehiscence after delivery followed by hysterectomy	1 (6.66)
Puerperal pyrexia	1 (6.66)
Cervical tear	1 (6.66)
Manual removal of placenta	2 (13)
Primary atonic postpartum hemorrhage	1 (6.6)
In repeat cesarean group (n=85)	
Wound infection requiring secondary suture	7 (8.23)
Puerperal pyrexia	4 (4.7)
Blood transfusion required	8 (9.41)
Operative bladder injury	1 (1.17)
Spinal headache	1 (1.17)
Pulmonary edema	01 (1.17)

intravenous fluids, uterine massage, methergine injections, and misoprostol.

Table 6 compares the neonatal complications in vaginal deliveries and repeat cesarean group. Some neonatal complications such as birth asphyxia, neonatal infection were more in repeat cesarean section than in vaginally delivered group.

## DISCUSSION

It is generally accepted that VD is associated with lower maternal morbidity and mortality as against cesarean section. The morbidity associated with successful vaginal birth is about one-fifth that of elective cesarean. Perinatal risk is more after a failed trial of labor compared to elective repeated cesarean section without labour.<sup>19-21</sup> Failed trials of labor, with the subsequent cesarean section, involve almost twice the morbidity of the elective section. The information is important for counseling women about their choices of delivery after a previous cesarean section. The adverse events include chorioamnionitis, postpartum endometritis, and uterine rupture requiring hysterectomy, blood transfusion, perinatal and neonatal deaths, and neonatal neurological impairment. Many of these adverse events seen in trial of scar are attributable to the failure of labor and the requirement for a repeated emergency cesarean section. However, in this study, there were fewer

**Table 5: Compares the maternal complication in vaginally delivered group (n=15) and repeat cesarean group (n=85)**

Parameter	Number (%)
Fetal distress	4 (30.76)
Scar tenderness	6 (46.15)
Failed progress of labor	2 (15.38)
Cervical dystocia	1 (7.6)

**Table 6: Neonatal complications in vaginal deliveries (n=15) and repeat cesarean group (n=85)**

Parameter	Number (%)
In vaginally delivered group	
Stillbirth	1 (6.66)
Birth asphyxia	1 (6.66)
Neonatal septicemia	2 (13.33)
Neonatal jaundice	2 (13.33)
Neonatal complications in repeat cesarean group	
Stillbirth	1 (1.17)
Neonatal death	1 (1.17)
Birth asphyxia	5 (5.88)
Neonatal jaundice	5 (5.88)
Neonatal infection	4 (4.7)

complications noted in those who underwent VBAC then elective or emergency repeat C/S. This study represents our observations for 1 year. The selection of women for VBAC is mainly influenced by woman's desire and conditions favorable for VD. The objective of this study was to evaluate the success rate and safety of attempted VBAC, in a tertiary care setting, after one previous cesarean delivery. In general, our institution offers a conservative approach both in the selection of women and in the management of their labor. In general, speaking women belonging to higher socioeconomic status were either not keen for VBAC or opted out of the study. Further, women with an unfavorable cervix who had gone beyond their due date and had to be induced with prostaglandin E2 gel combined with oxytocin were abandoned from the study. In the present study, suitable women were selected for VBAC during early pregnancy after a thorough assessment, and adhering to strict inclusion and exclusion criteria as mentioned earlier. Of the 100 women, 15 (15%) delivered vaginally and 85 (85%) had to be taken up for emergency LSCS for various indications as given in (Table 4). All the six women who had one previous VD delivered vaginally in the present study. This is in line with the fact that the history of a previous normal VD is the single most important predictor for a successful VBAC Farmer<sup>8</sup> and Turner<sup>9</sup> have highlighted that caution is to be exercised in inducing labor in these patients because of the relatively higher risk of scar dehiscence and rupture associated with induction.<sup>10,20,21</sup> Induction was withheld till 41 weeks in our study for this reason. No case of scar dehiscence occurred



in any of the 3 cases who underwent induction under close supervision. The maternal complications and perinatal morbidity in the present study are identical to those seen with other normal vaginal deliveries with the exception of scar dehiscence in one case (6.66%). The study shows the high success of VBAC and the fewer complications. Many women in the study were multiparous with a prior vaginal birth. Prior vaginal birth is a good predictor for the outcome of VBAC. An attempt for VBAC is well justified for post-caesarean pregnancies with nonrecurrent indications. Screening for this should preferably begin at antenatal booking itself to minimize the associated risks. Proper selection, appropriate timing and suitable methods of induction with close supervision by competent staff are the key factors to achieve greater degree of success.<sup>22-25</sup>

## CONCLUSION

VBAC should be considered in cases of previous one cesarean delivery for nonrecurrent indication.

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# Prevalence of Preterm Admissions and the Risk Factors of Preterm Labor in Rural Medical College Hospital

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## Abstract

**Background:** Preterm deliveries are important contributors for neonatal intensive care unit (NICU) admission. Preterm birth is a major problem associated with neonatal mortality and morbidity in developing countries. Early admission of mother and prolonged hospitalization of babies impart psychological and financial burden for the family.

**Aim:** To study on the prevalence of preterm admissions and etiology of preterm labor in newborn care unit of rural medical college hospital.

**Materials and Methods:** This retrospective study was conducted at rural tertiary care center NICU for 1 year. Maternal risk factors leading to preterm labor were also analyzed.

**Results:** During the study period 2156 total cases were admitted in newborn care unit. Among the total 2156 admissions 609 (28.25%) were preterm babies. 260 (12.06%) of total newborn admission were <34 weeks. 349 (16.19%) of total newborn admission were 34-37 weeks. The etiology of preterm birth is multifactorial. Prevalent causes of prematurity were anemia 173 (28.41%), preterm premature rupture of membrane 150 (24.63%) and pregnancy induced hypertension 111 (18.23%). Other prevalent causes were oligohydramnios, multiple pregnancies, antepartum hemorrhage, polyhydramnios, fetal distress, gestational diabetes mellitus, and cervical incompetence.

**Conclusion:** Prematurity is the main cause for admissions in newborn care unit. Modifiable risk factors have to be considered and counseling should be started from adolescent period. High-risk pregnancy and preterm babies have to be referred timely, and timely interventions have to be done.

**Key words:** Anemia, Etiology, Pregnancy induced hypertension, Preterm, Preterm premature rupture of membrane, Risk factors

## INTRODUCTION

The World Health Organization defines preterm birth as birth before 37 completed weeks. Each year 15 million babies are born preterm worldwide.<sup>1</sup> South Asia and sub-Saharan Africa account for almost two-thirds of the world's preterm babies. India is the biggest

contributor to the world's prematurity burden. According to the WHO fact sheet 2013, India has 35, 19,100 preterm birth. It is around 23.6% of the total 15 million world preterm birth.

Antenatal steroids, thermoregulation, good respiratory support (in the form of nasal oxygen, continuous positive airway pressure, and ventilator care), hygienic practices, feeding support, intravenous fluid, inotrope support antibiotics, parenteral nutrition, kangaroo mother care, and surfactant are claimed for the important improvements in today's neonatal care, diagnostic modalities such as portable X-ray, neurosonogram, echocardiography, and ultrasonography also plays a key role in early diagnosis and treatment of preterm complication.

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In spite of intensive neonatal care, immaturity at birth has lifelong impact on various systems. The babies may have feeding difficulty, temperature instability, hypoglycemia, infection, respiratory distress syndrome, bronchopulmonary dysplasia, apnea of prematurity, jaundice, necrotizing enterocolitis, gastroesophageal reflux, patent ductus arteriosus, retinopathy of prematurity, germinal matrix hemorrhage, intraventricular hemorrhage, periventricular leukomalacia, and anemia of prematurity. Moreover, the adverse long-term outcomes were motor disability, cognitive difficulties, attention deficit hyperactivity disorder, and long-term respiratory consequences such as asthma and bronchitis.<sup>2</sup>

In India, there is a high incidence of preterm labor. The etiology of preterm labor is multifactorial. The major cause is preterm premature rupture of membranes (PPROM). Other causes of preterm labor are uteroplacental insufficiency, intra uterine vascular lesions, uterine over distension (due to multiple gestation and polyhydromnias), and cervical incompetence.<sup>3,4</sup>

This study is done to find out the incidence of preterm birth, causative risk factors for preterm labor and to study preterm complication such as respiratory distress syndrome, intraventricular hemorrhage, and retinopathy of prematurity in our institute.

## MATERIALS AND METHODS

This study was conducted at rural tertiary care center neonatal intensive care unit (NICU). This was a retrospective study conducted for 1 year from September 2015 to august 2016. The study population included newborn babies admitted in NICU admitted with gestational age <37 weeks. The study excludes babies with gestational age more than 37 weeks.

The data were collected from admitted preterm babies' medical records and nominal registers from our NICU. Details such as gestational age, weight, and duration of hospital stay were reviewed. Maternal risk factors leading to preterm labor such as preterm premature rupture of membrane (PPROM), pregnancy-induced hypertension (PIH), antepartal hemorrhage (APH), fetal distress, multiple pregnancy, polyhydromnias, oligohydromnias, gestational diabetic mellitus, and cervical incompetence were analyzed. The prevalence of anemia among women with preterm labor was studied.

## RESULTS

During the study period, 2156 total cases were admitted in NICU. Out of the total 2156 cases, 1536 were inborn (71.24%) and 620 (28.76%) were out born. Among the total 2156 admissions 609 (28.25%) were preterm babies. Among the 609 total preterm admissions 461 (75.70%) were inborn and 148 (24.30%) were out born preterm (Table 1).

Out of the total 609 preterm admissions, 260 were <34 weeks. This contributes 12.06% of total newborn admission. 349 were late preterm (gestational age 34-37 weeks). This contributes 16.19 % of total newborn admission (Table 2).

The etiology of preterm birth is multifactorial. Prevalent causes of prematurity were anemia 173 (28.41%), PPRM 150 (24.63%) and PIH 111 (18.23%). Other prevalent causes were oligohydromnios 80 (13.14%), multiple pregnancy 57 (9.36%), APH 28 (4.60%), polyhydromnios 12 (1.97%), fetal distress 11 (1.81%), gestational diabetes mellitus (GDM) 9 (1.48%), and cervical incompetence 6(1%) (Table 3).

**Table 1: Admission patterns in NICU month wise**

Month from September 2015 To August 2016	Total admission	Inborn admission	Outborn admission	Total preterm admission	Inborn preterm admission	Outborn preterm admission	Percentage of preterm admission among total admission
September	197	139	58	46	35	11	23.35
October	193	139	54	47	40	7	24.35
November	192	134	58	56	43	13	29.17
December	168	119	49	46	34	12	27.38
January	141	108	33	46	34	12	32.62
February	195	140	55	72	58	14	36.92
March	179	135	44	58	44	14	32.40
April	184	124	60	58	40	18	31.52
May	179	120	59	40	29	11	22.35
June	178	130	48	50	39	11	22.09
July	169	121	48	49	36	13	28.99
August	181	127	54	41	29	12	22.65
Total	2156	1536	620	609	461	148	28.25

NICU: Neonatal intensive care unit

**Table 2: Admission of preterm according to gestational age**

Month from september 2015 To August 2016	No and percentage of preterm admitted with gestational age<34 weeks	No and percentage of preterm admitted with gestational age 34-37 weeks	Total preterm admission and percentage of preterm admission among total admission
September	22 (11.17)	24 (12.18)	46 (23.35)
October	24 (12.43)	23 (11.92)	47 (24.35)
November	24 (12.50)	32 (16.67)	56 (29.17)
December	20 (11.90)	26 (15.48)	46 (27.38)
January	19 (13.47)	27 (19.15)	46 (32.62)
February	36 (18.46)	36 (18.46)	72 (36.92)
March	23 (12.85)	35 (19.55)	58 (32.40)
April	19 (10.33)	39 (21.19)	58 (31.52)
May	15 (8.38)	25 (13.97)	40 (22.35)
June	19 (8.39)	31 (13.70)	50 (22.09)
July	16 (9.47)	33 (19.52)	49 (28.99)
August	23 (12.71)	18 (9.94)	41 (22.65)
Total	260 (12.06)	349 (16.19)	609 (28.25)

**Table 3: Various etiology of preterm labor**

Month from September 2015 to August 2016	Anemia	PPROM	PIH	Oligo hydromnios	Multiple pregnancy	APH	Poly hydromnios	Fetal distress	GDM	Cervical incompetence
September	12	9	8	5	9	1	0	1	1	0
October	11	10	12	6	2	5	1	0	0	0
November	15	15	10	9	9	1	0	2	0	0
December	13	11	8	9	4	3	0	1	1	0
January	11	12	6	6	3	3	4	2	1	2
February	20	19	10	5	6	2	2	1	3	1
March	11	12	12	10	4	1	0	0	1	1
April	12	10	9	5	2	2	0	1	0	0
May	15	10	6	7	2	3	1	2	1	0
June	22	15	15	5	6	2	0	1	0	0
July	17	14	8	8	8	2	3	0	1	0
August	14	13	7	5	2	3	1	0	0	2
Total	173	150	111	80	57	28	12	11	9	6
Percentage	28.41	24.63	18.23	13.14	9.36	4.60	1.97	1.81	1.48	1.00

PIH: Pregnancy induced hypertension, PPROM: Preterm premature rupture of membranes, APH: Antepartal hemorrhage, GDM: Gestational diabetes mellitus

## DISCUSSION

In this study, preterm admissions constituted 609 (28.25%) among the total 2156 admissions for 1-year period. Our preterm admission rate is more than the 23.8% (86 preterm admission among total 361 admission) reported by Shah *et al.*,<sup>5</sup> who conducted study at a tertiary care center in eastern Nepal from January 2012 to December 2012. Moreover, this is more than the 24% (152 preterm admission among 634 total admissions) reported by Kunle-Olowu *et al.*,<sup>6</sup> of Nigeria. In his study, the study period was three years (January 2010 to December 2012).

In our study, the most common risk factors for prematurity was anemia 173 (28.41%), PPROM 150 (24.63%), and PIH 111 (18.23%). In a retrospective study for 1 year 2012-2013 done by Chowdarareddy *et al.*,<sup>7</sup> of Bangalore, out of 58 preterm babies the main risk factors for preterm delivery were anemia 30 (51.7%) and PIH 15 (25.86%).

In our study, incidence of preterm premature rupture of membrane was 150 (24.63%). This is similar to findings by

Uma *et al.*,<sup>8</sup> of Lucknow (2007) who reported that preterm premature rupture of membrane was associated with 25.9% preterm birth. Von der Pool<sup>9</sup> also reported that 30% of preterm births are associated with rupture of membrane.

PIH is the third main cause for the prematurity. This is similar to studies from other authors in Nigeria,<sup>10</sup> Nepal<sup>11</sup> and Thailand.<sup>12</sup>

Other prevalent causes were oligohydromnios 80 (13.14%), multiple pregnancy 57 (9.36%), APH 28 (4.60%), polyhydromnios 12 (1.97%), fetal distress 11 (1.81%), GDM 9 (1.48%), and cervical incompetence 6(1%).

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# Serum High-sensitive C-reactive Protein and Insulin Resistance in Patients with Type 2 Diabetes Mellitus with Coronary Artery Disease

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## Abstract

**Introduction:** Patients with Type 2 diabetes mellitus (DM) are characterized by insulin resistance (IR) and a low-grade inflammation, which is reflected by the levels of serum high-sensitive C-reactive protein (hsCRP). A single hsCRP measurement is a strong predictor of myocardial infarction, stroke, peripheral vascular disease, and sudden cardiac death, in individuals without a history of heart disease.

**Aim:** The aim of this study was to assess the correlation between serum hsCRP levels with IR (homeostasis model assessment-IR [HOMA-IR]) and various biochemical parameters such as fasting and postprandial plasma glucose, hemoglobin A1c (HbA1c), lipid profile (serum triglycerides, total cholesterol, high-density lipoprotein cholesterol [HDL-c], and calculated low density lipoprotein cholesterol [LDL-c]) in controls, patients with Type 2 DM without coronary artery disease (CAD), and patients with Type 2 DM with CAD.

**Materials and Methods:** Totally 150 patients with diabetes and 50 controls were included in the study. hsCRP was estimated with Latex turbidimetry method and IR was estimated by calculating HOMA-IR. Descriptive statistical analysis was done by one-way ANOVA *F*-test for *P*-value. *P*=0.05 was considered statistically significant. The comparison of levels of each parameter among the various groups was analyzed by Bonferroni *t*-test. Chi-square test was done to analyze the male:female ratio in various groups. Karl Pearson's correlation coefficient was used to analyze the correlation between various parameters.

**Results:** Serum hsCRP level was increased in patients with Type 2 DM when compared with controls. In patients with Type 2 DM with CAD, the serum hsCRP level was increased when compared with those without CAD. There was, however, a fair, positive correlation between hsCRP and IR, HbA1c, serum triglycerides, total cholesterol, and LDL-c, and a moderate negative correlation with HDL-c in Type 2 DM.

**Key words:** Coronary artery disease, Insulin resistance, Serum high-sensitive C-reactive protein, Type 2 diabetes mellitus

## INTRODUCTION

Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia.<sup>1</sup>

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy. The two broad categories of DM are designated Type 1 and Type 2.<sup>1</sup>

Type 1A DM results from autoimmune beta-cell destruction, which leads to insulin deficiency. Individuals with Type 1B DM lack immunologic markers indicative of an autoimmune destructive process of the beta-cells. However, they develop insulin deficiency by unknown mechanisms and are ketosis prone. Relatively, few patients with Type 1 DM are in the Type 1B idiopathic category; many of these individuals are either African-American or Asian in heritage.<sup>1</sup>

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Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance (IR), impaired insulin secretion, and increased glucose production.<sup>1</sup>

The worldwide prevalence of DM has risen dramatically over the past two decades. Likewise, the prevalence rates of impaired fasting glucose are also increasing. Although the prevalence of both Type 1 and Type 2 DM is increasing worldwide, the prevalence of Type 2 DM is expected to rise more rapidly in the future because of increasing obesity and reduced activity levels.<sup>1</sup>

Patients with Type 2 DM show a 2- to 5-fold increase in coronary heart disease (CAD).<sup>2</sup> Both Type 2 DM and CAD are characterized by low-grade inflammation and IR.<sup>3,4</sup> Serum high-sensitive C-reactive protein (hsCRP) reflects low-grade inflammation.<sup>5</sup>

Serum hsCRP is increased in obese<sup>6</sup> and diabetic patients.<sup>7-9</sup> It predicts the onset of cardiovascular disease.<sup>5,10-12</sup>

With this background, the present study titled, “serum hsCRP and Insulin Resistance Levels in Patients with Type 2 Diabetes Mellitus with Coronary Artery Disease” was taken up.

## IR

IR is defined as a decreased biological response to normal concentration of circulating insulin.<sup>13</sup> It is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle, and liver cells. It is found in both obese non-diabetic individuals and patients with Type 2 DM. There is a broad clinical spectrum of IR, ranging from euglycemia (with marked increase in endogenous insulin) to hyperglycemia despite the large doses of exogenous insulin.<sup>14</sup>

### Measurement of IR

Measurement of IR in a routine clinical setting is difficult and needs surrogate methods, namely fasting insulin concentration or the euglycemic insulin clamp to provide an indirect assessment of insulin function.<sup>14</sup>

Simple fasting methods to measure IR, such as the homeostasis model assessment (HOMA), fasting glucose/insulin ratio (FGIR), and Quantitative Insulin Sensitivity Check Index (QUICKI) methods, have been widely promoted.<sup>15</sup>

The first is the HOMA, and a more recent method is the QUICKI. Both employ fasting insulin and glucose levels to calculate IR and both correlate reasonably with the results

of clamping studies.<sup>16</sup> A simpler tool such as HOMA is more appropriate for large epidemiologic studies and is more reliable than FGIR and QUICKI methods.<sup>15</sup>

## CRP

Tillet and Francis in 1930 described a substance that was present in the sera of acutely ill patients and able to bind the cell wall C-polysaccharide of *Streptococcus pneumoniae*. In 1941, the substance was shown to be a protein and given the name CRP.<sup>14</sup>

CRP was subsequently shown to be an acute-phase reactant and important in the non-specific host defense against inflammation, especially in infections. Routinely used methods for CRP estimation have a detection limit of 3-8 mg/L.<sup>14</sup>

CRP consists of five identical, non-glycosylated polypeptide subunits non-covalently linked to form a disk-shaped polymer with a molecular weight of about 115 kDa (Figure 1). It contains little or no carbohydrate and is synthesized in the liver. Its production is controlled by interleukin-6.<sup>14</sup>

Each of the five subunits of CRP contains one binding site for a phosphatidylcholine molecule and two binding sites for calcium. These binding sites allow CRP to recognize and bind to a variety of biologic substrates, including phosphatidylcholine and phospholipids, components of damaged cell walls, chromatin and nuclear antigens, polysaccharides present in many bacteria, fungi, and protozoal parasites, resulting in the formation of CRP-ligand complexes. CRP-ligand complexes can activate the complement system, thereby facilitating phagocytosis and the removal of materials released from damaged cells as well as potentially toxic materials from invading microorganisms. CRP-ligand complexes also bind directly to neutrophils, macrophages, and other phagocytic cells,

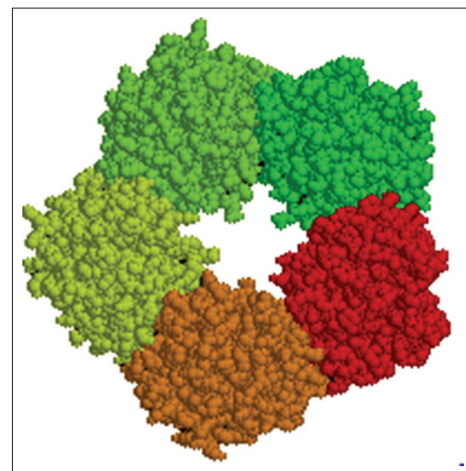


Figure 1: Structure of C-reactive protein

stimulating an inflammatory response and the release of cytokines.

The key functions of CRP within the innate immune system include the ability to:

1. Recognize and bind to phosphatidylcholine exposed in damaged cell walls and found in many bacteria, fungi, and parasites.
2. Act like an opsonin, marking bacteria, damaged cell walls, and nuclear debris for phagocytosis.
3. Bind to C1, the first component of the classical pathway of the complement system that triggers phagocytic activity.
4. Bind to polymorphonuclear leukocytes and monocytes, which stimulate the production of inflammatory cytokines.

Serum CRP concentrations are positively associated with a risk of future coronary events such as CAD.<sup>14</sup> The use of CRP for this purpose requires the use of hsCRP assays having detection limits <0.3 mg/L. A number of automated immunoturbidimetric and immunonephelometric assays are commercially available for sensitive and precise measurement of low concentrations of CRP.<sup>14</sup>

A single hsCRP measurement is a strong predictor of myocardial infarction,<sup>10,11,17,18</sup> stroke,<sup>10,11,18</sup> peripheral vascular disease,<sup>19,20</sup> and sudden cardiac death,<sup>21</sup> in individuals without a history of heart disease. The association between hsCRP and future vascular events is linear and is independent of age, smoking, hypertension, dyslipidemia, and diabetes.<sup>14</sup>

Serum hsCRP value <1 mg/L is considered as low risk, 1-3 mg/L is considered as intermediate risk, and >3 mg/L as high risk for primary prevention of atherosclerosis. Recent data suggest that using hsCRP value with the calculated low density lipoprotein (LDL) is a potent way to predict the risk.<sup>14</sup>

### Aim of the Study

The study was taken up after reviewing various literatures on serum hsCRP and IR in Type 2 DM and in CAD. The aim of the study is to assess the following:

1. To assess the levels of serum hsCRP and IR measured as HOMA-IR in controls, patients with Type 2 DM without CAD, and patients with Type 2 DM with CAD.
2. To assess the correlation between serum hsCRP levels and IR (HOMA-IR) in controls, patients with Type 2 DM without CAD, and patients with Type 2 DM with CAD.
3. To assess the correlation between serum hsCRP levels and various biochemical parameters such as

fasting and postprandial plasma glucose, hemoglobin A1c (HbA1c), lipid profile (serum triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-c), and calculated LDL-cholesterol [LDL-c]) in controls, patients with Type 2 DM without CAD, and patients with Type 2 DM with CAD.

## MATERIALS AND METHODS

### Study Population

The study was carried out in a total of 160 patients which included 110 patients with Type 2 DM and 50 controls.

For the DM group, patients with Type 2 DM were selected. The patients with DM were further categorized as those without CAD (normal electrocardiogram/treadmill test negative)  $n = 48$  (Group 1) and those with CAD (coronary angiogram-proven cases)  $n = 62$  (Group 2). The mean age of the DM group was 50.8 years.

For the control group (Group 0), age- and sex-matched apparently healthy controls were selected. The mean age of the controls was 49.4 years.

### Inclusion Criteria

The minimum duration of diabetes was 5 years in all patients with Type 2 DM. The patients were on oral hypoglycemic treatment.

### Exclusion Criteria

Patients who were on treatment with insulin and/or thiazolidinediones were excluded from the study.

Patients who had liver disorders, hepatitis, cirrhosis, renal failure, inflammatory disorder, or malignancy were also excluded from the study.

### Protocol of the Study

The patients were clinically examined, and height and weight measurements were recorded. Blood pressure was also recorded. The body mass index was calculated from the height and weight measurements using the following formula:

$$\text{Body mass index} = \frac{\text{Weight in kilograms}}{\text{Height in metre}^2}$$

Fasting blood samples were collected in three different tubes - plain tube, one containing 1% ethylenediaminetetraacetic acid (EDTA) and one containing sodium fluoride-potassium oxalate mixture (1:3). 2 h post-prandial blood samples were collected in tubes containing sodium fluoride-potassium oxalate mixture. Spot urine was collected for the estimation of urine microprotein.



Plasma was separated from fasting, and post-prandial blood samples collected in sodium fluoride-potassium oxalate tubes and were used for estimating plasma glucose immediately. Serum was separated from fasting blood samples collected in the plain tubes and divided into two parts. One part of the serum was used for estimating hsCRP, urea, creatinine, total cholesterol, HDL-c, and triglycerides immediately. The other part of the serum was stored at -20°C and was used for the estimation of insulin by enzyme-linked immunosorbent assay (ELISA) method. The ELISA procedure was carried out within 30 days of sample collection. HbA1c was estimated using blood collected in EDTA tubes.

### Estimation of Serum Insulin

#### Methodology

ELISA method using Insulin ELISA kit from DiaMetra was used for measuring serum insulin.

#### Instrument

Triturus analyzer - an open-system automatic ELISA analyzer.

### Estimation of Serum hsCRP

#### Methodology

Latex turbidimetry method for quantitative determination of hsCRP (low levels of CRP) in serum or plasma.

### Estimation of Plasma Glucose

**Kit used:** Erba Mannheim XL Systems Packs

**Method:** Glucose oxidase-peroxidase method - 1-point assay.

### Estimation of HbA1c

**Kit used:** Diatek glycohemoglobin

**Method:** Ion exchange resin method.

### Estimation of Urea

**Kit used:** Erba Mannheim XL Systems Packs

**Method:** Urease - GLDH method.

### Estimation of Serum Creatinine

**Kit used:** Erba Mannheim XL Systems Packs

**Method:** Modified Jaffe's method.

### Estimation of Serum Triglycerides

**Kit used:** Erba Mannheim XL Systems Packs

**Method:** Enzymatic method, end point.

### Estimation of Serum Total Cholesterol

**Kit used:** Erba Mannheim XL Systems Packs

**Method:** Enzymatic method.

### Estimation of Serum HDL-c

**Kit used:** Erba Mannheim XL Systems Packs

**Method:** Immuno-inhibition method.

### Determination of LDL-c

LDL-c was determined using Friedewald's formula:

$$\text{LDL-c} = \text{Total cholesterol} - (\text{HDL-c} + \text{VLDL-c})$$

$$\text{VLDL-c} = \frac{\text{Triglycerides}}{5}$$

### Determination of HOMA-IR

$$\text{HOMA-IR} = \frac{\text{Serum insulin } (\mu\text{IU} / \text{mL}) \times \text{Plasma Glucose } (\text{mmol} / \text{L})}{22.5}$$

### Estimation of Urine Microprotein

#### Method

Urine microprotein was estimated in spot urine sample by Pyrogallol Red microprotein kit method in semi-automated analyzer.

## RESULTS AND STATISTICAL ANALYSIS

The mean and standard deviation for the various parameters evaluated, namely, BMI, fasting plasma glucose, post-prandial plasma glucose, HbA1c, blood urea, serum creatinine, lipid profile, serum hsCRP, fasting serum insulin, HOMA-IR, and urine microprotein in the entire study population, in the controls (Group 0), in patients with Type 2 DM without CAD (Group 1), in patients with Type 2 DM with CAD (Group 2) is presented in Table 1.

Descriptive statistical analysis was done by one-way ANOVA *F*-test for *P*-value. The comparison of levels of each parameter among the various groups was analyzed by Bonferroni *t*-test. Chi-square test was done to analyze the male:female ratio in various groups. Karl Pearson's correlation coefficient was used to analyze the correlation between various parameters. *P* = 0.05 was considered statistically significant.

## DISCUSSION

One-way ANOVA *F*-test was used to analyze whether the three groups were age matched. The mean age of the control group (Group 0) was  $49.92 \pm 5.749$  years. For the group composed of patients with Type 2 DM without CAD (Group 1), it was  $50.94 \pm 5.61$  years, and in the group composed of patients with Type 2 DM with CAD, it was  $51.79 \pm 3.44$  years. All the three groups were found to be age matched (*P* = 0.14).

Similarly, Chi-square test was performed to find any difference in the male:female composition among the

three groups. It was found that the three groups were sex matched ( $P = 0.98$ ).

The mean BMI in control group was  $24.26 \pm 1.37 \text{ kg/m}^2$ , in Group 1, it was  $24.26 \pm 2.08 \text{ kg/m}^2$ , and in Group 2, it was  $26.54 \pm 2.35 \text{ kg/m}^2$ . The control group and Group 1 were found to be similar as far as BMI was concerned. Group 2 patients had a significantly higher BMI when compared to the other groups.

One-way ANOVA  $F$ -test and multiple comparison Bonferroni  $t$ -test were used to analyze the serum hsCRP and IR levels among the three groups.

The mean serum hsCRP level of Group 1 ( $5.742 \pm 1.8 \text{ mg/L}$ ) and Group 2 ( $6.803 \pm 1.929 \text{ mg/L}$ ) was found to be increased when compared to the control group ( $2.714 \pm 0.712 \text{ mg/L}$ ) and it was statistically significant ( $P = 0.001$ ) (Table 2).

A single hsCRP measurement is a strong predictor of myocardial infarction.<sup>17-20</sup> Serum hsCRP value  $<1 \text{ mg/L}$  is considered as low risk,  $1-3 \text{ mg/L}$  is considered as intermediate risk, and  $>3 \text{ mg/L}$  as high risk for primary prevention of atherosclerosis.<sup>14</sup> Thus, patients with DM (Group 1 and 2) were found to be at a high risk for coronary heart disease. The Group 2 patients had significantly higher hsCRP levels than Group 1 patients.

IR as measured by HOMA-IR was found to be significantly increased in Group 1 and Group 2 when compared with the control group. When Group 1 and Group 2 were compared, Group 2 had significantly higher IR ( $P = 0.001$ ) (Table 3).

In the control group, serum hsCRP had a significant positive correlation with HbA1c. However, serum hsCRP levels showed a poor correlation with plasma glucose levels and lipid profile.

**Table 1: Mean value of parameters among the various groups**

Parameter	Control	Overall Type 2 DM	Type 2 DM without CAD	Type 2 DM with CAD
Age (years)	49.92±5.75	51.42±3.48	50.94±5.61	51.79±3.44
Male:female ratio	28:22	60:50	26:22	34:28
Duration of diabetes (years)	-	8.74±2.89	8.33±3.15	9.05±2.98
Body mass index (kg/m <sup>2</sup> )	24.26±1.37	25.54±2.16	24.26±2.08	26.54±2.35
Fasting plasma glucose (mg/dL)	90.80±5.71	153.16±36.09	152.38±44.92	153.77±42.54
Post-prandial plasma glucose (mg/dL)	134.68±6.11	218.29±56.28	215.38±69.11	220.55±64.41
HbA1c (%)	5.26±0.46	8.30±1.52	7.90±1.87	8.62±1.45
Blood urea (mg/dL)	28.56±5.86	27.77±7.58	28.85±7.10	26.94±7.73
Serum creatinine (mg/dL)	0.96±0.14	1.00±0.19	0.98±0.15	1.01±0.17
Serum triglycerides (mg/dL)	134.66±48.93	162.91±54.40	150.94±34.56	172.18±53.80
Serum total cholesterol (mg/dL)	172.66±21.25	203.46±67.10	182.69±51.82	219.55±65.37
Serum HDL-c (mg/dL)	44.82±6.07	39.87±7.63	42.27±6.36	38.02±7.66
Serum LDL-c (mg/dL)	100.91±24.02	131.01±65.37	110.23±49.42	147.10±63.57
Serum hsCRP (mg/L)	2.71±0.71	6.34±2	5.74±1.81	6.80±1.93
Serum insulin (μIU/mL)	8.85±1.20	8.80±2.39	8.36±2.90	9.15±2.33
HOMA-IR	1.99±0.34	3.20±1.21	2.91±0.68	3.43±1.21
Urine microprotein (mg/dL)	23.48±6.49	24.92±14.58	25.29±18.68	24.63±16.37

hsCRP: High-sensitive C-reactive protein, DM: Diabetes mellitus, CAD: Coronary artery disease, HOMA-IR: Homeostasis model assessment-insulin resistance, HbA1c: Hemoglobin A1c, HDL-c: Highdensity lipoprotein-cholesterol, LDL-c: Lowdensity lipoprotein-cholesterol

**Table 2: Serum hsCRP levels among the various groups**

Parameter	Group	N	Mean	Standard deviation	One-way ANOVA $F$ -test	Multiple comparison Bonferroni $t$ -test
Serum hsCRP mg/L	0	50	2.714	0.7126	$F=93.48$ , $P=0.001$	0 versus 1, 2, 1 versus 0, 2
	1	48	5.742	1.8058		
	2	62	6.803	1.929		
	Total	160	5.207	2.3627		

hsCRP: High-sensitive C-reactive protein

**Table 3: IR among the various groups**

Parameter	Group	N	Mean	Standard deviation	One-way ANOVA $F$ -test	Multiple comparison Bonferroni $t$ -test
HOMA-IR	0	50	1.99	0.3406	$F=39.41$ $P=0.001$	0 versus 1, 2 1 versus 0, 2
	1	48	2.908	0.6758		
	2	62	3.434	1.2069		
	Total	160	2.825	1.0468		

HOMA-IR: Homeostasis model assessment-insulin resistance

IR as calculated by HOMA-IR in the control group had a significantly positive correlation with BMI, fasting plasma glucose, serum triglycerides, total cholesterol, and LDL-c, and a significantly negative correlation serum HDL-c.

In the Group 1, serum hsCRP had significantly positive correlation with serum triglycerides and IR. There was a poor correlation between serum hsCRP and BMI, plasma glucose levels, HbA1c, total cholesterol, HDL-c, and LDL-c.

IR in the Group 1 had a significantly positive correlation with HbA1c and serum hsCRP.

In the Group 2, serum hsCRP had significantly positive correlation with HbA1c, serum triglycerides, total cholesterol, LDL-c, and IR, and a significant negative correlation with serum HDL-c. However, there was a poor correlation between serum hsCRP and BMI, fasting and post-prandial plasma glucose levels.

IR in the Group 2 had a significantly positive correlation with BMI, fasting and post-prandial plasma glucose, HbA1c, serum triglycerides, total cholesterol, LDL-c, and hsCRP, and a significantly negative correlation with HDL-c.

## CONCLUSION

From the analysis of the data, the following conclusions were made:

1. Serum hsCRP level was increased in patients with Type 2 DM when compared with controls. In patients with Type 2 DM with CAD, the serum hsCRP level was increased when compared with those without CAD.
2. Serum hsCRP correlated poorly with IR in the controls. There was, however, a fair, positive correlation between hsCRP and IR in Type 2 DM.
3. Serum hsCRP was poorly correlated with plasma glucose levels and lipid profile parameters in the control group. In the patients with Type 2 DM, serum hsCRP had a positive correlation with HbA1c, serum triglycerides, total cholesterol, and LDL-c, and a moderate negative correlation with HDL-c.

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# Evaluation of Thyroid Profile in Gestational Diabetes Mellitus

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## Abstract

**Introduction:** Gestational diabetes mellitus (GDM) is when women without diabetes develop high blood sugar level during pregnancy.

**Materials and Methods:** This study comprised 100 patients with GDM selected from Obstetrics and Gynaecology Department of Rajendra Institute of Medical Sciences, Ranchi. All these patients were clinically euthyroid at the time of assessment and there was no history of thyroid disorder.

**Results:** Highest serum thyroid stimulating hormone value is 26.0 (μIU/ml) and lowest values <0.2 (μIU/ml) among GDM patients. Highest values of free T4 is 15.0 (μg/dl) and lowest value is 0.30 (μg/L). Value of glycosylated hemoglobin in gestational diabetes is in the range of 4.4-12.8% which is statistically significant. 100 GDM patients were studied. 19% patients had raised thyroid hormone, 23% had low level, and 58% patients were euthyroid.

**Conclusion:** The incidence of hypothyroidism is more in GDM compared to hyperthyroidism.

**Key words:** Gestational diabetes mellitus, Hypothyroidism, Thyroid stimulating hormone

## INTRODUCTION

Gestational diabetes mellitus (GDM) is when women without diabetes develop high blood sugar level during pregnancy.<sup>1</sup> It increases the risk of preeclampsia, depression, and requiring a cesarean section. Babies born to mother with poorly treated GDM are at increased risk of being too large, having hypoglycemia, and jaundice. If untreated can result in still birth. Children are higher risk of being overweight and developing Type 2 diabetes in later life.<sup>1</sup> GDM affects 3-9% of pregnancies depending on the population studied.<sup>2</sup> It affects 1% of those under the age of 20 and 13% of those over the age of 44. Diabetes and thyroid disease are two common endocrine disorders observed in the adult population with insulin and thyroid

being intimately involved in cellular metabolism and thus excess or deficit of either of these hormone could result in functional derangement of the other.

In euthyroid individuals with diabetes mellitus the serum T3 levels, basal thyroid stimulating hormone (TSH) level, and TSH response to thyrotropin releasing hormone (TRH) may all be influenced by glycemic status.<sup>3</sup> Poorly controlled diabetes may also result in impaired TSH response to TRH or loss of normal nocturnal TSH peak. TSH response may be normalized with improvement in glycemic status but even with good diabetic control the normal nocturnal TSH peak may not be restored in C-peptide negative patients, i.e., those with totally absent pancreatic beta-cell function.<sup>4</sup>

## MATERIALS AND METHODS

Our study comprised 100 patients with GDM selected from Obstetrics and Gynecology Department of Rajendra Institute of Medical Sciences, Ranchi. These patients were both insulin dependent and insulin independent diabetic being treated either by insulin injection or oral sulfonylurea drugs. Patients with clinical and biochemical evidence of

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hepatic or renal dysfunction as well as those with other significant diabetic complications were excluded from the study. All those patients were clinically euthyroid at the time of assessment and had no history of suggestive disease.

### Blood Glucose Estimation

Fasting blood was collected with a caution to avoid any hemolysis. Glucose estimation was done by glucose oxidase/peroxidase method.

### Calculation:

$$\text{Total glucose in mg/dl} = \frac{\text{Absorbance of the test sample}}{\text{Absorbance of the standard}} \times 100$$

Thyroid function test will be done by enzyme-linked immunosorbent assay method.

Quantitative determination of glycosylated hemoglobin in blood by ion exchange resin method.

## RESULTS

1. Blood sugar level in GDM. Blood sugar level (mg/dl)

GDM	Fasting		2 h postprandial	
	Range	Mean±SD	Range	Mean±SD
Diabetes	100-200	124.57±27.77	130-330	162.5±34.24

SD: Standard deviation

Highest fasting blood sugar level was 210 mg/dl and highest postprandial was 330 mg/dl.

2. Serum TSH in GDM was in the range of 0.10-26.0 (μIU/ml) mean 5-34 (Figure 2)
3. Serum T4 in GDM was in the range of 0.50-14.2 (μg/dl) mean was 7.41 (μg/dl)
4. Serum T3 in GDM was in the range of 30-280 (μg/dl) mean 121.20
5. Serum FT4 in GDM was in the range of 0.30-15.0 (μg/dl) mean 1.77 (μg/dl) (Figure 1)
6. Glycosylated hemoglobin in GDM was in the range of 4.4-12.8% mean 7.22%
7. 100 GDM patients were studied. 19 patients had raised thyroid hormone, 23 patients had low level, and 58 patients were euthyroid.

## DISCUSSION

GDM occurs in 2-9% of all pregnancies<sup>5,6</sup> and associated with substantial rates of maternal and paternal complications. The risk of perinatal mortality is not increased but the risk of macrosomia is high. Other perinatal risks include

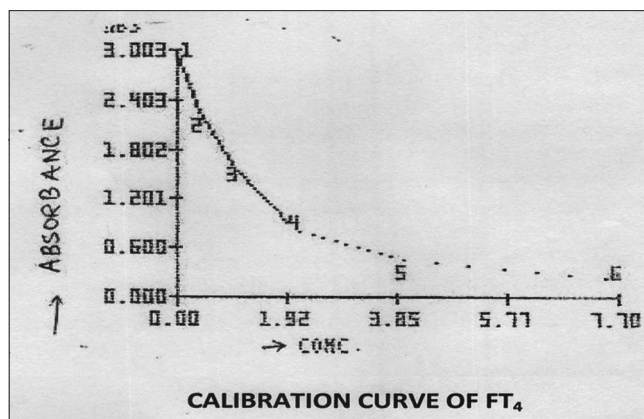


Figure 1: Calibration curve of FT<sub>4</sub>

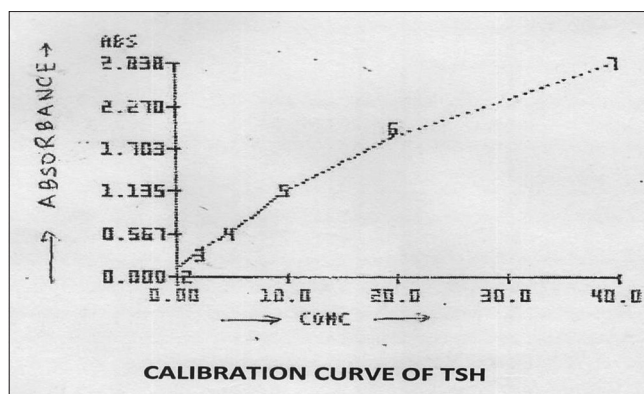


Figure 2: Calibration curve of thyroid stimulating hormone

shoulder dystocia, birth injuries such as bone fractures, nerve palsies, and hypoglycemia. Gestational diabetes is strong risk factor for diabetes in later life.<sup>8</sup>

Overtly abnormal amounts of thyroid hormone either excessive because of Grave's thyrotoxicosis or deficient because of hypothyroidism can have profound effect on glucose metabolism and insulin secretion. The resulting increase insulin resistance, glucose intolerance, and dyslipidemia are usually reversible when normal thyroid hormone levels are restored.<sup>9-11</sup> It is well known that marked insulin resistance progressively increases with gestational age during pregnancy.<sup>12</sup> Because of similar effects of thyroid hormone and pregnancy on glucose metabolism, it seems reasonable to posit that women either abnormally high or low level of thyroid hormone would be more likely to develop gestational diabetes. In our study, patients with GDM were evaluated for the functional status of thyroid gland. Among 100 GDM patients investigated 42% had abnormal thyroid hormone level. These finding show a high incidence of abnormal thyroid hormone level (low or raised) in diabetic population. This observation is in agreement with report of Smithson.<sup>13,14</sup> Mean of serum T4 in GDM was 7.41 and SD ± 2.78. This finding is in accordance with Saunders *et al.*<sup>15</sup>

Glycosylated hemoglobin gives average blood glucose level of preceding 90 days. In uncontrolled or poorly control diabetes, there is an increase glycosylation of number of proteins including hemoglobin and  $\alpha$ -crystalline of lenses. During diabetes excess glucose present in blood reacts with hemoglobin.<sup>16</sup> In our study, the mean of glycosylated hemoglobin in GDM was 7.22%. Thyroid dysfunctions and autoantibodies in early pregnancy are associated with increased risk of GDM and adverse birth outcome.<sup>17</sup> Thyroid antibodies and subclinical hypothyroidism occur more frequently in pregnant women with insulin-dependent diabetes mellitus than in healthy pregnant women.<sup>18</sup>

## CONCLUSION

In our study, high incidence of abnormal thyroid hormone level was noted among GDM patients. Recent publications have confirmed that gestational diabetes is a disease with adverse perinatal outcome, and is susceptible to effective management. Hence, during pregnancy thyroid evaluation and blood sugar estimation should be included in antenatal routine investigations. Women with GDM should have an annual fasting glucose performed for life and referred for prepregnancy counseling if contemplating a further pregnancy.

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# Serum Fetuin-A in Chronic Kidney Disease: A Promising Biomarker to Predict Cardiovascular Risk

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## Abstract

**Introduction:** Chronic kidney disease (CKD) is associated with adverse sequelae of cardiovascular disease, renal failure, and premature death. The key factors that could contribute to the development of cardiovascular disease in patients with CKD include inflammation and vascular calcification. Serum fetuin-A, a  $\alpha_2$ -glycoprotein is a systemically acting inhibitor of extraskelatal calcification and is down regulated following inflammation.

**Purpose:** To estimate serum fetuin-A levels in patients with CKD and to analyze its relationship with inflammatory biomarkers and calcium-phosphorus levels.

**Materials and Methods:** A total of 80 patients with CKD and 80 healthy, age and gender matched controls were enrolled in the study. Serum levels of fetuin-A, high-sensitivity C-reactive protein (hsCRP), calcium, phosphorus, albumin, lipid profile, glucose, urea, and creatinine were measured.

**Results:** A significant reduction of serum fetuin-A levels were observed in patients with CKD (mean =  $0.4416 \pm 0.17$  g/L) when compared to controls (mean =  $0.7527 \pm 0.18$  g/L;  $P = 0.001$ ). Serum fetuin-A levels also showed a significant negative correlation with creatinine clearance, hsCRP and calcium-phosphorus product and a significant positive correlation with albumin levels ( $P < 0.01$ ).

**Conclusion:** In CKD, progressive reduction of serum fetuin-A levels occur along with the gradual decline in renal function. The reduced production and increased consumption of serum fetuin-A in CKD could promote vascular calcification and contribute to the cardiovascular disease. Hence, in patients with CKD, measurement of serum fetuin-A could be a promising biomarker to prognosticate cardiovascular risk.

**Key words:** Chronic kidney disease, Fetuin-A, High-sensitivity C-reactive protein, Inflammation, Vascular calcification

## INTRODUCTION

Chronic kidney disease (CKD) refers to an irreversible progressive deterioration in renal function.<sup>1</sup> It is a worldwide, chronic, noncommunicable disease epidemic with a prevalence of 0.79% in India.<sup>2</sup> CKD is frequently complicated by accelerated cardiovascular disease.

Over 80-90% of patients with CKD die primarily of cardiovascular disease before reaching the need for dialysis.<sup>3</sup> This emphasizes the importance of early detection of cardiovascular disease in CKD.

Alteration of mineral metabolism occurs in CKD and promotes vascular calcification which poses an increased risk of cardiovascular and all-cause mortality in patients with CKD.<sup>4</sup> CKD is also associated with chronic inflammation, which promotes endothelial dysfunction, vascular remodeling, and progression of atherosclerosis. Hence, an active interplay occurs between atherosclerosis, vascular calcification, and inflammation against a background of severe calcium-phosphorus disturbances in CKD, contributing to the development of cardiovascular disease.

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The serum protein fetuin was initially identified as the major globulin in calf and fetal serum by Pedersen in 1944. The human homolog was named fetuin-A/ $\alpha_2$ -heremans-schmid glycoprotein, after the two codiscoverers, Heremans and Schmid. During fetal development, fetuin-A is expressed in most organs including liver, kidney, gastrointestinal tract, skin, and brain. In adults, it is produced primarily by the hepatic parenchymal cells.<sup>5</sup> The human gene was mapped to the region 3q21-29 of chromosome 3.<sup>6</sup> It is a 59 kDa glycoprotein belonging to the cystatin superfamily of cysteine protease inhibitors. It has a binding site for calcium-phosphate near the N-terminus.<sup>7</sup> The serum fetuin-A concentration of adult humans ranges from 0.5 to 1 g/L.<sup>8,9</sup>

Fetuin-A is an anti-inflammatory protein that can attenuate the inflammatory responses. However, the expression of fetuin-A is negatively regulated by several pro-inflammatory cytokines which produces downregulation of its synthesis during inflammation; hence fetuin-A is regarded as a “negative acute phase reactant.”<sup>10</sup> Fetuin-A is also a systemic inhibitor of calcification and is present throughout the extracellular space. Approximately, 50% of calcification inhibitory capacity of the human plasma is contributed by fetuin-A. In the serum, fetuin-A stabilizes calcium and phosphate and prevents their precipitation by binding basic calcium phosphate (BCP).<sup>11,12</sup> Surface binding of calcium is mediated by the negative charges on the extended  $\beta$  sheet of the D1 domain of fetuin-A resulting in high affinity binding despite its relatively low serum concentration. Fetuin-A thus acts as a systemic inhibitor of pathological mineralization which complement the local inhibitors such as matrix-Gla protein and pyrophosphate that act in a cell/tissue-restricted fashion.<sup>13</sup>

Measurement of serum fetuin-A levels could, therefore, have potential value to predict vascular calcification and hence the cardiovascular risk in CKD. Hence, in this study, the serum levels of fetuin-A were estimated in patients with CKD and its relationship between inflammation and abnormalities in calcium-phosphorus levels were analyzed.

## MATERIALS AND METHODS

The study was conducted at a tertiary care hospital in South India after getting approval from the ethical committee. 80 patients (55 males and 25 females) were selected as cases from the outpatients and ward of the Department of Nephrology. 80 age and gender matched individuals from the general population without any history or clinical evidence of CKD were taken as the control group.

## Inclusion Criteria

1. Patients with established diagnosis of CKD
2. Age more than 18 years.

## Exclusion Criteria

Patients with acute or chronic inflammatory diseases, previous history of cerebrovascular diseases, acute kidney injury, nephrotic syndrome, malignancy, those who underwent renal transplant, and those on lipid lowering drugs, calcium/phosphate binders and on immunotherapy or immunosuppressive treatment were excluded from the study.

Informed consent was obtained from all subjects before the study. Blood samples were collected from them after an overnight fasting of 12 h. Under aseptic precautions, 5 ml of venous blood sample was collected and centrifuged. An aliquot of the serum (0.5 ml) was taken for the estimation of fetuin-A and stored at  $-20^{\circ}\text{C}$  in the deep freezer. The remaining serum was used for the estimation of glucose, urea, creatinine, calcium, phosphorus, high-sensitivity C-reactive protein (hsCRP), albumin, total cholesterol (TC), triglycerides (TGLs), and high-density lipoprotein (HDL).

Serum fetuin-A was estimated by enzyme immunoassay using the kit obtained from R & D systems, USA. Serum hsCRP was estimated by turbidimetric immunoassay. Serum glucose was estimated by glucose-oxidase/peroxidase method, urea by urease method, creatinine by modified Jaffe's method, albumin by bromocresol green dye binding method, calcium by Arsenazo method, phosphorus by ultra-violet molybdate method, TC by cholesterol-oxidase - PAP method, TGLs by GPO - PAP method, and HDL-cholesterol by phosphotungstate/magnesium precipitation method in XL 300 auto analyzer. Low-density lipoprotein (LDL) was calculated using Friedwald's formula. Creatinine clearance (CrCl) was calculated using Cockcroft-Gault formula.

## Statistical Analysis

Statistical analysis was done using SPSS software. The data were expressed in terms of mean and standard deviation. Student's *t*-test and Chi-square test were employed for the analysis of data.  $P < 0.05$  was taken as the significant value. Correlation between the measured parameters was assessed using Pearson's correlation coefficient.

## RESULTS

A total of 160 subjects were selected as the study group for this study. This included 80 cases with CKD and 80 healthy controls.



The mean values of serum fetuin-A and other estimated parameters of the study group are given in Table 1. Table 2 shows the gender matched comparison of serum fetuin-A levels in the study group which was statistically not significant. Table 3 shows the comparison of serum fetuin-A levels in various age groups in the study subjects. Serum fetuin-A levels were significantly lower in the cases than controls in all the included age groups. We further compared the parameters of CKD case group with CrCl values. Figures 1 and 2 show a gradual decline in Fetuin-A and CaxP levels, respectively, as the CrCl decreases. Figure 3 shows a gradual increase in hsCRP levels with the decrease in CrCl.

Table 4 shows the Pearson's coefficient of correlation between serum fetuin-A and the other studied biochemical parameters in the cases. There is a highly significant negative correlation of fetuin-A with hsCRP and CaxP ( $P < 0.01$ ) and a highly significant positive correlation of fetuin-A with CrCl and albumin ( $P < 0.01$ ) (Figures 4-7).

## DISCUSSION

Cardiovascular disease is the most frequent cause of death among people with CKD. The overall mortality rate in CKD from cardiovascular disease has been found to be about 30 times greater than that of general population.<sup>14</sup> The nontraditional risk factors of cardiovascular disease such as inflammation and vascular calcification accelerate the onset of cardiovascular complications in CKD.

Serum fetuin-A is regarded as a negative acute phase reactant which is down regulated following inflammation.

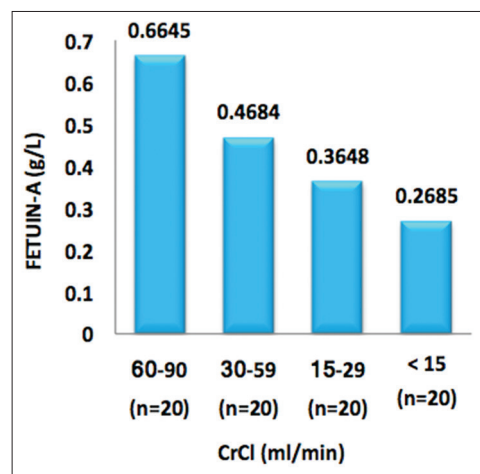
**Table 1: Descriptive statistics of the study group**

Parameters	Mean±SD	
	Controls (n=80)	Cases (n=80)
Age (years)	47.85±10.552	50.40±11.895
BMI (kg/m <sup>2</sup> )	24.561±2.700	21.942±4.163
Fetuin-A (g/L)	0.752±0.176	0.4416±0.170
Glucose (mg/dl)	91.05±9.657	103.67±23.098
Urea (mg/dl)	22.92±3.244	99.95±27.731
Creatinine (mg/dl)	0.841±0.082	3.068±2.153
CrCl (ml/min)	96.476±8.409	32.994±21.241
hsCRP (mg/L)	0.568±0.232	4.618±3.037
Calcium (mg/dl)	9.905±0.497	9.542±0.675
Phosphorus (mg/dl)	3.410±0.367	4.539±1.105
CaxP (mg <sup>2</sup> /dl <sup>2</sup> )	33.711±3.285	42.844±8.718
Albumin (g/dl)	4.005±0.332	3.208±0.432
TC (mg/dl)	173.575±14.501	175.375±16.343
TGL (mg/dl)	133.96±16.363	182.50±26.576
HDL (mg/dl)	41.72±3.368	38.03±5.202
VLDL (mg/dl)	26.792±3.272	36.500±5.315
LDL (mg/dl)	105.057±14.74	101.065±18.089

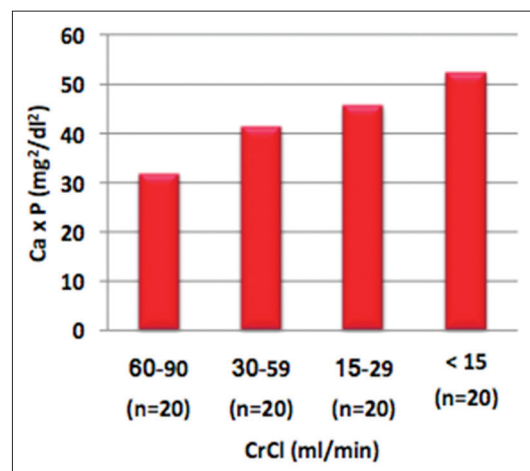
BMI: Body mass index, CrCl: Creatinine clearance, hsCRP: High sensitive C-reactive protein, CaxP: Calcium-phosphorus product, TC: Total cholesterol, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation

Further, fetuin-A has also been identified as a potent circulating inhibitor of systemic calcification by inhibition of calcium-phosphate precipitation. In this study, we estimated the levels of serum fetuin-A in patients with CKD and analyzed its relationship with inflammation and altered mineral metabolism.

Serum fetuin-A concentrations were found to be significantly decreased in patients with CKD (Mean =  $0.4416 \pm 0.17$  g/L) when compared to the control group (mean =  $0.7527 \pm 0.18$  g/L;  $P = 0.001$ ). Further, fetuin-A levels were found to be progressively decreased from Stage 2 (CrCl = 60-90 ml/min) to Stage 5 (CrCl <15 ml/min) of CKD. This shows that reduction in serum fetuin-A levels develop relatively in the early stages of CKD. These findings conform to those of the study of Caglar *et al.*, which reported a decrease in serum fetuin-A levels in all stages of CKD, except Stage 1.<sup>15</sup> Lower levels of serum fetuin-A were also reported in hemodialysis patients in the previous studies.<sup>16,17</sup>



**Figure 1: Comparison of serum fetuin-A levels in chronic kidney disease cases in relation to creatinine clearance**



**Figure 2: Comparison of serum CaxP levels in chronic kidney disease cases in relation to creatinine clearance**

**Table 2: Gender matched comparison of serum fetuin-A levels (g/L) in the study group**

Control			Study		
Male n=55	Female n=25	P value	Male n=55	Female n=25	P value
0.7112±0.16	0.8441±0.19	0.886*	0.4293±0.16	0.4686±0.19	0.661*

\*P>0.05 - Not significant

**Table 3: Age matched analysis of serum fetuin-A levels in the study group**

Age	Serum fetuin-A (g/L)			P value
	Groups	n	Mean±SD	
<30 years	Controls	3	0.7390±0.2211	P=0.007*
	Cases	3	0.6440±0.1187	
31-40 years	Controls	17	0.7532±0.1938	P=0.0001**
	Cases	17	0.4648±0.1518	
41-50 years	Controls	23	0.7932±0.1694	P=0.0001**
	Cases	23	0.4893±0.1871	
51-60 years	Controls	19	0.7598±0.1816	P=0.0001**
	Cases	19	0.3936±0.1187	
>60 years	Controls	18	0.6916±0.1618	P=0.0001**
	Cases	18	0.3667±0.1525	

\*P<0.05 - Significant, \*\*P<0.001 - Highly significant, SD: Standard deviation

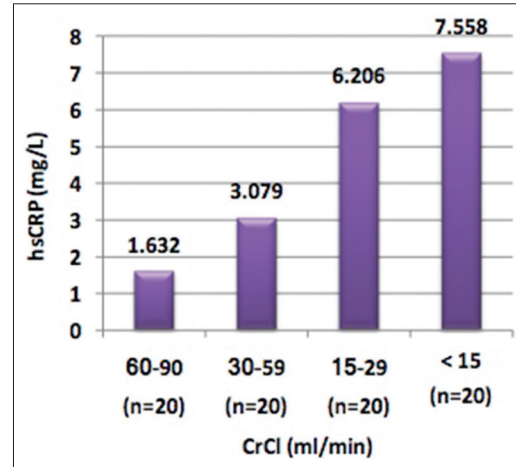
**Table 4: Pearson's correlation coefficient between fetuin-A and other biochemical parameters in cases**

Parameters	Correlation value	P value
Urea	-0.691**	P<0.01*
Creatinine	-0.595**	P<0.01*
CrCl	0.855**	P<0.01*
hsCRP	-0.756**	P<0.01*
Calcium	0.464**	P<0.01*
Phosphorus	-0.819(**)	P<0.01*
CaxP	-0.818**	P<0.01*
Albumin	0.616**	P<0.01*
TC	-0.078	P>0.05**
TGL	-0.366**	P<0.01*
HDL	0.443**	P<0.01*
VLDL	-0.366**	P<0.01*
LDL	-0.086	P>0.05†

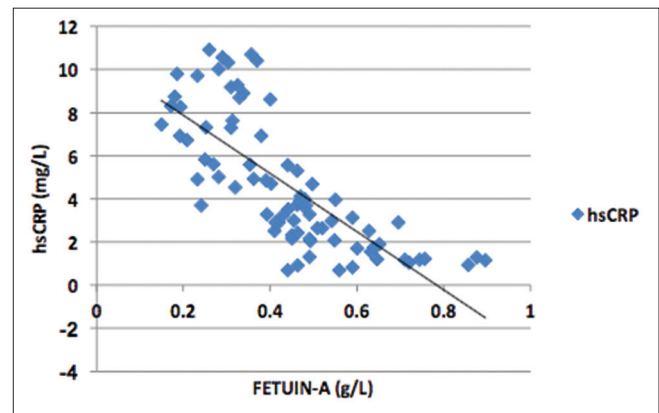
\*\*Correlation is significant at P<0.01 level; \*P<0.05 - Significant; †P>0.05 - Not significant

The mean level of serum fetuin-A in CKD cases in this study is  $0.4416 \pm 0.17$  g/L. This finding is fairly concordant with that of Cottone *et al.*, where the mean fetuin-A concentration was  $0.53 \pm 0.17$  g/L in patients with CKD.<sup>9</sup> We also observed that serum fetuin-A levels were significantly lower in all age groups and in both genders when compared to controls, which indicates that age and gender does not have an impact on serum fetuin-A levels.

CKD is a state of chronic persistent low-grade inflammation in which there is a chronic systemic elevation of pro-inflammatory markers. The prototypic marker of inflammation in the clinical setting is hsCRP, a positive acute phase reactant and a higher level of this inflammatory biomarker is associated with cardiovascular



**Figure 3: Comparison of serum high-sensitivity C-reactive protein levels in chronic kidney disease cases in relation to creatinine clearance**



**Figure 4: Scatter diagram of serum fetuin-A versus high-sensitivity C-reactive protein in chronic kidney disease cases**

mortality in patients with renal insufficiency.<sup>18,19</sup> In this study, we observed significantly higher levels of hsCRP in CKD cases when compared to controls (mean level: Cases -  $4.618 \pm 3.03$  mg/L; controls -  $0.567 \pm 0.23$  mg/L;  $P = 0.001$ ). As the renal function declined, we observed a progressive increase in the hsCRP levels. Further, a strong inverse correlation was found between fetuin-A and hsCRP levels ( $r = -0.756$ ;  $P < 0.01$ ) which shows that fetuin-A is a negative acute phase reactant.

Serum albumin is regarded as one of the negative acute phase reactant and a low serum albumin level in CKD is a well-established predictor of mortality.<sup>20</sup> In this study,

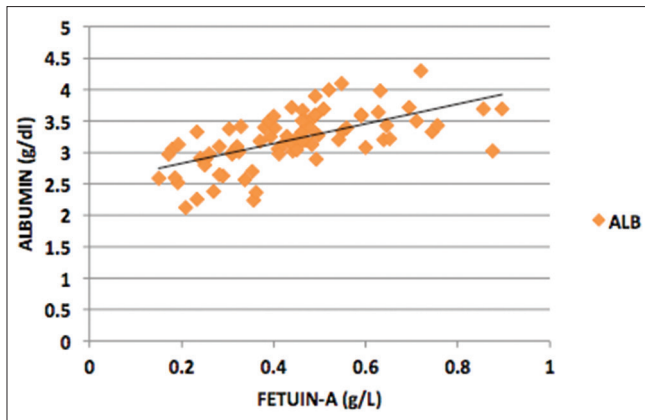


Figure 5: Scatter diagram of serum fetuin-A versus albumin in chronic kidney disease cases

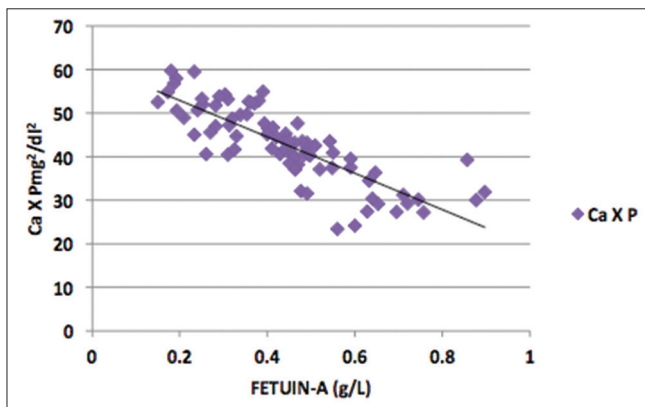


Figure 6: Scatter diagram of serum fetuin-A versus CaxP in chronic kidney disease cases

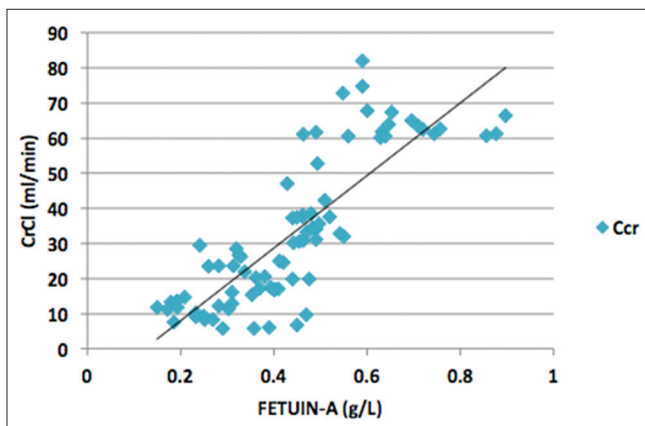


Figure 7: Scatter diagram of serum fetuin-A versus creatinine clearance in chronic kidney disease cases

serum albumin was found to be significantly reduced in CKD cases ( $P = 0.001$ ). We also observed a progressive decrease in the serum albumin levels with declining renal function. The results also revealed a strong positive correlation of serum fetuin-A with albumin levels ( $r = 0.616$ ;  $P < 0.01$ ). These results are in accordance with the previous studies<sup>21,22</sup> and suggest a global proatherogenic

inflammatory activation beginning from the early stages of CKD leading onto the downregulation of serum fetuin-A.

Our results also showed a highly significant increase of calcium-phosphorus product (CaxP) in CKD cases ( $P = 0.001$ ) and a progressive increase in CaxP as the renal function declined. We also found a strong significant inverse correlation of serum fetuin-A with CaxP ( $r = -0.818$ ;  $P < 0.01$ ). Similar findings were observed in the previous studies.<sup>23,24</sup> The mechanism accountable for this observation could be that serum fetuin-A dynamically binds to the BCP in the serum. During this process it forms transiently soluble, colloidal complexes called calciprotein particles, which are 30–150 nm in diameter. Fetuin-A coating of BCP nuclei will delay the growth of insoluble crystals and also favors mobilization and removal of the previously formed insoluble calcium salts by phagocytosis.<sup>25</sup> Fetuin-A thus acts as a “buffer” of BCP to prevent extraskeletal calcification. In CKD, increased serum levels of calcium and phosphorus devour the circulating fetuin-A and deplete its levels.

Dyslipidemia, an atherosclerotic risk factor, contributes to the initiation and progression of CKD partly by stimulating and amplifying the effect of inflammatory mechanisms.<sup>26</sup> In this study, we observed a significantly higher serum TGL and VLDL levels in cases than controls ( $P = 0.001$ ). Serum TC and LDL were found to be within the normal reference range in our study group. We also observed a significant negative correlation of serum fetuin-A with TGL and VLDL ( $r = -0.366$ ;  $P < 0.01$ ) and a positive correlation with HDL ( $r = 0.443$ ;  $P < 0.01$ ). These findings are in accordance with the study of Zeidan *et al.*, who in addition observed elevated levels of TC and LDL.<sup>27</sup> This discordance could be explained by the fact that with concurrent inflammation and malnutrition in CKD, TC, and LDL levels might decrease.

Previous studies have demonstrated that reduced serum fetuin-A levels could be considered as a predictor of both cardiovascular and noncardiovascular mortality.<sup>28,29</sup> Hermans *et al.* found that an increment of 0.1 g/L concentration of serum fetuin-A resulted in a 13% reduction in the all-cause mortality.<sup>10</sup> Cagler *et al.* demonstrated that short-term treatment with sevelamer, a noncalcium-based phosphate binder in patients with CKD, increased serum fetuin-A concentration which in turn improved the endothelial dysfunction in these patients.<sup>30</sup>

The observations from this study imply that the available circulating fetuin-A is depleted in dealing with the elevated CaxP commonly found in CKD. Further, in the chronic

inflammatory state of CKD, the synthesis of fetuin-A is down regulated.

## CONCLUSION

This study shows that fetuin-A is a promising biomarker to predict cardiovascular risk in patients with CKD. Since the levels of fetuin-A begin to decline from the early stages of CKD, its estimation may facilitate early prediction of vascular calcification. However, currently, no authorized strategies are on hand to increase the serum levels of fetuin-A in CKD. Early and prompt intervention of the factors causing reduced production (inflammation) and increased consumption (elevated CaxP) of fetuin-A may increase the serum fetuin-A levels and decelerate the course of cardiovascular disease in CKD.

Our study had few potential limitations such as small sample size and lack of application of imaging techniques to evaluate the extent of vascular calcification in CKD. The association between fetuin-A levels and vascular calcification, therefore, could not be precisely investigated.

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# Carcinoma of Penis: A Clinical Study

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## Abstract

**Background:** Carcinoma penis is potentially curable if detected and treated early. Quite a number of patients refuse to mutilate amputation (partial/total) of penis out of ignorance, social and sexual reasons.

**Materials and Methods:** This prospective study was conducted on 20 patients. In the management of carcinoma penis patients in MGM Hospital, Warangal from a period between October 2009 and October 2011.

**Results:** Carcinoma of the penis has an incidence of 1.3% of all malignancies and 4.6% of all male malignancies in our hospital. Carcinoma penis was not found in first two decades of life. Youngest patient was 32 years old and oldest was 71 years old. Maximum incidence was found in 5<sup>th</sup> decade of life (45%). All the cases in our study were Hindus in whom circumcision is not practiced ritually. In present series, this disease mostly affected people who came from rural areas and belong to low-income group, illiterate, ignorant class of society. This can be attributed to lack of health education regarding exposure to venereal diseases, lack of personal hygiene, and social taboos.

**Conclusion:** Patients who undergo surgery for carcinoma penis should be explained the need for regular follow-up and self-examination of groin to detect early regional nodal metastasis so that they can be managed appropriately.

**Key words:** Carcinoma, Patients, Penis

## INTRODUCTION

Carcinoma of the penis is an uncommon malignancy in Western countries, representing 0.4% of malignancies in males and 3.0% of all genitourinary cancers. However, penile cancer constitutes a major health problem in many countries in Asia, Africa, and South America, where it may comprise up to 10% of all malignancies. Despite these statistics, the incidence of penile cancer has been declining in many countries, partly because of increased attention to personal hygiene. It most commonly presents in the sixth decade of life but may occur in men younger than 40 years.<sup>1-3</sup>

Cancer of the penis has been strongly associated with Phimosis<sup>4</sup> and poor local hygiene. Phimosis is found in more than half the patients. The irritative effect of smegma, a by-product of bacterial action on desquamated epithelial cells within the preputial sac, is well known, although definitive evidence of its role in carcinogenesis. Neonatal circumcision<sup>5</sup> as is practiced by Muslims virtually eliminates the occurrence of penile carcinoma. Delaying circumcision until puberty does not have the same benefit as neonatal circumcision, and adult circumcision certainly does not provide any protection against carcinoma of the penis. Neonatal circumcision protection against penile cancer.<sup>6</sup>

Local penile symptoms and signs most often draw attention to penile cancer. The clinical spectrum of penile cancer is varied, subtle areas of erythema or induration to a frankly ulcerated, fungating, and foul-smelling mass. As a rule, penile cancer is an “infected” malignancy, with infection playing an important role in the pathogenesis and ultimately in the presentation of the disease.

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Pain usually is not a prominent feature and is not proportional to the extent of local destruction. The lesion initially involves the prepuce and glans, often under a tight phimotic ring. In late stages, involvement and eventual destruction of the shaft of the penis are seen. Urethral involvement is usually a late feature, and even in advanced stages urethral obstruction is rarely seen. Instead, erosion of the urethra with the development of multiple fistulae leading to the so-called water can perineum may be seen. Rarely, inguinal ulceration may be the presenting symptom, and in such cases, the primary tumor is usually concealed within a phimotic preputial sac or the patient delays seeking medical help for social reasons. Patients with penile cancer, more than with other types of cancer, seem to delay seeking medical attention

More than 95% of penile carcinomas are squamous cell in origin. Non-squamous cell carcinomas consist of melanomas, basal cell carcinomas, lymphomas, and sarcomas.

In contrast to other malignancies, this carcinoma can be prevented by early circumcision. The prepuce, especially when phimosis is present is subjected to chronic irritation from retained smegma and infection (balanoposthitis). This ultimately leads to malignant degenerative changes in the lining epithelium.

Carcinoma penis is potentially curable if detected and treated early. Quite a number of patients refuse mutilating amputation (partial/total) of the penis out of ignorance, social and sexual reasons.

Carcinoma of the penis is quite prevalent in this region of Telangana which is still backward, and the majority of people of Telangana are poor, illiterate and exposed to sexually transmitted diseases (STD). Since much can be done both for its prevention and cure an attempt has been made in this study to look into various effective treatment modalities currently available for the management of carcinoma penis (Table 1).

## METHODOLOGY

### Inclusion Criteria

Patients with carcinoma penis.

### Exclusion Criteria

Patients with carcinoma penis not willing for surgery.

Number of patients: 20.

All the patients ( $N = 20$ ) selected as per criteria from October 2009 to October 2011 were admitted in surgical

unit of Mahatma Gandhi Memorial Hospital, Kakatiya Medical College, Warangal, Telangana, India, after Ethical Committee approval and patient consent.

## RESULTS

A detailed study of carcinoma penis was made in all cases of carcinoma penis admitted from October 2009 to October 2011 in MGM Hospital, Warangal. Details of history, physical examination, investigations, management, and follow-up were recorded.

### Hospital Incidence

A total number of male cases admitted to MGM Hospital during October 2009-2011 = 49,424.

Incidence of carcinoma penis in male hospital admissions = 0.0404%.

Total number of male cancer patients admitted = 431.

Incidence of carcinoma penis among male cancer patients = 4.64%.

Reddy *et al.* from Vishakhapatnam reported an incidence of 6.9 in Vizag and 13.76% of all male malignancies.

Gheckler *et al.* (1990) reported an incidence of 0.4-0.6% of all male cancers in the USA.

### Age Incidence

The peak age incidence is in the fifth and sixth decade. Youngest patient is 32 years old and oldest is 71. A maximum number of cases were seen in the age group of the fifth decade. This coincides with the incidence given by various western authors.

Mean age of carcinoma penis in our study is 57 years.

Guerel *et al.* (1973) reported a mean age of 58 years and Derrick reported as 55 years.

### Community Incidence

Hindus: 20

Muslims: 0

Christians: 0

Carcinoma Penis is not seen frequently in Muslims because of ritual circumcision practiced in early childhood.

### Economic Status

Out of 20 patients, 16 patients belong to low socioeconomic status, 4 belong to middle socioeconomic status.

**Table 1: Age distribution of carcinoma penis in our study**

Age group	Number of patients (%)
0-10	0 (0)
11-20	0 (0)
21-30	0 (0)
31-40	1 (5)
41-50	4 (20)
51-60	9 (45)
61-70	5 (25)
71-80	1 (5)

**Table 2: Frequency of symptoms**

Symptom	Number of patients
Ulcer penis	15 patients
Foul discharge	8 patients
Phimosis	12 patients
Bleeding	6 patients
Pain	9 patients
Difficulty in micturition	5 patients
Itching	8 patients

**Table 3: Site of lesion**

Site	Number of patients
Glans penis	12 patients
Prepuce	5 patients
Shaft	1 patient
Corona	2 patients

**Extramarital Sex**

About 10 patients had extramarital sex which is a risk factor.

**Personal Hygiene**

Many patients had poor personal hygiene. Only 3 patients with carcinoma penis maintained good genital hygiene.

**Smoking**

About 14 out of 20 are smokers in the study which is an independent risk factor for penile cancer.

**Antecedent Genital Lesions**

History of phimosis was present in 12 patients, 8 patients had no phimosis, and only 3 patients underwent circumcision in adulthood. None underwent circumcision in childhood.

- History of balanoposthitis was present in 9 patients
- History of exposure to STD is present in patients
- History of hepatitis B surface antigen positive in 2 cases
- Venereal disease research laboratory was positive in 2 patients.

**Clinical Symptomatology**

Time lag between the onset and presentation at the hospital is between 3 months, more than 2 years. Majority presented within 1 year.

**Table 4: Inguinal lymphadenopathy**

Nodal status	Clinical	FNAC+VE	FNAC-VE
Unilateral N1	8	2	6
Bilateral N2	6	4	2
Pelvic N3	0	0	0

**Table 5: Clinical staging (TNM)**

Stage	n (%)
I	2 (10)
II	12 (60)
III	6 (30)
IV	0 (0)

This is due to ignorance in public to seek medical advice early for genital lesions.

There is a necessary to educate the general population about this cancer.

**Frequency of Symptoms**

The following is the prevalence of symptoms in the series (Table 2).

**Presentation of Lesions**

- Ulcerative growth 14 patients
- Ulcer 5 patients
- Ulcer hidden under phimosis 1 patient.

In this series, the glans penis was the most frequent site affected by carcinoma penis is glans followed by prepuce. This can be attributed to the fact that glans is more sensitive to irritation produced by collected smegma and chronic balanitis giving rise to changes in surface epithelia resulting in metaplasia and neoplasia (Table 3).

Heynes *et al.* in South African Journal of Surgery August 1997 reported T2 lesions comprising 48%.

**Inguinal Lymphadenopathy**

Significant lymphadenopathy was seen in 14 of 20 patients of which 8 cases had unilateral, 5 cases bilateral nodes. 2 of the unilateral and 4 of bilateral nodes persisted after treatment with antibiotics for 4 weeks and are positive for metastasis on fine-needle aspiration cytology (FNAC) (Table 4).

**Other Regional Lymph Nodes**

None of the patients had external or internal iliac lymphadenopathy.

**Clinical Staging (TNM)**

Sarin *et al.* (UK) reported prevalence of stage I lesion as 36%, stage II as 18%, stage III as 28%. In our study, the

prevalence of stage I is 10%, stage II is 60%, stage III is 30%, stage IV is 0% (Table 5).

### Histological Diagnosis

In all the cases, the diagnosis was squamous cell carcinoma penis.

### Distant Metastasis

No patient had evidence of distant metastasis.

### Hospital Death

No patient suffered hospital death.

### Treatment and Follow-up

Table 6 shows surgical treatment.

### Radiotherapy

No patient was subjected to radiotherapy as all cases were operable.

### Follow-up

Partial penectomy was done in 10 patients. Out of them, 2 did not come for follow-up. 6 cases had meatal stenosis subsequently for which urethral dilatation was done. None had loko-regional recurrence during the study period.

Total amputation and perineal urethrostomy were done in 4 patients. Out of them, one did not come for follow-up. 2 had meatal stenosis subsequently for which urethral dilatation was done. No loko-regional recurrence was found in the patients during the follow-up.

Total amputation with bilateral block dissection done for 6 cases, during post operative period wound infection occurred in all 6 patients and was managed by antibiotics. 5 patients developed flack neckrosis among them 3 cases were managed with ASD and SSG and 2 cases were managed with secondary suturing. 3 patients developed Lymphedema and managed with limb elevation and crape bandage. 4 patients had metal stenosis urethral dilatation done.

## DISCUSSION

Carcinoma of the penis has an incidence of 1.3% of all malignancies and 4.6% of all male malignancies in our hospital.

**Table 6: Surgical treatment**

Nature of surgery	Number of patients (%)
Circumcision	0 (0)
Partial penectomy	12 (60)
Total penectomy with perineal urethrostomy	4 (20)
Emasculatation with block dissection	6 (30)

Carcinoma penis was not found in first two decades of life. Youngest patient was 32 years old and oldest was 71 years old. Maximum incidence was found in fifth decade of life (45%).

All the cases in our study were Hindus in whom circumcision is not practiced ritually. In the present series, this disease mostly affected people who came from rural areas and belong to low-income group, illiterate, and ignorant class of society. This can be attributed to lack of health education regarding exposure to venereal diseases, lack of personal hygiene, and social taboos.

In the majority of patients, the presenting complaint was an ulcerative growth. Most patients presented between 3 months and 1 year of onset of symptoms. Modesty, ignorance, and poverty on the part of the patient are main causes for the delay. It should be impressed on the people that early detection and adequate treatment offer better prognosis.

Phimosis is present in 60% of cases. History of STD and multiple sexual partners was present in 70% of cases.

Carcinoma of penis rarely involved urethra. In our series, glans was the most frequent site of involvement 55%.

Ultrasound of abdomen and pelvis was found to be useful in locally advanced cases to pick up pelvic node enlargement. However, none of the patient had pelvic lymphadenopathy.

Very early cases with lesion localized to prepuce can be treated by circumcision when a margin of 1 cm of healthy tissue is available proximal to growth. Those lesions limited to the glans and have not spread to the shaft should be treated either with radiation molds or by partial amputation of penis. It prevents a great psychological trauma which is common after total amputation of penis.

When the shaft is infiltrated up to the root of penis and when it is not possible to leave behind 2 cm healthy stump, total amputation of penis is the treatment of choice. It is combined with bilateral orchidectomy. When the growth has already spread to the root of the penis and the pre-pubic region, emasculation with post-operative radiotherapy should be added.

Most of the patients during follow-up complained of difficulty in passing urine due to meatal stenosis. During regular follow-up, urethral dilatation was done.

In the present study, 14 patients had inguinal lymphadenopathy at presentation. However, 8 of them



regressed after 4 weeks course of antibiotics showing inflammatory nature of the lymph nodes. 6 of the patients had lymph node positive for metastasis. Most of the unilaterally enlarged nodes regressed (87.5%). In bilaterally enlarged nodes, only 33% regressed. Pathologically positive nodes mostly presented with ulcer type of lesion.

Bilateral block dissection is recommended for unilateral adenopathy at the time of presentation because there is 50% chance of metastasis.

Flap necrosis and post-operative lymphedema were found to be the most common complications of inguinal dissection.

FNAC or frozen section proved metastatic nodes should be removed by block dissection. Advanced (fixed node, more than 4 cm node) lesions should be treated by combination chemotherapy followed by surgery or radiotherapy.

## CONCLUSION

Patients who undergo surgery for carcinoma penis should be explained the need for regular follow-up and self-examination of groin to detect early regional nodal metastasis so that they can be managed appropriately.

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# Incidence of Eosinophilic Cholecystitis in Northwestern Region of Rajasthan: A Study in Consecutive 867 Cholecystectomies

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## Abstract

**Introduction:** Eosinophilic cholecystitis (EC) is an uncommon and poorly understood inflammatory condition of the gall bladder. EC is prevalent in 0.25-6.4% of all cholecystitis. The diagnosis of EC cannot be made before surgery and the histopathological examination remains the gold standard for diagnosis.

**Materials and Methods:** This prospective study was carried over a period of 22 months from January 2015 to October 2016, to find out the incidence of EC in cholecystectomy specimens received.

**Results:** A total of 867 cases were examined, out of which EC was found in 15 patients (1.73%). 4 out of 15 patients had pre-operative peripheral eosinophilia and 2 out of 15 patients had history of allergy to dust and smoke.

**Conclusion:** From the study it was concluded that there is a need for complete workout of patient by clinician, to exclude other organ involvement and associated syndrome. Furthermore, there is a need to understand the molecular mechanism predisposing to eosinophilic infiltration in patient with EC.

**Key words:** Eosinophilia, Eosinophilic cholecystitis, Histopathological examination

## INTRODUCTION

Eosinophilic cholecystitis (EC) is an uncommon inflammatory condition of gall bladder, the pathogenesis and etiology of which still remains unknown. It was first described by Albot *et al.*<sup>1</sup> The clinical presentation is similar to that of typical cholecystitis with right hypochondrial pain, nausea, vomiting, fever, and an elicited murphy sign.

Histopathological examination of resected gall bladder remains the gold standard for diagnosis. EC is said to be present when cellular infiltrate in the gall bladder is more than 90% eosinophil. When the infiltrate comprises 50-70%

eosinophils along with other inflammatory cells in gall bladder they are termed lympho-EC.<sup>2,4</sup>

The incidence of EC is very low in India. It is prevalent in 0.25-6.4% of all cholecystitis.<sup>5,6</sup> Pathogenesis of eosinophilic infiltration is poorly understood. Eosinophils are one of the immune system of body responsible for combating parasitic infections and along with mast cells control the mechanism associated with allergy and asthma. The proposed etiology for eosinophilic infiltration include local and systemic inflammatory reaction to parasite,<sup>7-9</sup> bile or gall stone impacted at neck or hypersensitivity to antibiotics and herbal medicines.<sup>10-12</sup>

EC may appear alone or in association with hypereosinophilic syndrome,<sup>13</sup> eosinophilic gastroenteritis,<sup>3</sup> eosinophilic myalgia syndrome, parasitic infections (such as hydatid cyst, clonorchis sinensis, and ascaris),<sup>8,9</sup> few herbal medicines, certain drugs such as erythromycin and cephalosporin.<sup>11,12</sup> Therefore, the possibility of associated disorder must be ruled out once the diagnosis of EC is made. When the disease is confined to the gall bladder the treatment

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of choice is cholecystectomy. However, if a causative factor is discovered treatment may warrant more than cholecystectomy or may lead to findings of other organ infiltration. With this background, we carried out this study to find the incidence of EC in northwestern region of Rajasthan.

## MATERIALS AND METHODS

This was a prospective study carried out over a period of 22 months from January 2015 to October 2016, in the department of Pathology, S.P. Medical College, Bikaner, Rajasthan.

Cholecystectomy specimens received were fixed in 10% neutral buffered formalin and embedded in paraffin. Three full thickness sections were obtained from fundus, body, and neck of the gall bladder. Additional sections were taken from any grossly abnormal area if present. Sections were then stained with H and E stain and examined microscopically.

## RESULTS

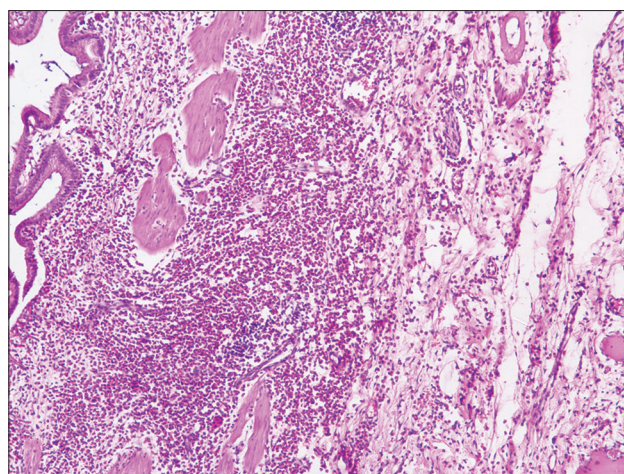
A total of 867 gall bladder specimens were received during the period of January 2015 to October 2016. This included open cholecystectomy, laparoscopic cholecystectomy, and partially resected specimens. 15 out of 867 cholecystectomy patients (1.73%) aged between 20-60 years showed EC (Figures 1 and 2).

The patients with EC comprised 9 females (60%) and 6 males (40%) (Table 1) with median age of 39.8 years.

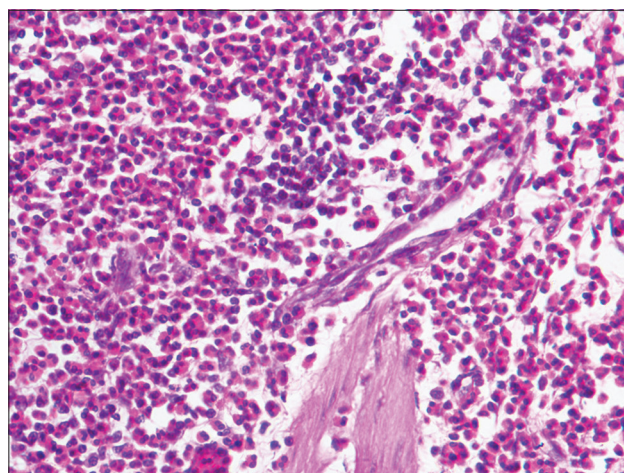
The main presenting complaint was upper abdominal pain and dyspepsia. Pre-operative eosinophilia was present in 4% patients (26.6%) and one patient had bilious perforation with peritonitis. Gall stone was present in 7 patients (46.6%) out of which 6 were female and 1 male. 2 of the patients had history of allergy to dust and smoke (Table 2). Remaining patients had no previous relevant preexisting medical condition and were considered idiopathic EC.

## DISCUSSION

EC is an uncommon form of cholecystitis that was first described by Albot *et al.* in 1949.<sup>1</sup> The incidence of EC is low in India. Studies across the world showed its prevalence to be 0.25-6.4% with average age of presentation being 37 years.<sup>5,6,10</sup> In this study, EC was diagnosed in 15 of 867 specimens (1.73%) which was comparable to the results of other reported cases.



**Figure 1: Histopathological slide of patient showing eosinophilic infiltration of gall bladder wall (H and E, x100)**



**Figure 2: Histopathological slide of patient showing eosinophilic infiltration of gall bladder wall (H and E, x400)**

**Table 1: Age and sex distribution of patients with EC**

Age group (years)	N (%)		Total
	Sex		
	Female	Male	
20-30	5 (55.6)	1 (16.7)	6 (40.0)
31-40	0 (-)	2 (33.3)	2 (13.3)
41-50	2 (22.2)	1 (16.7)	3 (20.0)
51-60	2 (22.2)	2 (33.3)	4 (26.7)
Total	9 (100)	6 (100)	15 (100)

EC: Eosinophilic cholecystitis

Histopathological examination of resected gall bladder remains the gold standard for diagnosis of EC. EC does not present any specific laboratory manifestation to distinguish from other causes of cholecystitis. In our study, the main presenting complaint was abdominal pain and epigastric discomfort. One patient had bilious perforation with peritonitis.

**Table 2: Features of reported cases of eosinophilic cholecystitis**

Case No.	Age (years)	Sex	Allergy/preexisting medical condition	Pre-operative peripheral eosinophilia	Gall stone present
1	24	Female	No	No	No
2	42	Male	No	No	No
3	51	Female	No	Yes (9%)	No
4	27	Male	No	Yes (14%)	No
5	30	Female	No	No	Present
6	27	Female	Allergy+	No	Present
7	60	Female	Allergy+	No	Present
8	30	Female	No	No	Present
9	20	Female	No	Yes (10%)	No
10	49	Female	Bilious perforation with peritonitis	No	Present
11	35	Male	No	No	No
12	56	Male	No	No	No
13	36	Male	No	No	No
14	50	Female	No	Yes (16%)	Present
15	60	Male	No	No	No

+Allergy to dust and smoke

Dabbes *et al.*<sup>5</sup> reviewed 217 consecutive cholecystectomy specimens and found that eosinophilic infiltration is three times more common in acalculous cholecystitis. In our study, 7 out of 15 cases (46.6%) of EC had associated gall stone. The remaining 8 (53.4%) had acalculous cholecystitis, which on histopathological examination revealed EC.

Although there are quite few case reports on EC, the pathogenesis of eosinophilic infiltration is poorly understood. The proposed etiologies include local allergic reaction to substances released at foci of inflammation, local reaction to parasite, bile or gall stone impacted at neck.<sup>7-9</sup> Certain drugs such as erythromycin, cephalosporin, and herbal medicine have been implicated in pathogenesis of EC.<sup>10-12</sup>

Eosinophilic infiltration may be limited to the gall bladder or associated with multiple organ involvement or several disease conditions like syndrome.<sup>3,13</sup> A suspicion of this entity can be kept if peripheral eosinophilia is present. Kim reported that peripheral eosinophilia occurred in 4 of 15 cases.<sup>8</sup> In the absence of any apparent precipitating etiology, it is considered idiopathic EC.

In our study, a thorough work up of patients was done to find possible etiology. 2 of the patients had history of allergy to dust and smoke and 4 patients had pre-operative eosinophilia. When peripheral eosinophilia is observed EC may be an expression of hypereosinophilic syndrome. However, we did not find any associated disease condition in our patients. Remaining patients had no previous relevant preexisting medical condition and were considered idiopathic EC.

The treatment of EC is cholecystectomy. Steroids may be used as an adjuvant therapy if the disorder is associated with gastroenteritis.<sup>3</sup> In our patients, definitive therapy with cholecystectomy led to full recovery.

## CONCLUSION

EC is a rare entity. EC is significant because it is not apparent solely through laboratory test. Once the diagnosis of EC is made by histological examination, there is a need for complete workout of patient by clinician to exclude other organ involvement and associated syndrome. The mechanism for recruitment of eosinophil is unknown. Therefore, there is a need to understand the molecular mechanism predisposing to eosinophilic infiltration in patients with EC.

## ACKNOWLEDGMENT

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# Hemodynamic and Sedative Effects of Intrathecal Tramadol with Bupivacaine and Bupivacaine Alone in Patients Undergoing Elective Lower Abdominal Surgery: A Comparative Study

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## Abstract

**Background:** Effective pain control is essential for optimum care of patients in the post-operative period. Epidural and intrathecal administration of drugs have been used increasingly for relief of post-operative pain. Intrathecal adjuvants apart from producing postoperative analgesia cause respiratory depression and haemodynamic instability like morphine, clonidine, dexmedetomidine etc. The purpose of this study is to compare the hemodynamic changes and level of sedation following intrathecal administration of tramadol with bupivacaine and bupivacaine alone in patients undergoing lower abdominal surgical procedures.

**Materials and Methods:** 60 ASA I and II patients were randomly assigned to two groups. Group B ( $n = 30$ ) received 3 ml of 0.5% hyperbaric bupivacaine with 0.5 ml of normal saline and Group BT ( $n = 30$ ) received 3 ml of hyperbaric bupivacaine with 0.5 ml (25 mg) of preservative free tramadol by intrathecal route at L3-L4 intervertebral space. Patient's vital parameters, sedation scores and side effects were recorded every 2 min for the first 20 min and then every 10 min for the rest of surgical procedure.

**Results:** The vital parameters such as heart rate, blood pressure, oxygen saturation, and respiratory rate were comparable and were within normal limits in both the groups. Sedation score in both the groups was well comparable.

**Conclusion:** Tramadol (25 mg) with hyperbaric bupivacaine intrathecally provides a better post-operative analgesia with preserved hemodynamic stability and minimal sedation.

**Key words:** Bupivacaine, Intrathecal adjuvants, Sedation, Spinal anesthesia, Tramadol, Vital parameters

## INTRODUCTION

The provision of effective anesthesia during the procedure and post-operative analgesia is still evolving and getting fine-tuned in the specialty of anesthesia. One of the primary aims of anesthesia is to provide analgesia during the surgical procedure.

Anesthesiologists are the leaders in the development of acute post-operative pain services and application of evidence-

based practice to acute post-operative pain and creation of innovative approaches to acute pain management. If we can provide post-operative analgesia in a simple and inexpensive manner, it may go long way in alleviation of pain and suffering. In order to do these, a number of adjuvants have been added to spinal anaesthetics. During the past two decades epidural and intrathecal administration of drugs have been used increasingly for relief of post-operative pain. Various drugs have been studied including morphine, pethidine, ketamine, tramadol, clonidine, neostigmine, dexmedetomidine, and midazolam.

Although various drugs used as adjuvants in spinal anesthesia provide good post-operative analgesia they are also associated with various side effects such as respiratory depression,<sup>1</sup> sedation, hypotension, bradycardia, nausea, and vomiting. Tramadol in contrast to a centrally acting

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opioid analgesic has minimal respiratory depressant effect,<sup>2,3</sup> because it has 6000-fold less affinity for  $\mu$  receptors compared to morphine.<sup>4,5</sup> It also inhibits serotonin and norepinephrine reuptake in the spinal cord and has no reported neural toxicity.<sup>6</sup> Therefore, tramadol has the potential to provide effective post-operative analgesia with no risk of respiratory depression after central neuraxial administration. Hence, we thought it would be appropriate to study the hemodynamic and sedative effects of intrathecally administered tramadol and compare it with intrathecally administered hyperbaric bupivacaine in patients posted for lower abdominal surgical procedures.

## MATERIALS AND METHODS

This prospective randomized control study was done after obtaining institutional ethical committee approval and written informed consent. 60 patients of physical status ASA I and II aged between 18 and 50 years of both the sexes posted for elective lower abdominal surgical procedures from various specialties under subarachnoid block were included in this study. This study was carried out at Kempegowda Institute of Medical Sciences and Hospital, Bangalore during the period of 2004-2005. Patients with spinal deformity, history of allergy to the drugs used and having contraindications to regional anesthesia were excluded from the study.

Patients were randomly divided into two groups (B and BT) of 30 each. Group B received 3 ml of 0.5% bupivacaine heavy with 0.5 ml of 0.9% normal saline intrathecally and Group BT received 3 ml of 0.5% bupivacaine heavy with preservative free tramadol 0.5 ml that is 25 mg intrathecally. In the operating room, after securing intravenous access with appropriate sized cannula, intravenous fluid started. Pulse rate, blood pressure (BP), respiratory rate (RR), oxygen saturation ( $\text{SpO}_2$ ), and electrocardiogram monitoring were applied and recorded before the induction of spinal anesthesia and thereafter during the procedure. Spinal anesthesia was carried out in sitting position, with 26 G Quincke's needle at  $\text{L}_{3-4}$  interspace by a standard technique. After free flow of cerebrospinal fluid, 3.0 ml of hyperbaric bupivacaine 0.5% with 0.5 ml of 0.9% normal saline was deposited slowly in patients of Group B. In patients of Group BT 3.0 ml of 0.5% hyperbaric bupivacaine with 0.5 ml (25 mg) of preservative free tramadol was deposited. After the drug was deposited, the patients were made to lie down in supine position immediately. Pulse rate, BP were recorded immediately and at 5, 10, 15, 30, 60, 120, 180 min. Side effects of intrathecal administration of tramadol such as nausea, vomiting, hypoxemia, hypotension, bradycardia,

and sedation were noted down during the intra-operative and post-operative period. The patients were followed up for 24 h after surgery.

Hypotension (defined as decrease in systolic BP more than 20% of the base line value or  $<90$  mm of Hg) after spinal injection was treated by increasing the rate of intravenous fluid administration and/or 5-10 mg of intravenous administration of bolus dose of ephedrine hydrochloride as and when required. Bradycardia (heart rate  $<60$  bpm) was treated with intravenous atropine 0.2 mg as and when needed. Respiratory depression defined as RR  $<8$ /min and or  $\text{SpO}_2$   $<85\%$ . This was planned to be managed with bag and mask ventilation or intubation and invasive positive-pressure ventilation if necessary.

The degree of sedation was assessed by "Ramsay sedation scale."

### Ramsay Sedation Scale

1. Patient is anxious and agitated or restless, or both
2. Patient is cooperative, oriented, and tranquil
3. Patient responds to commands only
4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6. Patient exhibits no response.

### Statistical Analysis

All the parametric data were analyzed using Student's *t*-test and nonparametric data by Chi-square test, statistical software SPSS 11.0, and Systat 8.0 were used for the analysis of the data and the result was considered to be statistically significant only if  $P < 0.05$ .

## RESULTS

Both the groups were comparable with respect to age, sex, height, and weight distribution (Table 1), ASA grade and duration of the surgery (Table 2).

**Table 1: Basic characteristics of the study**

Basic characteristics	Group B	Group BT
Number of patients	30	30
Age in years (Mean $\pm$ SD)	36.53 $\pm$ 8.83	36.63 $\pm$ 7.89
Height in cm (Mean $\pm$ SD)	158.60 $\pm$ 9.98	157.73 $\pm$ 8.17
Weight in kg (Mean $\pm$ SD)	57.47 $\pm$ 8.66	55.73 $\pm$ 5.54
Sex N (%)		
Male	15 (50.0)	16 (53.3)
Female	15 (50.0)	14 (46.7)

SD: Standard deviation, Group B: Bupivacaine, Group BT: Bupivacaine-tramadol

The mean SpO<sub>2</sub> of both the groups are shown in Figure 1, the values between both the groups are well comparable. The mean pulse rate and RR of both the groups are shown in Table 3. The pulse rate and RR between both the groups at 5, 10, 15, 20, 25, 30, 60, 120, and 180 min were comparable with no statistical differences. Table 4 shows mean systolic and diastolic BP values at different intervals in both the groups, which were comparable.

## DISCUSSION

A revolution in the management of acute post-operative pain has occurred during the past two decades. Anesthesiologists

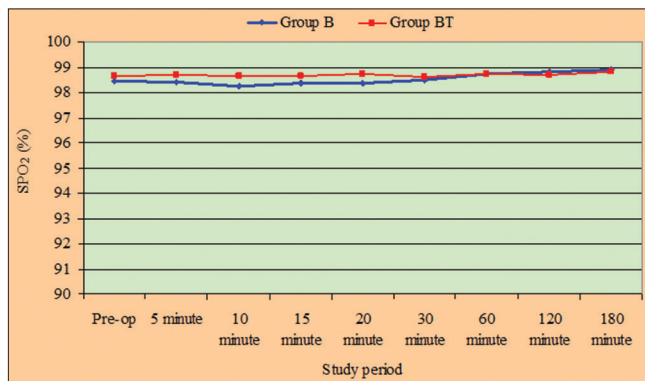


Figure 1: Comparison of oxygen saturation between two groups

with their knowledge of and familiarity with pharmacology, various regional techniques and the neurobiology of nociception are continually in the forefront of clinical and research advances in acute post-operative pain management.

Spinal anesthesia with bupivacaine hydrochloride is popular for longer procedures due to its prolonged duration of action, but there is a need to intensify and increase duration of sensory blockade without increasing the intensity and duration of motor blockade and thus prolong the duration of post-operative analgesia. The addition of opioids has been suggested as a method to accomplish these goals. Several drugs have been added as adjuvants to bupivacaine for intrathecal anesthesia namely opioids, midazolam, clonidine, dexmedetomidine, but they are also associated with side effects like respiratory depression, pruritus, hypotension, bradycardia, sedation, nausea and vomiting. Therefore, our study was performed to demonstrate that intrathecal administration of 25 mg of tramadol when used with 0.5% bupivacaine for prolongation of post-operative analgesia produces less hemodynamic instability with minimal sedation.

The result of the study showed that there was no significant difference between groups in the pattern of decrease in systolic or diastolic BP, RR, heart rate, and SpO<sub>2</sub>.

Table 2: Comparison of duration of surgery and ASA grade between two groups

Basic characteristics	Group B	Group BT	Remarks
ASA grade (%)	I - 26 (86.7) II - 4 (13.3)	I - 25 (83.3) II - 5 (16.7)	ASA grade is statistically similar between two groups with $P=0.718$
Duration of surgery (Mean±SD)	93.50±39.53	96.00±43.52	Duration of surgery is statistically similar between two groups with $P=0.817$

SD: Standard deviation, Group B: Bupivacaine, Group BT: Bupivacaine-tramadol

Table 3: Comparison of pulse rate (beats/min) and RR between two groups

Study period (minutes)	Pulse rate (beats/min)		P value	RR		P value
	Group B	Group BT		Group B	Group BT	
Pre-operative	77.53±7.57 (64-88)	79.13±7.73 (68-92)	0.421	13.10±0.66 (12-14)	12.97±0.81 (12-14)	0.487
5	79.13±7.12 (66-90)	77.20±8.98 (62-90)	0.359	12.50±0.63 (12-14)	12.57±0.68 (11-14)	0.695
10	79.60±8.50 (64-99)	76.67±9.40 (60-96)	0.210	12.47±0.57 (12-14)	12.20±0.41 (12-13)	0.042*
15	79.87±8.37 (60-92)	76.13±9.74 (62-94)	0.117	12.67±0.76 (12-15)	12.33±0.48 (12-13)	0.046*
20	78.97±8.33 (62-92)	76.67±10.93 (60-98)	0.383	12.77±0.68 (12-14)	12.73±0.45 (12-13)	0.823
30	81.07±7.71 (60-99)	77.67±10.93 (62-96)	0.160	12.67±0.61 (12-14)	12.23±0.50 (12-14)	0.004**
60	80.33±6.62 (64-90)	77.93±8.76 (64-94)	0.236	12.93±0.73 (12-15)	12.27±0.50 (11-14)	0.001**
120	80.67±6.09 (68-90)	79.07±9.09 (64-96)	0.426	12.87±0.82 (12-15)	12.60±0.56 (12-14)	0.147
180	81.40±6.24 (64-90)	80.27±9.23 (64-94)	0.580	13.23±0.73 (12-15)	12.70±0.47 (12-13)	0.001**

Results are presented in Mean±SD (Min-Max). \*\*\*:  $P<0.05$ , RR: Respiratory rate, SD: Standard deviation, Group B: Bupivacaine, Group BT: Bupivacaine-tramadol



**Table 4: Comparison of systolic and diastolic BP between two groups**

Study period (minutes)	Systolic BP (mmHg)		P value	Diastolic BP (mmHg)		P value
	Group B	Group BT		Group B	Group BT	
Pre-operative	120.00±6.95 (110-130)	123.20±7.91 (108-138)	0.103	76.03±6.29 (60-90)	78.13±5.48 (64-86)	0.173
5	110.80±6.80 (100-122)	113.13±8.15 (100-130)	0.233	71.13±7.18 (56-80)	75.07±5.79 (60-82)	0.023*
10	108.80±4.29 (100-120)	111.13±7.42 (100-126)	0.141	70.37±6.64 (58-82)	73.80±6.42 (58-82)	0.046*
15	109.07±4.72 (100-120)	111.87±7.57 (100-126)	0.091	70.40±7.13 (56-82)	72.93±5.65 (60-82)	0.133
20	110.67±5.23 (102-124)	113.33±7.43 (100-130)	0.114	71.22±6.74 (54-84)	73.80±5.10 (62-82)	0.166
30	110.80±4.63 (102-124)	115.60±8.64 (102-132)	0.009**	71.67±6.01 (58-82)	74.93±4.98 (68-84)	0.026*
60	112.67±5.71 (104-126)	117.93±8.14 (104-134)	0.005**	73.20±6.05 (60-82)	76.27±4.89 (64-84)	0.035*
120	114.40±5.79 (106-130)	120.80±7.16 (104-130)	<0.001**	74.33±5.85 (60-80)	77.07±5.14 (64-84)	0.059*
180	116.27±6.19 (108-130)	122.27±6.88 (110-134)	0.001**	75.40±5.64 (60-82)	76.67±4.65 (66-84)	0.346

Results are presented in Mean±SD (Min-Max). \*\*\*, P<0.05, SD: Standard deviation, Group B: Bupivacaine, Group BT: Bupivacaine-tramadol, BP: Blood pressure

Wang *et al.*<sup>7</sup> in their experimental work found that the decrease in sympathetic efferent activity after spinal anesthesia is related to bupivacaine and not to the intrathecal opioid which was added.

Alhashemi and Kaki<sup>8</sup> in 2003 found that Intrathecal tramadol did not seem to influence the intraoperative hemodynamic profile.

In our study, none of the patients experienced respiratory depression. Baraka *et al.*<sup>9</sup> in 1993 found that mean PaO<sub>2</sub> values did not change in the epidurally administered tramadol group. Similar findings were also observed by Yaddanapudi *et al.*<sup>10</sup> in 2000 with epidurally administered tramadol.

## CONCLUSION

It can be inferred that tramadol 25 mg (preservative free) in combination with bupivacaine 0.5% heavy can be safely administered intrathecally for better post-operative analgesia in lower abdominal surgical procedures without producing hemodynamic instability and minimal sedation.

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# Dermatological Infections in Pregnancy and their Obstetric Outcome in Madurai, India

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## Abstract

**Background:** The purpose of this study is to evaluate the effect of infectious dermatological diseases on pregnancy outcome. It also aims to study the onset of new dermatological lesions in the milieu of altered immune response during pregnancy.

**Materials and Methods:** It is an observational prospective study conducted in antenatal women who were admitted at Government Rajaji Hospital, Madurai over a period of 1 year. 12 women with dermatological infections were identified and they were followed up till delivery. The effect of the dermatological infection on the newborn was also looked for.

**Results:** Viral infections are the most common affecting the skin during pregnancy. Furthermore, due to early referral to tertiary center, secondary bacterial infection is prevented. These dermatological infections did not significantly affect the pregnancy outcome. The decreased reporting of dermatological infections may also be due to the myths around these and many sorts to native treatment. Much more information may be obtained by a field study.

**Conclusion:** Although pregnancy boosts up the humoral immune response, there is a depression of cellular immunity that results in occurrence of viral infections during pregnancy. Early diagnosis and appropriate management, results in an uneventful pregnancy outcome.

**Key words:** Dermatological infections, Obstetric outcome, Pregnancy

## INTRODUCTION

During pregnancy, there is alteration of the immunological and endocrine milieu. Due to this change, there is a wide range of infectious diseases that can occur during pregnancy. The acquisition, clinical presentation, and course of these diseases are also altered during pregnancy. It may be due to impairment of the cellular immunity. These diseases may affect the outcome of pregnancy by affecting the mother and the fetus. This study is to analyze the prevalence of dermatological infections during pregnancy and to evaluate the maternal and fetal outcome.<sup>1-3</sup>

## MATERIALS AND METHODS

1. The study is conducted on pregnant patients admitted at Government Rajaji Hospital during their second and third trimester
2. Informed oral and written consent of the patient
3. Counseling and communication about the need and methods of the study
4. The relevant history is obtained from the patient and documented
5. Investigations: Hemoglobin %, ultrasonography, investigations to confirm the dermatological condition if needed
6. Photography of the dermatological lesion with the consent of the patient
7. Dermatologist opinion regarding the confirmation of diagnosis and further management plan is obtained.

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## RESULTS

Among the mothers who were admitted in their second or third trimester for various other reasons, the occurrence of skin infection was observed. 12 patients were found to have skin infections at the time of admission.

Among that viral infections were the most common, occurring in 9 out of 12 patients (75%). These women presented with active lesions. Of these, 2 women had miscarriage. One had cesarean section for obstetric indication and the others delivered vaginally. None of the term babies born had active infection.

The other 25% were contributed by parasitic infections. These women had uneventful delivery and both mother and fetus were not affected. (Table 1)

## DISCUSSION

### Bacterial Infections: Skin and Soft Tissue Infections

Community acquired methicillin-resistant *Staphylococcus aureus* is becoming increasingly relevant in pregnancy and puerperium with infections of the breast, buttock, and vulvovaginal area. Risk of vertical transmission of infection is very low.

### Mycobacterial Infection

- Leprosy  
Leprosy reactions may be triggered by pregnancy. Type I reaction occur maximally postpartum. Type II reaction may occur throughout pregnancy and lactation. Silent neuritis may occur 6-9 months following delivery especially in patients with borderline leprosy. Leprosy reactions to be managed with oral

corticosteroids and vigilance for neuritis postpartum are important.

- Tuberculosis (Tb)  
Cutaneous Tb has very rarely been reported.

### Fungal Infections

- Dermatophytoses  
The onset of tinea corporis and tinea pedis in pregnancy has been reported. Topical azoles can be safely used in pregnancy
- Tinea versicolor and pityrosporum folliculitis  
Caused by *Malassezia*. Higher degree of colonization noted in the end of pregnancy and postpartum. Topical ciclopirox, topical clotrimazole, and terbinafine are the treatment options available.
- Sporotrichosis  
No fetal risk is associated. Treated with amphotericin B
- Systemic mycoses
  - i. Coccidioidomycosis - disseminated disease is associated with third trimester and immediate postpartum period with the neonate acquiring the infection due to aspiration of vaginal secretions. If untreated leads to mortality. Should be promptly treated with amphotericin B. Presence of erythema nodosum is associated with positive outcome
  - ii. Blastomycosis can never cause severe illness in pregnancy
  - iii. Cryptococcosis predominantly affects the immunocompromised individuals and maternal morbidity includes meningitis and pulmonary involvement. To be managed with amphotericin B.

### Parasitic Infections

- Scabies - prevalence in pregnancy has been systematically studied. Permethrin 5% cream can be tried
- Leishmaniasis - amphotericin B is the safest treatment option
- Toxoplasmosis - skin lesions of toxoplasmosis are not affected by pregnancy.

### Viral Disease

- Herpes simplex virus  
Disseminated disease may lead to encephalitis, hepatitis, coagulopathy, thrombocytopenia, and leukopenia. Fetal risks include - spontaneous abortion, prematurity, congenital herpes, neurological complications, microcephaly, hydrocephalus, and chorioretinitis. Early identification and treatment with acyclovir is essential.
- Varicella zoster virus (VZV)  
It may cause intrauterine growth restriction (IUGR) and low birth weight. Congenital varicella syndrome is rare but devastating complication. Maternal pneumonia

**Table 1: Dermatological Infections and their Obstetric Outcome**

Diagnosis	Parity	Obstetric outcome
Tinea	Primi	Labomaturale
Tinea	Primi	Labomaturale
Chicken pox	Primi	Spontaneous abortion
Chicken pox	Primi	Labomaturale
Chicken pox	g2p111	Labomaturale
Chicken pox	g3p212	Labomaturale
Herpes labialis	g2p111	Labomaturale
Herpes labialis	g2p111	Cesarean section
Scabies	g2p111	Labomaturale
Genital herpes	g2p111	Spontaneous abortion
Molluscum contagiosum	Primi	Labomaturale
Molluscum contagiosum	g2p111	Cesarean section

can occur. If a pregnant woman is exposed to varicella, varicella-zoster immunoglobulin administered at time of exposure or up to 96 h later may prevent or lessen the severity of the illness.

- HIV  
Associated skin disorders include eosinophilic folliculitis, molluscum contagiosum, Kaposi sarcoma, VZV infection, and genital warts. Management includes counseling, cesarean delivery and avoidance of breastfeeding and antiretroviral therapy.
- Rubella  
Congenital rubella syndrome is the most severe fetal risk. Managed by routine measles, mumps, and rubella vaccination.
- Parvovirus B19  
Characteristic slapped cheek exanthema associated with vertical transmission, spontaneous abortion, low birth weight, and hydrops.

### Sexually Transmitted Diseases

- Syphilis  
It caused by *treponemapallidum*. Infection of the fetus can occur as early as 9-10 weeks gestation during primary or secondary syphilis. Fetal risks include spontaneous abortion, prematurity, infant death, and congenital syphilis. A course of penicillin administration 4 weeks or more before delivery is considered adequate for the prevention of congenital syphilis.
- Chlamydia trachomatis  
Recent acquisition of infection is associated with increased fetal risk. Treatment reduces the rate of premature rupture of membranes.
- Gonorrhea  
Associated with prematurity, PROM, fetal death, IUGR, and neonatal diseases. Ceftriaxone is the most

effective treatment

- Trichomoniasis  
Managed with metronidazole.
- Bacterial vaginosis  
Diagnosed when three of the four Amsel criteria are present, treatment is recommended only for symptomatic group.
- Vulvovaginal candidiasis  
Neonatal candidiasis can result from passage of the infant through the birth canal. Congenital candidiasis can result from an ascending infection in utero. Treated with topical azole.<sup>4,5</sup>

### CONCLUSION

The dermatological infections that affect during pregnancy are predominantly viral. Prompt treatment in the tertiary center with early diagnosis and appropriate drugs has resulted in good obstetric outcome in many pregnant women.

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# Liquid-based Cytology versus Conventional Cytology for Evaluation of Cervical Cytology in a Tertiary Care Center of Chhattisgarh

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## Abstract

**Introduction:** Cervical cancer is the second most common type of cancer among women's according to the World Health Organization. Worldwide screening programs for cervical cancer-based on the Papanicolaou smear have contributed to the decrease in incidence and mortality of cervical cancer.

**Objective:** To compare the adequacy of smears and diagnostic difference of conventional conventional pap smear [CPS] versus liquid-based cytology (LBC).

**Materials and Methods:** A prospective observational study was conducted in a tertiary care referral institute in 80 consecutive cervical "split samples" over a period of 1-year. Samples were taken with cervix-brush, first a CPS was prepared then for LBC same brush head was suspended in preservative fluid after detachment and processed by SurePath™ LBC.

**Results:** There were 92.5% satisfactory smears in LBC while in CPS it was 78.8%, with statistically significant difference  $P = 0.02$ . Endocervical cells were present in 57.5% of cases in CPS, while in LBC, it was present in 18.8%. Clarity of background was significantly increased with LBC. Infectious organisms were better detected in LBC. Sensitivity for detection of low-grade squamous intraepithelial lesion (LSIL) (78.6%) and for high-grade squamous intraepithelial lesion (HSIL) (72.7%) was higher in LBC as compare to 71.4% and 63.6% in CPS, respectively. Specificity was also higher in LBC 100% for both LSIL and HSIL, whereas in CPS, it was 95.8% for LSIL and 96.3% for HSIL.

**Conclusion:** In the present study, adequacy rate for LBC significantly increased, and the performance of LBC technique was better than CPS.

**Key words:** Liquid-based cytology, Conventional pap smear, Split sample, Adequacy rate, SurePath™

## INTRODUCTION

Cervical cancer is the second most common type of cancer among women's according to the World Health Organization.<sup>1</sup> Worldwide screening programs for cervical cancer-based on the Papanicolaou smear have contributed to the decrease in incidence and mortality of cervical

cancer.<sup>2</sup> One of the major advance in cervical cancer screening was the pap test. The second major advance was liquid-based cytology (LBC).<sup>3</sup> Screening programs for cervical cancer using the conventional pap smear (CPS) technique have been in place for decades and have been successful in detecting cancers of the cervix significantly. However, CPS technique has many limitations.<sup>4</sup>

The LBC corresponds to a sampling where cells are put in suspension in a conversation liquid.<sup>5</sup>

LBC is proposed to have many benefits over CPS such as less number of unsatisfactory (U/S) smears, more representative transfer of cells from collecting device, evenly distributed cellular material, the choice of using

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residual cellular material for human papillomavirus testing.<sup>6</sup>

Diagnostic accuracy of LBC when compared to CPS is a matter of great debate. Several studies have shown increased sensitivity of LBC over CPS, whereas others showing decreased or equal sensitivity and specificity.<sup>6</sup>

So with this background the present study was undertaken, to study the differences in diagnosis between conventional and LBC methods in cervical cytology in our setting.

## MATERIALS AND METHODS

Prospective cross-sectional, observational hospital-based study was conducted in the Department of Pathology and Department of Obstetrics and Gynaecology, Pt. J.N.M. Medical College and Dr. B.R.A.M. Hospital Raipur Chhattisgarh, India, from February 2015 to January 2016.

Women attending gynecology OPD with complaints of symptoms related to cervical lesion and unhealthy cervix at Dr. B.R.A.M. Hospital, Raipur, were included in the study after written consent. A detailed clinical history and examination of the patient was taken and all details of clinical examination were noted as per pro forma.

### Inclusion Criteria

Women between 20 and 65 years of age presenting with complaints and symptoms related to cervical lesion and unhealthy cervix.

### Exclusion Criteria

- Women <20 years of age and >65 years of age
- Patients with total hysterectomy
- Presence of intrauterine device
- Pregnant women
- Patients taking treatment (chemo and radiotherapy) for any type of cancer.

The samples (pap smears) were taken with cervex-brush (split-sample technique), first a CPS was prepared and immediately alcohol-fixed. For LBC same brush head was suspended in preservative fluid after detachment. Preservative fluid was transferred to the cytopathology laboratory for further processing which took place as per the prescribed protocol for the LBC equipment. Both the slides were stained by papanicolaou technique. Pap smear reporting was done according to the New Bethesda System 2014 for both. Cervical samples were compared for multiple parameters like unsatisfactory rates, diagnostic difference in various parameters for two methods.

## RESULTS

This study was conducted in 80 patients having uterine cervix lesions, from those attending the outpatient Department of Obstetrics and Gynecology in Pt. J.N.M. Medical College and associated Dr. B.R.A.M. Hospital Raipur during the 1-year period from February 2015 to January 2016. The results of LBC and CPS were compared and analyzed. The peak age group of patients for cervical lesion was between 31 and 40 years (36.2%).

Figure 1 shows the most common presenting complaints was white discharge per vagina in 33 cases (41.25%).

Table 1 shows most common per speculum finding was cervical erosion in 58.75%.

Table 2 shows in LBC 92.5% cases showed satisfactory smears while in CPS 78.8% cases showed satisfactory results ( $P = 0.02$ ).

Figure 2 shows clarity of background was more in LBC as compared to CPS.

Figure 5 shows comparison of Photomicrograph finding of CPS & LBC, liquid-based cytology smear showing clear background, while conventional pap smear showing presence of marked inflammatory cells which obscured the smear

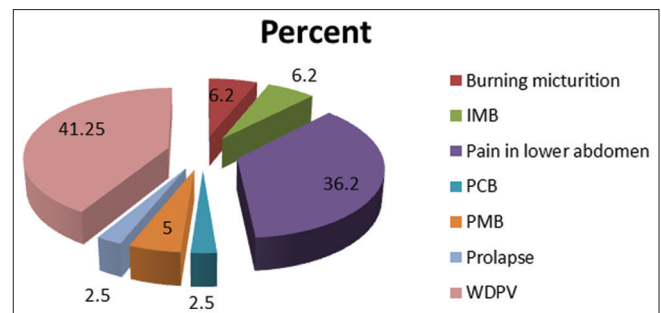


Figure 1: Distribution of cases in relation to presenting complaints ( $n = 80$ )

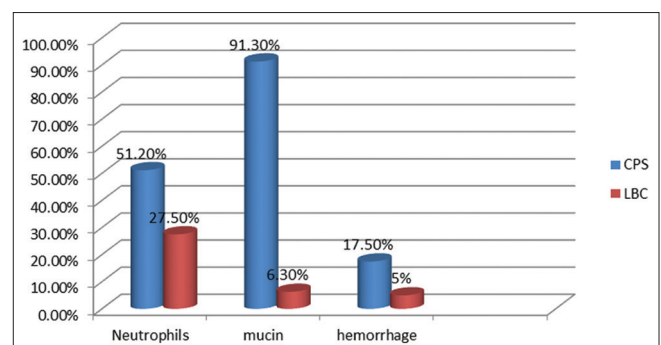


Figure 2: Comparison of clarity of background, between conventional pap smear and liquid-based cytology

Table 3 shows detection of endocervical cells significantly increased with CPS ( $P < 0.0001$ ).

Figure 3 shows in CPS distribution of microscopic finding were as follows, normal smear (5%) cases, negative for intraepithelial lesion or malignancy (NILM) (37.5%) cases, epithelial abnormalities (36.25%) cases. Whereas in LBC normal smear were found (7.5%) cases, NILM (45%) cases, and epithelial abnormalities (40%) cases.

Table 4 shows in LBC no of cases of atypical squamous cells of undetermined significance were 11.2%, while in CPS, it was 10% of cases. Our study shows that in LBC (13.7%) cases of low-grade squamous intraepithelial lesion (LSIL) were reported while 12.5% of cases were reported in CPS. In high-grade squamous intraepithelial lesion (HSIL) category, 10% of cases reported in LBC; while in CPS, it was 8.7% of cases. Detection of cases in squamous cell carcinoma (SCC) and AGS-NOS category were same in LBC and CPS, 3.75% and 1.25%, respectively.

**Table 1: Distribution of cases according to per speculum finding**

Perspeculum finding	Frequency (%)
Cervical erosion	47 (58.75)
Cervical growth	3 (3.75)
Cervical hypertrophy	27 (33.8)
Cervical polyp	1 (1.2)
Procedentia	2 (2.5)
Total	80 (100.0)

**Table 2: Comparison of satisfactory/unsatisfactory rate, in between conventional pap smear and liquid-based cytology**

Detection rate	Diagnostic technique n (%)			P value
	Conventional pap smear	Liquid-based cytology	Total	
Smear				
Satisfactory	63 (78.8)	74 (92.5)	137 (85.6)	0.02
Unsatisfactory	17 (21.2)	6 (7.5)	23 (14.4)	
Total	80 (100.0)	80 (100.0)	160 (100.0)	

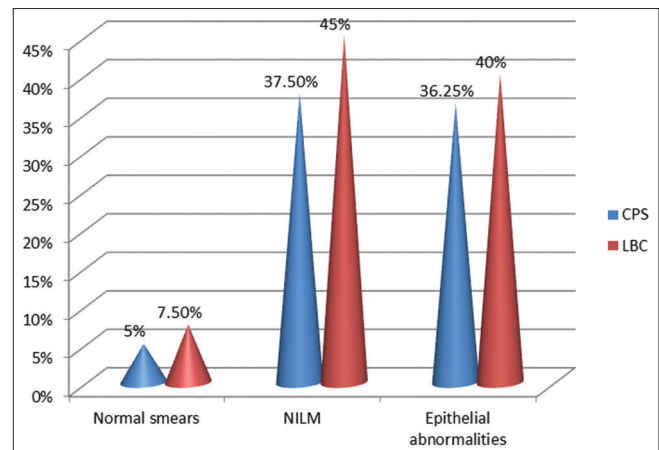
**Table 3: Comparison of endocervical cells detection in between conventional pap smear and liquid-based cytology**

Endocervical cells	Diagnostic technique n (%)			P value
	Conventional pap smear	Liquid-based cytology	Total	
Absent	34 (42.5)	65 (81.3)	99 (61.8)	<0.0001
Present	46 (57.5)	15 (18.8)	61 (38.1)	
Total	80 (100.0)	80 (100.0)	160 (100.0)	

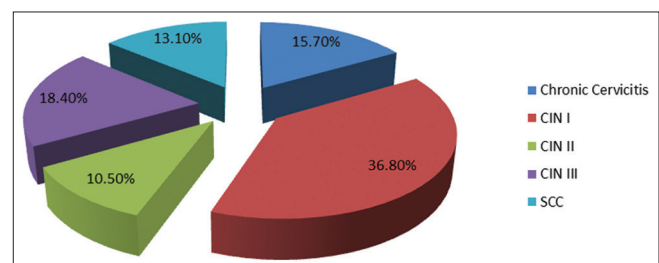
Figure 7 shows comparison of Photomicrograph finding of CPS & LBC pap smear, of a case of low-grade squamous intraepithelial lesion showing mature squamous cells with enlarged nuclei with variable chromatin and nuclear membranes,

Figure 4 shows histopathological finding observed in our study. The most common finding was cervical intraepithelial neoplasia (CIN) I (36.8%) followed by CIN III (18.4%), chronic cervicitis (15.7%), and CIN II (10.5%), and SCC (13.1%).

Table 5 shows diagnostic efficacy of CPS and LBC for evaluation of cervical cytology. Sensitivity of CPS for detection of LSIL lesions was 71.4% for HSIL lesions (63.6%). While sensitivity of LBC was 78.6%, 72.7% for LSIL, HSIL, lesions respectively. Specificity of LBC was 100% for all categories of epithelial abnormalities; while in CPS, it was 95.8% for LSIL, 96.3% for HSIL. Positive predictive value (PPV) of CPS for LSIL lesions were 90.9%, for HSIL lesions (87.5%), whereas PPV of LBC was 100% for both categories of epithelial abnormalities. Negative predictive value of CPS for LSIL lesions (85.1%) and for HSIL lesions (86.6%); while for LBC, it was 88.9% for LSIL, 90% for HSIL.



**Figure 3: Comparison of microscopic findings in between conventional pap smear and liquid-based cytology**



**Figure 4: Histopathological finding (n = 38)**



## DISCUSSION

In the present study, a maximum number of cases were noted between 31 and 40 years. Similar finding of a maximum number of patients presenting to the age group of 30-35 years were observed by Siebers *et al.* (2009)<sup>7</sup> and Ranjana and Sadhna (2016).<sup>4</sup>

Whereas Afsan *et al.* (2007)<sup>8</sup> and Longatto-Filho (2015)<sup>9</sup> observed maximum no of cases in age group was 21-40 years and 25-44 years, respectively.

In the present study, the most common presenting complaint was white discharge per vagina (41.25%). Similar finding was observed by Afsan *et al.* (2007)<sup>8</sup> and Neelima (2012).<sup>10</sup>

Table 6 shows that in our study presence of satisfactory smears were found to be significantly higher in LBC as compared to CPS. In LBC it was (92.5%) while in CPS it was (78.8%).

Our finding was in concordance with the studies of Bergeron (2001),<sup>5</sup> Afsan *et al.* (2007),<sup>8</sup> Strander *et al.* (2007),<sup>11</sup> Beerman *et al.* (2009),<sup>2</sup> Singh *et al.* (2015),<sup>6</sup> and Costa (2015).<sup>12</sup> They also reported an increased number of satisfactory cases on LBC than conventional smears, which was statistically significant.

**Table 4: Comparison of distribution of epithelial abnormalities between conventional pap smear and liquid-based cytology**

Microscopic finding	Diagnostic technique n (%)		P value
	Conventional pap smear	Liquid-based cytology	
Microscopic findings			
ASCUS	8 (10)	9 (11.2)	0.99
LSIL	10 (12.5)	11 (13.7)	
HSIL	7 (8.7)	08 (10)	
SCC	3 (3.75)	03 (3.75)	
AGC-NOS	1 (1.25)	01 (1.25)	
Total	29 (36.25)	32 (40)	

LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, SCC: Squamous cell carcinoma

**Table 5: Diagnostic efficacy of CPS and LBC for evaluation of cervical cytology**

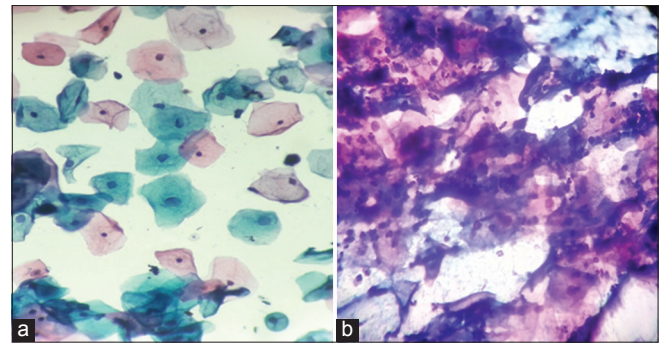
Diagnostic parameters	LSIL		HSIL	
	CPS	LBC	CPS	LBC
Sensitivity (%)	71.4	78.6	63.6	72.7
Specificity (%)	95.8	100	96.3	100
PPV (%)	90.9	100	87.5	100
NPV (%)	85.1	88.9	86.6	90

LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, CPS: Conventional pap smear, LBC: Liquid-based cytology, PPV: Positive predictive value, NPV: Negative predictive value

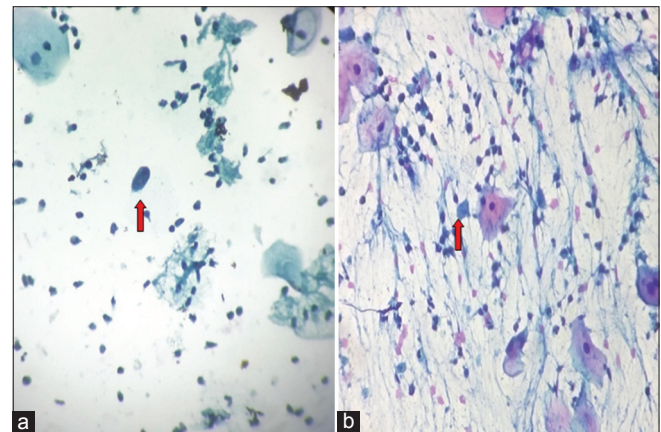
Afsan *et al.* (2007)<sup>8</sup> observed that all drying artefact and cytolysis is almost absent or minimal with LBC because of immersion of cells into the liquid fixative and specimen adequacy was greatly improved due to the absence of limiting factors such as blood, mucus, and inflammatory cells. Only conventional smears were unsatisfactory due to thick smear, which was not a problem with LBC due to even distribution of cells. These findings are in concordance with our study.

Our finding is in discordance with the studies of Stabile *et al.* (2015),<sup>13</sup> Sharma *et al.* (2015).<sup>14</sup> They reported that there was no statistically significant difference between adequacy rate of CPS and LBC.

In the present study, the percentage of background inflammation significantly reduced with LBC (27.5%) compared to CPS (51.2%) with *P* value (0.002). This is in



**Figure 5: Photomicrograph of liquid-based cytology smear showing clear background, while conventional pap smear showing presence of marked inflammatory cells which obscured the smear (PAP, x400). (a) Liquid based cytology (satisfactory), corresponding. (b) Conventional pap smear (unsatisfactory)**



**Figure 6: Photomicrograph of pap smear of a case of trichomonas vaginalis showing rounded or ovoid cyanophilic organism, cytoplasmic granules and outline of a nucleus can be discerned, the organism may be better visualized on liquid based preparations (PAP, x400). (a) Liquid based cytology, corresponding (b) conventional pap smear of same patient**



**Table 6: Comparison of detection of satisfactory smears in between conventional and LBC reported by different authors**

Authors	Years	Satisfactory smears in CPS (%)	Satisfactory smears in LBC (%)	P value
Bergeron <i>et al.</i> <sup>5</sup>	2001	88.4	99.2	<0.001
Afsan <i>et al.</i> <sup>8</sup>	2007	31.9	83.1	-
Strander <i>et al.</i> <sup>11</sup>	2007	99.7	99.3	0.002
Beerman <i>et al.</i> <sup>2</sup>	2009	99.11	99.87	<0.0001
Singh <i>et al.</i> <sup>6</sup>	2015	95.7	98.3	0.0006
Costa <i>et al.</i> <sup>12</sup>	2015	98.29	95.62	0.02
Stabile <i>et al.</i> <sup>13</sup>	2015	98	99	NS
Sharma <i>et al.</i> <sup>14</sup>	2016	92	93	NS
Present study	2016	78.8	92.5	0.02

CPS: Conventional pap smear, LBC: Liquid-based cytology

**Table 7: Comparison of endocervical cells detection in between conventional pap smear and LBC reported by different authors**

Authors	Year	CPS (%)	LBC (%)	P value	Sample technique
Bergeron <i>et al.</i> <sup>5</sup>	2001	6.2	6.8	-	Not split sample
Kirschner <i>et al.</i> <sup>16</sup>	2006	-	-	<0.005	-
Beerman <i>et al.</i> <sup>2</sup>	2009	86.1	89.01	<0.0001	Not split sample
Sueli Aparecida Batista Stabile <sup>13</sup>	2015	93	84	Statistically significant	Split sample
Longatto-Filho <i>et al.</i> <sup>9</sup>	2015	58	56.7	No difference	Not split sample
Sharma <i>et al.</i> <sup>14</sup>	2016	16	31	0.008	Not split sample
Present study	2016	57.5	18.8	<0.0001	Split sample

CPS: Conventional pap smear, LBC: Liquid-based cytology

**Table 8: Comparison of sensitivity and specificity of CPS and LBC methods (by taking LSIL as a cytology cut-offs), reported by different authors**

Authors	Years	Sensitivity (%)		Specificity (%)	
		CPS	LBC	CPS	LBC
Longatto Filho <i>et al.</i> <sup>21</sup>	2005	49.8	70	88.2	75.4
Beerman <i>et al.</i> <sup>2</sup>	2009	92.04	96.24	98.2	97.8
Arbyn <i>et al.</i> <sup>22</sup>	2008	75.6	79.1	81.2	78.8
Present study	2016	71.4	78.6	95.8	100

CPS: Conventional pap smear, LBC: Liquid-based cytology, LSIL: Low-grade squamous intraepithelial lesion

**Table 9: Comparison of sensitivity and specificity of CPS and LBC methods (by taking HSIL as cytology cut-offs), reported by different authors**

Authors	Years	Sensitivity (%)		Specificity (%)	
		CPS	LBC	CPS	LBC
Bergeron C <i>et al.</i> <sup>5</sup>	2001	82	86	40	43
Longatto Filho <i>et al.</i> <sup>21</sup>	2005	72.8	91.3	85.2	70.9
Taylor <i>et al.</i> <sup>23</sup>	2006	69.1	60.3	94.5	94.1
Afsan <i>et al.</i> <sup>8</sup>	2007	53.7	97.6	50	50
Zhu <i>et al.</i> <sup>24</sup>	2007	47	66	-	-
Beerman <i>et al.</i> <sup>2</sup>	2008	93.46	97.19	98.2	97.8
Arbyn <i>et al.</i> <sup>22</sup>	2008	55.2	57.1	96.7	97
Present study	2016	63.6	72.7	96.3	100

CPS: Conventional pap smear, LBC: Liquid-based cytology, HSIL: High-grade squamous intraepithelial lesion

concordance of the study of Costa (2015)<sup>12</sup> and Sharma *et al.* (2016);<sup>14</sup> they also observed reduction of background inflammation with LBC.

Our study found that mucin was present in the background in CPS was higher as compared to LBC, which is similar to study done by Sulochana *et al.* (2014).<sup>15</sup>

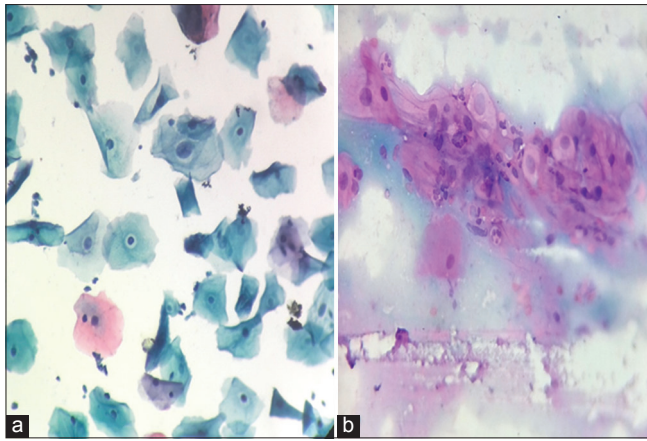
In our study, hemorrhage was present in the background in 17.5% case in CPS as compared to 5% case in LBC. These finding depicted that by using LBC hemorrhage in background was reduced. This is in concordance with the study of Sharma *et al.* (2015)<sup>14</sup> (Table 7).

In our study, we observed that endocervical cells were present in 57.5% cases in CPS while in LBC it was 18.8% which is statistically significant with  $P < 0.0001$ .

This is in concordance of the studies of Kirschner *et al.* (2006)<sup>16</sup> and Stabile *et al.* (2015).<sup>13</sup> They also observed statistically significant difference in endocervical cells detection in between CPS and LBC.

This finding in our study in consistence with other studies is justified because smears were collected by split sample technique. First, slide for CPS was prepared, then for LBC same brush head was suspended in the preservative fluid after detachment so that this technique would provide more transfer of such cells to the slide.<sup>13</sup>

Endocervical cells are less adequately transferred to the vial because they are more likely to be trapped in endocervical mucus that is held by the collection hairs of the cervix-brush and thus are less easily dispersed in the



**Figure 7: Photomicrograph of pap smear of a case of low-grade squamous intraepithelial lesion showing mature squamous cells with enlarged nuclei with variable chromatin and nuclear membranes, in liquid-based cytology, nuclear hyperchromasia is less evident (PAP,  $\times 400$ ). (a) Liquid based cytology (b) conventional pap smear**

PreservCyt fixative. Furthermore, trapping of cylindrical cells in endocervical mucus during the processing of the LBC sample could potentially affect the recovery of these specific cells.<sup>17</sup>

Our finding showed discordance with the studies of Beerman *et al.* (2009),<sup>2</sup> Sharma *et al.* (2016),<sup>14</sup> who reported that with regard to the presence of endocervical cells/metaplastic squamous cells, LBC gave better results.

Their method of collection of the sample was not split sample technique; they used to collect two samples in one sitting. Initially, a direct pap smear was made (CPS) using an Ayre spatula, for conventional Pap staining. The second sample was collected in a vial for LBC using the detachable endocervical brush. CPS is usually associated with some loss of cells in the collecting device while LBC is likely to be more representative due to direct transfer of the entire collecting device for the preservation and homogenization of the sample during processing.

Detection of epithelial cell abnormalities between the two methods LBC versus CPS was significantly not different. Similar result were found by studies done by Siebers *et al.* (2008),<sup>18</sup> Beerman *et al.* (2009),<sup>2</sup> Am Fam Physician (2010),<sup>19</sup> Hideki Taoka *et al.* (2010),<sup>20</sup> Singh *et al.* (2015),<sup>6</sup> Ranjana and Sathna (2016),<sup>4</sup> and Sharma *et al.* (2016).<sup>14</sup>

In the present study, in CPS out of 30 NILM cases, three cases were of trichomonas, two cases of bacterial vaginosis and candida each, while in LBC out of 36 NILM cases, six cases of trichomonas, five cases of candida and three cases of bacterial vaginosis. In our study, detection of infectious organism was higher (39%) in LBC as compared to 23.4% in CPS.

Figure 6 shows comparison of Photomicrograph finding of CPS & LBC pap smear, of a case of trichomonas vaginalis showing rounded or ovoid cyanophilic organism, the organism may be better visualized on liquid based preparations

This finding is supported by study done by Afsan *et al.*<sup>8</sup> This finding is in discordance with the study of Sharma *et al.* (2016).<sup>14</sup>

Table 8 shows that in present study sensitivity of LBC (78.6%), for detection of a histological proven lesions (CIN I/ LSIL) was significantly higher than CPS (71.4%). Similar observation was reported by Adhemar Longatto Filho *et al.*<sup>21</sup> and Beerman *et al.*<sup>2</sup>, they observed that Liquid based cytology had a significantly higher sensitivity than the conventional Pap to detect LSIL+ lesions. Arbyn *et al.*<sup>22</sup> reported similar sensitivity and specificity of two methods. This is in discordance with our study. Our study also showed significantly higher specificity of LBC (100%) than CPS (95.8%) when using LSIL as a cytological cutoffs. This is in discordance with Arbyn *et al.*<sup>22</sup> and Beerman *et al.*<sup>2</sup>, They reported similar specificity between the two methods. Adhemar Longatto Filho *et al.*<sup>21</sup>, reported that specificity of conventional smear in their study (88.2%) was significantly higher than LBC (75.4%) considering LSIL+ lesions. This finding is in discordance with our study.

Table 9 shows that in present study, sensitivity of LBC (72.7%) was significantly higher than CPS (63.6%) for detection of histologically proven HSIL lesions and specificity was also significantly higher in LBC (100%), as compared to CPS (96.3%). Studies done by Bergeron *et al.*<sup>5</sup>, Adhemar Longatto Filho *et al.*<sup>21</sup>, Afsan *et al.*<sup>8</sup>, Jie Zhu *et al.*<sup>24</sup> and Beerman *et al.*<sup>2</sup> found that in their studies sensitivity of LBC were higher than CPS, this is consistent with our study. Adhemar Longatto Filho *et al.*<sup>21</sup> observed that Liquid based cytology had a significantly higher sensitivity (91.3%) than the conventional Pap (72.8%) to detect HSIL+ at histology. Study done by Taylor *et al.*<sup>23</sup>, of 5652 cases, shows that CPS & LBC performance and accuracy were statistically similar in their study. This finding is in discordance with our study. Large meta-analyses by Arbyn *et al.*<sup>22</sup> included 109 studies where positivity and/or adequacy rate was studied. In their analyses, there was no statistically difference in sensitivity and specificity between the two different methods for detection of CIN2+, these findings are in discordance with our study.

## CONCLUSION

LBC shows an almost complete elimination of most causes for unsatisfactory CPS such as mucin, hemorrhage, inflammatory cells with scant cellularity remaining as the

sole cause for unsatisfactory LBC. Using LBC, it was possible to detect infective organism even when their load was low. LBC can be considered superior to conventional smear with respect to adequacy of smear, clarity of background, detection of infective organisms and increased sensitivity and specificity for detection of LSIL and HSIL lesions. Considering the higher cost of LBC, especially in low-resource setting like ours, it could not be generalized but wherever it is feasible LBC can be used instead of conventional cytology.

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# Analyzing Predictive Factors for Major Lower Extremity Amputations in Diabetic Foot Infection: A Prospective Study

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## Abstract

**Introduction:** Diabetic foot is a common entity in developing nations. Amputation due to diabetic foot infection adds up burden to an individual as well as to the economy of the country. Moreover, there are no separate criteria/scoring for detecting early unsalvageable limb.

**Materials and Methods:** This is a prospective observational study which was carried out in 120 patients who were admitted with diabetic foot infections in Government Rajaji Hospital, Madurai for a period of 18-month and they were observed for gangrene, pulse status, ankle-brachial index (ABI), infection patterns, osteomyelitis, hemoglobin (Hb), total white blood cells (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Lipid profile Lipoprotein (LDL), and cardiac status at the time of admission. A scoring system was devised using these parameters.

**Results:** Out of these parameters - gangrene, pulse status, infection, osteomyelitis, and ABI were found to be major contributory factors and Hb, duration of diabetes, total WBC count, CRP, cardiac status, ESR, and lipid profile were found to be minor contributory/predictive factors. In this scoring system, patients with score 13 and below were managed by conservative procedures, those with 14-17 went for minor amputation and scores 18 and above went for major amputation.

**Conclusion:** Using our scoring system, we can separate the patient who is more likely to go for amputations as early as possible and provide them an early apt intervention to save his/her limb.

**Key words:** Amputation, Diabetes, Diabetic foot, Predictive factors, Scoring

## INTRODUCTION

India with approximately 42 million cases is ranked on top of the list of 10 nations massively affected with diabetes.<sup>1,2</sup> Among diabetes related complications, ulceration of foot is the most common one, affecting about 15% of diabetic patients in their lifetime.<sup>2</sup> This can be attributed to several day to day social and cultural practices. Among those barefoot walking, inadequate facilities for diabetes care, poor hygiene, illiteracy, and poor socioeconomic conditions

are important which lead to ulceration.<sup>3</sup> Limb amputation has a significant impact on an individual, not only by affecting the physical status but also leads to increasing dependency, loss of income and expenses of treating foot ulcers if patients require admission in a hospital.<sup>4</sup> Sporadic qualitative research suggests that diabetic foot ulceration (DFUs) has a significant social impact with patients reporting stigma, isolation from society, loss of basic social role, and unemployment.<sup>5</sup>

Foot ulceration is absolutely preventable and by simple interventions one can reduce amputations up to 80%. Good hemoglobin (Hb) status, adequate control of blood pressure, and prompt lipid levels are well established crucial elements in the reduction of risk related to complications of diabetes.<sup>6,7</sup> Regular evaluation and early treatment are the most effective mechanisms to prevent the devastating diabetic foot complications. Unfortunately, the majority of

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patients admitted in the health-care center for DFUs receive an inadequate lower extremity evaluation.<sup>8</sup> Although, there is an obvious increase in diabetic foot care awareness, there are tremendous gaps in routine foot evaluations. To achieve such aims, early detection of the foot at risk should be afforded a high clinical priority. Our interest in identifying the prevalence of risk factors aroused mainly due to the fact that the number of cases attending to our hospital with DFUs has increased tremendously during the last 3-4 years. To our knowledge, this is probably the first report wherein a hospital-based survey from India was conducted to evaluate the role of risk factors involved in DFUs to devise a scoring system.

## MATERIALS AND METHODS

This study was conducted in the Department of General Surgery, Government Rajaji Hospital, Madurai. It was conducted after seeking prior approval from the Ethical Committee of the institute. Prior written consent was obtained from every recruited patient.

In total, 403 diabetic patients attending the hospital were examined and 120 were diagnosed to have diabetic foot infections in the span of 18 months.

Diabetes was diagnosed following the criteria of the World Health Organization of a fasting venous plasma glucose  $>7.0$  mmol/L or a 2 h postprandial venous plasma glucose level of  $>11.1$  mmol/L using the glucose oxidase method.<sup>9</sup> Patients were interviewed using a pretested structured questionnaire to document clinical history namely family/social history, age, sex, routine habits (smoking, tobacco chewing, and alcohol intake), duration of diabetes and diabetic foot, treatment, and causes of foot ulcer. Patients were critically asked to provide details related to the duration of the DFUs and possible causative factors if they were able to sense the presence of the foot ulcer before its actual appearance.

A complete clinical examination was performed on the foot to identify any presence of gangrene, involvement of bone, cellulitis, pulse status, and ankle-brachial index (ABI).

Complete biochemical investigations such as Hb%, total white blood cells (WBC) count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lipid profile (LDL), and renal function tests were performed.

X-ray of concerned local part, bacteriological tissue culture, and echocardiogram were also taken.

Using these data and clinical analysis, a scoring system was formulated (Table 1).

## RESULTS

Total number of patients - 120

Conservatively managed - 76

Major amputations - 35

- Amputation at transtibial level (below knee amputation) or higher.

Minor amputations - 9

- Toe disarticulation
- Ray amputation
- Midtarsal amputation
- Tarso-metatarso amputation.

Age distribution of 120 cases was studied. Out of which, youngest patient was 35 years old and eldest patient was 75 years old. Highest number of cases was found in the age group of 61-70 (Table 2). By age distribution, patients with younger age tend to have aggressive disease.

Out of 120 patients, 96 were male and 24 were female (Table 3). Males are more commonly affected in diabetic foot infections and amputation rates are also higher compared to females.

100% of patients with complete gangrene went for amputation (Table 4).

100% of patients with absent pulse went for amputations. In case of weak pulse, out of 48 patients, 9 went for minor amputation (Table 5).

In case of ABI, patients with critical limb (i.e.,  $<0.3$ ) were 100% unsalvageable (Table 6).

In case of bony involvement, i.e., osteomyelitis, out of 30 patients with osteomyelitis, 17 went for amputation, 9 went for minor amputation; in comparison with nonosteomyelitic limb out of 90 patients 18 alone went for amputation (Table 7). Infections tend to be more severe in case of polymicrobes. Out of 35 amputations, 34 are infected with polymicrobes (Table 8). In all those 35 amputations, amputees had resistant organisms invariably (Table 9).

With regards to duration of diabetes, out of 35 patients, 30 were having diabetes for more than 5 years and within a year of diagnosis of diabetes no one was going for amputation (Table 10).

Out of 35 patients, who went for amputation, 25 patients were with Hb  $<8$  g/DL (Table 11). Patients with total WBC count more than 15000 cells/cumm, 22 patients went for amputation. And with count 10000 cells/cumm to 15000 cells/cumm, 13 patients went for amputation (Table 12).

**Table 1: Scoring system**

Madurai medical (MM) scoring system for analyzing major contributing factors for lower limb amputations in diabetic foot infections			
	0	1	2
Presence of gangrene	Nil	Minimal color change	(+)(+) Complete gangrene
Pulse status of concerned part	(+) (+)	(+)	(-)
ABI	0.9-1.1	0.9-0.3	<0.3
Bony involvement	Nil		Osteomyelitis (+)
Infections	Nil	Monomicrobial	Polymicrobial
Duration of diabetes	<1 year	1-5 yr	More than 5 years
Antibiotic sensitivity	No resistance		Resistant to any drug
HB%	>12 g	8-12 g	<8 g
TC	<10000 cells/cumm	10000-15000 cells/cumm	>15000 cells/cumm
ESR	<20 mm/h	20-100 mm/h	>100 mm/h
CRP	<0-10 mg/l	10-15 mg/l	>15 mg/L
LDL	<100 mg/dl	100-189 mg/dl	>190 mg/dl
Cardiac status	Normal ECHO study	LVEF<50%	LV thrombus; EF<40%

LVEF: Left ventricular ejection fraction, ABI: Ankle-brachial index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, TC: Total count, Hb: Hemoglobin, LDL: Lipid profile

**Table 2: Age distribution**

Age	Conservative	Amputation	Minor
<50	9	14	0
51-60	17	12	3
61-70	39	7	4
>70	11	2	2

**Table 3: Sex distribution**

Sex	Conservative	Amputation	Minor
Male	62	27	7
Female	14	8	2

**Table 4: Presence of gangrene**

Presence of gangrene	Conservative	Amputation	Minor
Nil	41	0	0
Minimal color change	35	0	9
(+)(+) Complete gangrene	0	35	0

**Table 5: Pulse status of concerned part**

Pulse status of concerned part	Conservative	Amputation	Minor
(+)(+)	37	0	0
(+)	39	0	9
(-)	0	35	0

**Table 6: ABI**

ABI	Conservative	Amputation	Minor
0.9-1.1 (38)	38	0	0
0.9-0.3 (47)	38	0	9
<0.3 (35)	0	35	0

ABI: Ankle-brachial index

Out of 35 amputations, 32 patients had high levels of CRP, i.e., more than 10 mg/L (Table 13). In case of ESR

<20 mm/h, all those patients were managed conservatively while patients with ESR>100 mm/h went for amputation invariably (Table 14).

Lipid profile plays an important role in influencing diabetic foot amputation. Out of the total 35 amputees, 10 had LDL level <100 mg/dl whereas 25 had >100 mg/dl (Table 15). Cardiac status of the patient was evaluated by left ventricular ejection fraction (LVEF). In almost 60% of amputated patients, the LVEF is <50% (Table 16).

#### Scoring System Observed from Above Study (Table 17)

Scores 13 or below went for debridement alone.

Scores 14-17 went for minor amputation.

Scores 18 and above went for major amputation.

## DISCUSSION

In our study, among those amputees, patient with age <50 years - 40% went for amputation, 51-60 - 34.3% went for amputation, 61-70 - 20% went for amputation, and >70 - 5.7% went for amputation. Young people tend to have more aggressive disease. Patients with presence of gangrene, absent local pulse, critical ABI went for major amputations, whereas patients with pregangrenous change, weak local pulse there is increased chances of minor amputation. Persistent infection may occur due to underlying osteomyelitis.<sup>10</sup> In case of bony involvement, i.e., patients with features of osteomyelitis 56.6% went for major amputation and 30% went for minor amputation. A diabetic patient with neuropathy is more prone for repetitive trauma and infection.<sup>11</sup> Polymicrobes are invariably common in amputees and accounts for about 97.1%. Moreover, they are resistant to at least one drug. Among amputees, 85.7% of patients have diabetes >5 years.

**Table 7: Bony involvement**

Bony involvement	Conservative	Amputation	Minor
Nil	72	18	0
Osteomyelitis (+)	4	17	9

**Table 8: Infections**

Infections	Amputation
Nil	0
Monomicrobial	1
Polymicrobial	34

**Table 9: Antibiotic sensitivity**

Antibiotic sensitivity	Amputation
No resistance	0
Resistant to any drug	35

**Table 10: Duration of diabetes**

Duration of diabetes (year)	Amputation
<1	0
1-5	5
More than 5	30

**Table 11: Hemoglobin**

Hb%	Amputation
>8 g	10
<8 g	25

Hb: Hemoglobin

**Table 12: Total WBC count**

TC (cells/cumm)	Amputation
<10000	0
10000-15000	13
>15000	22

WBC: White blood cells, TC: Total count

Hb level plays an important role since it is responsible for the cellular oxygen supply.<sup>12</sup> Hence, amputation tendency increases with fall in Hb% levels due to reduced oxygen supply. Total WBC count reflects the wound infection rate and it increases in infection.<sup>13</sup> In our study, amputation rate increases with increase in total count (TC). Among those 35 amputations, 62.8% of patients had TC >15000 cells/cumm.

CRP provides a direct index of acute inflammatory process<sup>13</sup> and 91.4% of total amputees had elevated CRP levels.

ESR denotes an indirect measure of acute phase response.<sup>13</sup> Out of 35 amputees, 17.2% had elevated

**Table 13: C-reactive protein**

CRP	Amputation
<0-10 mg/dl	3
>10 mg/dl	32

CRP: C-reactive protein

**Table 14: ESR**

ESR	Amputation
<20 mm/h (8 patients)	0
20-100 mm/h (106 patients)	29
>100 mm/h (6 patients)	6

ESR: Erythrocyte sedimentation rate

**Table 15: LDL**

LDL	Amputation
<100 mg/dl (80 patients)	10 (29%)
>100 mg/dl (40 patients)	25 (71%)

LDL: Lipid profile

**Table 16: Cardiac status**

Cardiac status	Conservative	Amputation	Minor
Normal ECHO study	65	11	4
LVEF<50%	11	24	5

ECHO: Echocardiogram, LVEF: Left ventricular ejection fraction

**Table 17: Conclusion**

Score	Surgical management
13 and below	Debridement alone
14-17	Minor amputation
18 and above	Nonsalvageable

ESR >100 mm/h and 82.8% had elevated ESR levels but <100 mm/h.

Dyslipidemia is a risk factor for peripheral arterial disease.<sup>14</sup> High LDL is a major risk factor for atherosclerosis<sup>15</sup> and peripheral arterial disease. Among those amputation, 71.4% of patients had elevated LDL levels. A decrease in ejection fraction compromises cardiac function and may lead to cardiac failure,<sup>16</sup> which aggravates ischemic changes.<sup>11</sup> In almost 60% of amputated patients, LVEF is <50%.

From the above study, the following factors are considered as major contributory/predictive factors for amputation in diabetic foot patients - presence of gangrene, pulse status of concerned part, ABI, presence of osteomyelitis, and soft tissue infections. The minor contributory/predictive factors for amputation in diabetic foot patients are as follows - hemoglobin status, total WBC count, ESR, CRP, lipid profile (LDL), duration of diabetes, and cardiac status.

## CONCLUSION

Diabetic foot infection should be treated aggressively to prevent morbidity and mortality of the patient. Our study concluded about the major and minor predictive/contributory factors for amputation. Moreover, we also devised a scoring system to predict the early unsalvageable limb so as to attain the best possible outcome for the patient, i.e., a stable limb with intact sensation that can engage in everyday activities.

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# Two versus Three Ports Technique for Laparoscopic Cholecystectomy: A Randomized Comparative Study

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## Abstract

**Introduction:** Laparoscopic cholecystectomy (LC) using 3 or 4 surgical ports has been previously compared in various clinical trials. However, LC using 3 or 2 surgical ports has not been evaluated.

**Materials and Methods:** Patients were randomized into two groups: L2 using 2 ports for LC and L3 using 3 standard ports for LC.

**Results:** Pain was evaluated at recovery, 4<sup>th</sup> h and then every 24 hourly up to the 5<sup>th</sup> post-operative day, using a visual analog pain scale. Patients in Group L2 and L3 had similar post-operative pain scores and analgesic consumption.

**Conclusion:** In terms of post-operative pain score and analgesic consumption, 2 post-LC does not offer any added benefit over 3 ports LC.

**Key words:** Pain in laparoscopic cholecystectomy, 3 ports laparoscopic cholecystectomy, 2 ports laparoscopic cholecystectomy

## INTRODUCTION

Laparoscopic cholecystectomy (LC) emerged as a new modality in 1989 for the treatment of symptomatic biliary lithiasis and very soon after it became the new gold standard for the treatment.<sup>1-3</sup> The benefits of LC include lower post-operative pain, shortened hospital stay, early recovery, and better cosmetic results. Although initially the technique was started as a surgical procedure with 4 ports but with time various modifications were made to make it less invasive. Initially, a 3 ports laparoscopic approach was preferred based on proper anatomical visualization of the operative site at the time of the initial laparoscopic evaluation. The introduction of the working channel laparoscope had further made it possible to use only 2 ports, along with

transdermal sutures and needles, for cholecystectomy. To our knowledge, there are no studies that have compare between 3- and 2-port approaches for LC; therefore, to elucidate which of these two approaches is better we aimed to compare the post-operative analgesic consumption and pain perception in these 2 groups of patient: LC performed with 3 and 2 ports.

## MATERIALS AND METHODS

After Institutional Ethical Clearance and Departmental permission this prospective randomized, observational study was done concurrently in the various medical colleges of Assam, among the patients presenting for LC by a total of five surgeons from January 2013 till September 2015. Inclusion criteria were as follows: Consecutive patients who were scheduled for elective LC due to gallstones, with American Society of Anesthesiology Grade I or II classification. Patients having severe systemic disease were excluded from the study group. Patients were familiarized with the study procedure and consent was obtained from all patients. A total of 70 patients were enrolled into this study who presented for elective LC. Eight patients

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were excluded due to demand for open surgery, not consenting for the study and due to associated severe systemic disease. A total of 62 patients were observed after exclusion. Informed consent was obtained from all patients included in our study. Patients were then assigned into the Group L2 or the Group L3 based on computer generated random numbers. Group L2 contain 30 patients and Group L3 contained 32 patients, respectively. The patient's age, weight, and other relevant demographic data were recorded. In Group L2 patients, LC was performed using 2 surgical ports where as in Group L3 patients it was performed using 3 surgical ports. Patients requiring conversion to open surgery were eliminated from our study. The same general anesthesia protocol was used in all patients. At the beginning of the surgery, all port sites were infiltrated with 0.25% bupivacaine 5 ml per port site. All patients were managed on an ambulatory basis when possible. When 10-12 mm ports were used, the fascia was routinely closed with polyglactin, and skin ports with polypropylene. In all of our study patients a standard high-definition laparoscopic module was used (Karl Storz, Tuttlingen, Germany), a urinary catheter was inserted for the duration of surgery, no routine gastric cannulation was done and pneumoperitoneum was created with the Veress needle, keeping intra-abdominal pressure below 12 mmHg in all our study patients. Patients were placed in a reverse Trendelenburg position, with slight rotation to their left side. In L3 group: One 10 mm umbilical port, one 10 mm subxiphoid port, and a 5 mm port in the right subcostal area of the midclavicular line were installed, the standard rigid 10 mm 08 optics and standard straight instruments were used, the gallbladder was pulled to expose Calot's triangle and the dissection made to obtain a critical view,<sup>4</sup> the cyst duct and the artery were ligated with titanium clips and the gallbladder dissection of the hepatic bed was performed with an electrosurgical hook. In L2 group: One umbilical 12 mm port and a 10 mm port in the right flank midaxillary line were installed, a rigid 12 mm 30 degree laparoscope with a working channel was introduced through the umbilical port, the right flank port was used with the auxiliary standard instruments to pull and fix the gallbladder, the clip applier was used to ligate the cyst duct and the artery dissection was made with instruments introduced through the working channel and a 65 cm Maryland dissector, and hook and scissors were used. In this technique, the patient was placed in lithotomy position, with the surgeon standing between the legs. The gallbladder was extracted via the umbilical port.

Postoperatively all patients were observed in the recovery room where pain was assessed using a standard visual analog pain scale (VAS) (on a scale of 0-10), pain scores were recorded at recovery, then at 4<sup>th</sup> h and thereafter at every 24 hourly, till the 5<sup>th</sup> post-operative day by an observer

who was blinded to the study group. Rescue analgesic in the form of injection tramadol 50 mg intravenous was administered on demand and repeated every 8 hourly thereafter if necessary, total analgesic requirement for the first 48 h postoperatively was also recorded.

In all cases, the intraoperative goal was to obtain the critical view of the Calot's triangle<sup>4,5</sup> before any clip was applied or any cut was made. No drains were placed in any of our patients. Patients were discharged as per hospital protocol and asked to come for review at the outpatient department after 7 days or immediately if they had any wound discharge. The study was done as a pilot study hence sample size calculation was not done. The data obtained from these patients were analyzed using SPSS version 21.0. The data were tested for normality and compared using appropriate statistical tests. A  $P < 0.05$  was considered statistically significant.

## RESULTS

In our study, the 2 surgical ports technique was used in 30 patients whereas the 3 surgical ports technique was used for 32 patients undergoing LC in our study. There was no statistically significant difference in the demographic parameters of the patients in both the groups.

The mean age of the L2 group was 46.25 years, and the mean age of the L3 group was 47.63 years. The L2 group consisted of 22 males (73.3%) and 8 females (26.7%), and the L3 group consisted of 24 males (75%) and 8 females (25%). The mean body mass index of the IU and PU groups was 24.65 and 23.89 kg/m<sup>2</sup>, respectively. There operation time between the two groups (65.82 min for L2, 64.78 min for L3) was comparable (Table 1).

Duration of post-operative hospital stay was 6 days in both the groups IU and PU. The mean post-operative tramadol consumption was 216 mg in the L2 group and 221 mg in the L3 group (Table 2). Post-operative pain scores observed were similar in both the Groups L2 and L3. There was no incidence of wound infection or internal organ injury caused by trocar insertion in any group.

## DISCUSSION

Laparoscopy has hugely modified the basic concepts and goals of modern day surgery, reducing operative trauma, recovery time, and improving cosmetic results. These benefits have become particularly desirable in the most common surgical procedures done worldwide, such as appendectomy and cholecystectomy. Today LC currently stands as the gold standard in the treatment of

**Table 1: Demographic parameters between the Groups L2 and L3**

Variable	Group L2 (n=30)	Group L3 (n=32)	P value
Age (years)	46.25±6.75	47.63±8.35	0.47 (t)
Sex ratio (male/female)	22/8	24/8	0.89 (c)
BMI (kg/m <sup>2</sup> )	24.65±4.23	23.89±6.53	0.58 (t)
Operation time (min)	65.82±9.5	64.78±9.34	0.66 (t)

BMI: Body mass index

**Table 2: Post-operative outcomes in both Groups L2 and L3**

Variable	L2 group (n=30)	L3 group (n=32)	P value
Duration of hospital stay (days)	6	6	1 (c)
Post-operative tramadol consumption (mg)	216±35	221±45	0.62 (t)
Wound infection (%)	0	0	-
Major organ injury (%)	0	0	-

symptomatic biliary lithiasis because of its clear advantages over open cholecystectomy in reducing recovery time and post-operative pain, shortening hospital stay and allowing patients an earlier return to everyday living.<sup>3</sup> Inspired by the success obtained with conventional LC, surgeons are now even striving to further reduce the invasiveness of laparoscopy by reducing the size of the ports or their number.<sup>6</sup> laparoscopic procedures have been extensively studied and ample literature is available on it.<sup>1-3</sup> But there is no study which has compared 2 versus 3 ports LC in Indian population, so we conducted this study.

Theoretically, if surgical trauma is reduced to a minimum it will lead to improved outcomes in pain management, patient comfort, post-operative complications, and shortened hospital stay. In our opinion, the added benefit of improving cosmesis is a natural consequence of the less invasive techniques but should not be a goal by itself.<sup>7</sup> Lee *et al.*<sup>8</sup> had observed that there is no difference between 3 versus 1 ports LC regarding pain as the most important variable. This was similar to our study results where we observed no difference in the post-operative pain scores in our patients. Pain after LC has been differentiated into three components: Visceral, abdominal wall, and that referring to the shoulder.<sup>9</sup> In our study, we observed not only similar

post-operative VAS scores but also similar rescue analgesic consumption in the 48 h postoperatively. In our study, the operative time was similar in our study patients, suggesting that both 2 and 3 ports laparoscopic procedure have similar operative ease. In summary, our study does not support 2 ports over 3 ports technique for LC in terms of reduction of post-operative pain and recovery time. Multicentric trials are required to confirm our study results. This study was somewhat limited in that it was a prospective study and we did not evaluate the incidence of incisional hernia which may occur in our patients after few years. Effects of systemic disease on the wound healing such as perioperative glycemic status and body oxygen levels were not assessed.

## CONCLUSIONS

LC performed with 2 ports approach does not seem to offer any advantage over the 3 ports approach with both the techniques having similar procedure time, post-operative pain score, and post-operative rescue analgesic consumption.

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# Multimodality Diagnostic Features and Treatment by Sialography of Juvenile Recurrent Parotitis: A Case Report

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## Abstract

Juvenile recurrent parotitis (JRP) is a rare disorder characterized by recurrent painful enlargement of the parotid gland on either one or both sides in children without suppuration or ductal obstruction. The etiology is unknown. The severity and frequency of the attacks vary and are characterized by enlargement of the gland, pain, fever, and decreased function of the gland. The diagnosis is usually made clinically and confirmed by imaging. We report a case of JRP in a 12-year-old girl and describe the imaging features of JRP in various modalities.

**Key words:** Juvenile recurrent parotitis, Magnetic resonance imaging, Ultrasound

## INTRODUCTION

Juvenile recurrent parotitis (JRP) is recurrent inflammation of parotid gland occurring in children between 4 months and 15 years of age, is of unknown etiology without suppuration or ductal obstruction and subsides at puberty.<sup>1-7</sup> The inflammation episodes are characterized by enlargement of unilateral or bilateral parotid glands with pain, erythema, sometimes fever, and decreased function of the gland.<sup>1-7</sup> The disease is more common in boys, commonly unilateral than bilateral, and if bilateral it is more severe on one side.<sup>1,2,4,5</sup> Diagnosis is made by clinical examination and parental history of recurrent swelling in the region of parotid gland and confirmation is usually done by imaging techniques.<sup>1-7</sup>

## CASE REPORT

A 12-year-old female child presented with complaints of swelling around both ears, more on the left side since

the last 4 days. There was history of multiple previous such episodes during the last three years. There was no history of fever, joint pain, rashes or dryness of mouth or eyes. There was no family history of similar episodes of swelling around the ear. Examination revealed a diffuse, firm, mildly tender swelling at the left parotid region and a milder nontender swelling over the right parotid gland. There was serous discharge at the Stensen's duct orifice on applying pressure over the gland and there was no erythema surrounding the orifice. Blood counts were normal and the erythrocyte sedimentation rate was mildly raised (45 mm). Serology for human immunodeficiency virus, rheumatoid factor, anti-Ro, anti-La, and antinuclear antibodies were negative. The child was diagnosed to have JRP. Ultrasound showed multiple round hypoechoic areas interspersed on a background of heterogeneous glandular echotexture, and no vascularity on color Doppler (Figure 1). Magnetic resonance T2 weighted thin slice images of the parotid gland showed enlarged left parotid gland and small cystic areas scattered within the glands bilaterally (Figure 2). There were also mildly enlarged bilateral jugulodigastric nodes. Symptom relief was suboptimal on conservative management with analgesics and intravenous antibiotics for three days, and a sialography was planned. Sialogram showed multifocal sialectasis in the form of multiple small contrast filling cysts communicating with the ductal system (Figure 3). Further copious irrigation of the parotid

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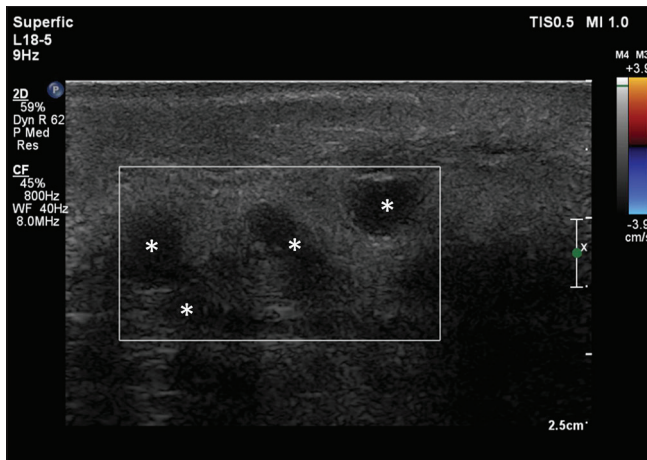
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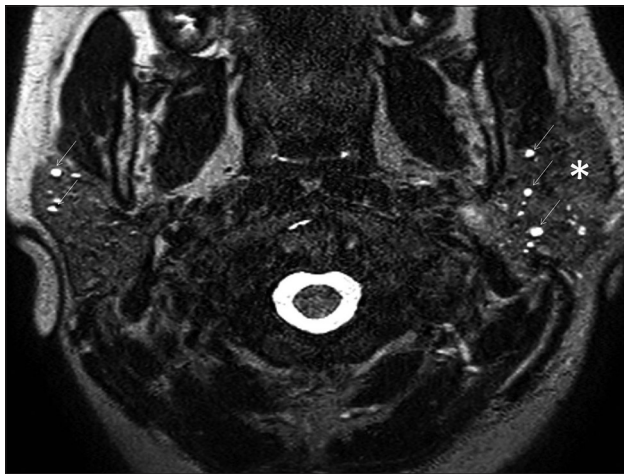
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**Figure 1: 12-year-old child with juvenile recurrent parotitis. Ultrasound image with Doppler showing multiple round hypoechoic areas (\*) without any Doppler signal representing multifocal sialectasia**

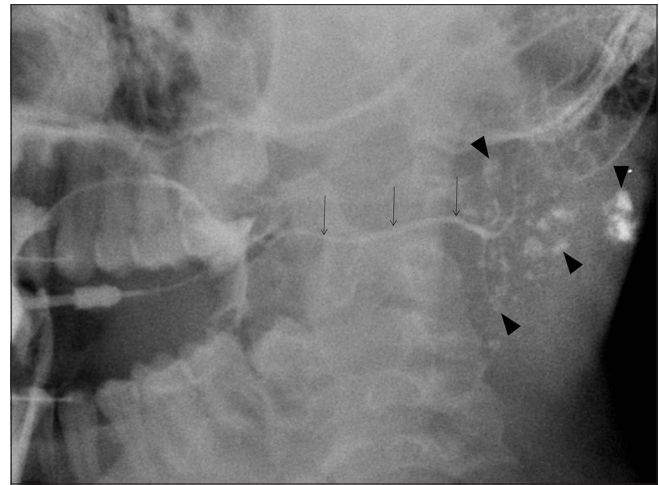


**Figure 2: 12-year-old child with juvenile recurrent parotitis. Magnetic resonance T2-weighted thin slice image at the level of parotid glands showing enlarged left parotid gland (\*) and multiple small cysts (some of them marked with white arrows) scattered within the glands bilaterally**

ductal system with normal saline was performed and the symptoms drastically improved within a day and she was discharged the next day. Parents were counseled that the disease would wear out as the child grows.

## DISCUSSION

JRP is usually misdiagnosed as mumps, ear or pharyngeal disease but the history of recurrent inflammation usually points toward proper diagnosis.<sup>1,3</sup> Etiology is unknown and disputed but the disease is considered multifactorial, factors including a congenital ectatic malformation of the salivary ducts, autoimmune factors, viral or bacterial infection, and altered salivary enzyme activity.<sup>2,3,5,8-11</sup> Another hypothesis based on endoscopic picture is decrease in glandular



**Figure 3: 12-year-old child with juvenile recurrent parotitis. Sialogram showed multifocal sialectasis in the form of multiple small contrast filling cysts (some of them marked with black arrowheads) communicating with the ductal system. Stensen's duct is shown by black arrows**

vasculature causing hyposecretion and resultant recurrent infection.<sup>12</sup>

Although the diagnosis is suggested clinically, it is usually confirmed by ultrasound. Ultrasound shows a heterogeneous glandular echotexture representing lymphocytic infiltrate and interspersed small cysts representing multifocal sialectasia.<sup>1-3,6,7,9</sup> The cysts may sometimes show debris within. Magnetic resonance imaging (MRI) of salivary glands with heavy T2-weighting is called MR sialography, which shows gland enlargement, heterogeneous signal intensity of the gland, and multiple interspersed cysts.<sup>2,13</sup> MRI performed during an active phase of inflammation shows enhancement of the gland and cysts are seen in children with previous recurrent parotitis episodes.<sup>8,13</sup> Sjogren's syndrome and sarcoidosis can have similar appearance but have different clinical features.<sup>2</sup>

Sialography performed by injecting contrast medium through a cannula placed in the parotid duct shows intraparenchymal multifocal areas of sialectasis with contrast stasis which is the hallmark of the disease.<sup>1,2,11</sup> Sialendoscopy is another diagnostic modality where the duct walls appear whitish with the absence of ductal wall blood vessels.<sup>1,2,4,5,14</sup> Sialography and sialendoscopy is seldom used currently for diagnosis unless they are used as a therapeutic measure in cases where conservative treatment which consists of analgesics, antibiotics, and plenty of oral fluids fails.<sup>5,15</sup> After sialography or sialendoscopy, the parotid ductal system is irrigated either with saline, steroid or antibiotic solution to clear off viscous saliva, debris, and mucus plugs.<sup>2,4,12,16,17</sup> Our patient showed significant improvement after sialography. Tympanic neurectomy and

parotidectomy have been tried in adult patients with severe parotitis and are not recommended for children.<sup>18,19</sup>

## CONCLUSION

Juvenile recurrent parotitis is a rare pediatric non-suppurative recurrent inflammatory disorder of the parotid gland diagnosed clinically, confirmed by imaging, and treated conservatively. Sialography and sialendoscopy have a therapeutic role in patients failing conservative management.

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# Dental Rehabilitation of Patients with Amelogenesis Imperfecta using Zirconia Crowns, Stainless Steel Crowns, and Composite Veneers: A Case Report

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## Abstract

Amelogenesis imperfecta (AI) is related to a group of developmental tooth abnormalities (also referred as hereditary dysplasia), which affect the genome of the individual and retard at least one of the stages of enamel formation. AI is, in general, a hereditary disorder with clinical impact on both deciduous and permanent teeth. Patients with AI often complain of tooth sensitivity, difficulty in chewing, self-consciousness about the appearance of their teeth, and an anterior open bite. We present a case report of AI (hypocalcified), which was diagnosed based on classical clinical and radiographic features.

**Key words:** Amelogenesis imperfecta, Composite, Esthetics, Stainless steel crowns, Zirconia crowns

## INTRODUCTION

Amelogenesis imperfecta (AI) is a group of inherited disorders characterized by abnormal or incomplete formation of the dental enamel; it manifests itself in both the primary and the permanent dentition. Estimates of the prevalence of AI appear to vary from one population to another. A Swedish study arrived at the conclusion that one out of every 700 individuals is affected by AI, while a study conducted in North America determined that it affects one person out of every 14,000 individuals.<sup>1</sup> Patients with AI are frequently complain of tooth sensitivity. Anterior open bite frequently occurs as a consequence of AI.

Four types of AI have been identified, and they are classified according to the phenotypes associated with them. Type I is characterized by hypoplastic enamel;

the enamel that is present is well mineralized, but the amount of enamel present is less than normal. Type II is characterized by hypomineralized enamel; its most noticeable feature is discolored enamel. Hypomineralized enamel can appear brown, yellow, or mottled. Type III is characterized by hypocalcified enamel; the enamel is dark and so soft that it is easily scraped by the instruments used in dental prophylaxis. Type IV is characterized by dental enamel that is both hypomatured and hypoplastic. By far, the most common type of AI is the hypoplastic type, which accounts more than 60% of cases. The hypomaturational type accounts for at least 20% of cases, and 7% of cases of AI are of the hypocalcified type.<sup>1</sup>

Inheritance patterns of AI can be autosomal dominant, autosomal recessive, or X-linked. Haldane identified AI as the first dominant X-linked trait found in humans.<sup>2</sup> While AI affects both sexes, its presentation in males is different from that in females. Schulze and Lenz (1952) noted that hypoplastic AI tends to present as uniform hypoplasia in males. Whereas in females, the hypoplasia appears as vertical ridges in the dental enamel.<sup>3</sup> Likewise, in males with hypomaturational type AI, the mottling of tooth enamel is present all over the tooth, but in affected females, the mottling occurs in vertical bands and is less noticeable than

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the mottling in the teeth of affected males. These findings are consistent with the Lyon hypothesis.<sup>4</sup>

All types of AI present substantial challenges from the perspective of dental care and orthodontics. Patients with AI usually have tooth sensitivity that makes everyday maintenance of dental hygiene even more difficult. Manifestations such as decreased occlusal vertical dimension and anterior open bite can make chewing difficult; because of these orthodontic factors and because of the tooth sensitivity, some patients with AI avoid eating hard foods.<sup>5</sup> Other complications of AI can include congenitally missing teeth, impacted teeth, root and crown resorption, abnormal root formation, pulpal calcification, and taurodontism.<sup>6</sup>

Despite these problems that can arise from AI, the concerns that lead many parents of children with AI to seek treatment for the condition are esthetic ones. The abnormalities associated with AI are so noticeable and so troubling to affected children and their parents that early and radical interventions should be done as early as possible on early mixed dentition to reduce tooth sensitivity, restore normal chewing function, and improve the esthetic appearance of the teeth to minimize negative social consequences.<sup>7</sup>

## CASE REPORT

An 8-year-old male reported to the Pediatric Dentistry Department at King Abdulaziz University Dental Hospital with the chief complaint of yellowish discoloration of his primary and permanent teeth, which manifested thermal sensitivity and bad breath. A detailed medical, dental, and social history was obtained. The patient was examined dentally and medically. However, medical history and family history were unremarkable.

Clinically, the child's oral hygiene was unsatisfactory, he brushes his teeth irregularly, and he exhibited chronic marginal gingivitis. Clinical examination also showed that enamel thickness of all teeth was reduced, and in some teeth, dentin was exposed. The teeth had dark yellowish discoloration with severe anterior open bite (Figure 1a-e). Radiographic investigation included an orthopantomogram done (Figure 2).

### Treatment Objectives

The treatment objectives were to improve the esthetics, eliminate the tooth sensitivity, prevent further loss of tooth structure, modify the child's attitude and behavior toward dental treatment, and improve his periodontal health by using a model to demonstrate proper brushing techniques to the patient and his family.

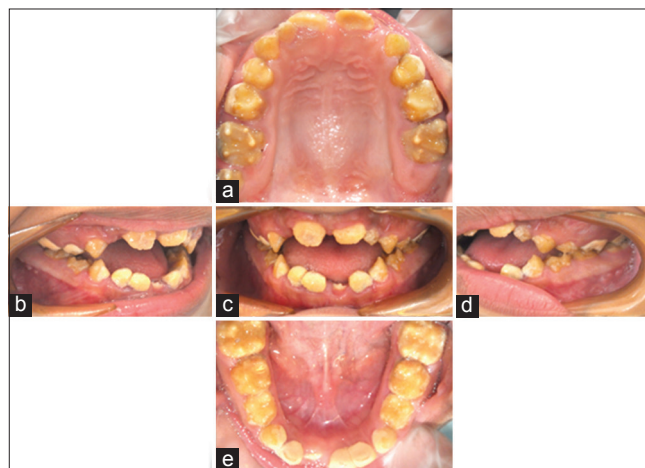
### Treatment Plan

The parents were informed of the diagnosis, and all the treatment modalities were discussed with them. As part of the treatment plan, the treatment alternatives were explained to the child and his parents. This included the amount of tooth structure that needs to be removed, the expected clinical longevity of the restorations, and the length of the treatment period. After considering all the treatment options, it was decided to place direct composite veneers (3M™ ESPE™ Filtek™ Z250 universal restorative) on the permanent lower and upper incisors, zirconia crowns (NuSmile) on the primary molars and canines, and stainless steel crowns (SSCs) (3M™ ESPE™) on the 1<sup>st</sup> permanent molars. After completing the dental rehabilitation, the patient will be referred to an orthodontist.

### Clinical Managements

Initial periodontal therapy consisted of oral prophylaxis and oral hygiene instructions, scaling, and root planing.

A universal restorative composite was chosen to restore the defective tooth structure of the permanent incisors. No preparations were performed on the incisors, other than cleaning with a rotary bristle brush with pumice



**Figure 1: (a-e) Pre-operative clinical picture showing irregular dark yellow-discolored labial surface of maxillary and mandibular teeth**



**Figure 2: Pre-operative panoramic radiograph**



prior to acid etching with 35% phosphoric acid for 30 s followed by rinsing with water spray and after that, bonding and light curing. The labial surfaces of the maxillary and mandibular incisors were then directly restored with resin composite. Mandibular right lateral incisor was left un-restored as it partially erupted (Figure 3).

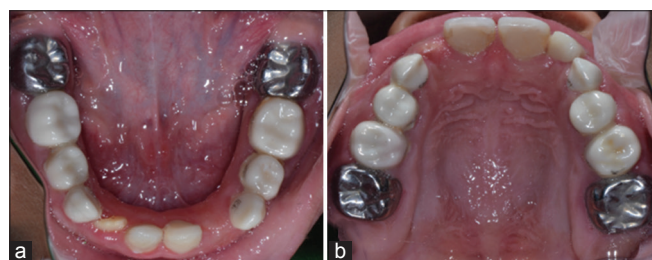
Preformed SSCs (3M) were placed following minimal slice preparations of the permanent 1<sup>st</sup> molars (Figure 4a and b). Preformed zirconia crowns (NuSmile) were placed following moderate preparation of the primary molars and canines (Figure 4a and b).

The adaptation and quality of the margins of the preformed SSCs and the zirconia crowns were evaluated using panoramic (Figure 5) and bitewings radiographs (Figure 6a and b).

The SSCs on the first permanent molars are temporary restorations only. Once the second permanent molars and premolars established the level of the occlusal plane, and the SSCs on the first permanent molars were replaced by cast full-coverage restorations, the patient was referred to an orthodontist.



**Figure 3:** Post-operative clinical picture showing esthetic composite veneering in mandibular and maxillary incisors



**Figure 4:** (a) Post-operative clinical picture showing composite veneering and stainless steel crowns in 1<sup>st</sup> permanent molars and zirconia crowns in primary molars and canines in mandibular arch. (b) Post-operative clinical picture showing composite veneering and stainless steel crowns in 1<sup>st</sup> permanent molars and zirconia crowns in primary molars and canines in maxillary arch

## Follow-up

Every 6 monthly follow-ups were done at 18-month period.

### 6 months

After the completion of treatment, no deterioration was visible in the restorations. The gingiva was slightly inflamed, and heavy calculus accumulation was seen due to insufficient brushing. The lateral incisors erupted (Figure 7a-c).

Scaling and root planing were done, and oral hygiene was reinforced.

### 18 months

No deterioration was visible in the restorations. The 1<sup>st</sup> upper left premolar erupted, gingiva was slightly inflamed due to insufficient brushing and calculus accumulation (Figure 8a-c).

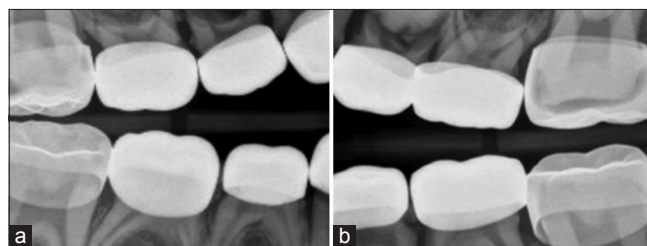
Scaling and root planing were done, and oral hygiene was reinforced.

## Treatment Outcomes

The application of zirconia crowns, composite veneers, and SSCs was a success. The treatment improved the vertical dimension of the patient's teeth, made chewing easier, and reduced tooth sensitivity. The zirconia crowns and composite veneers on the anterior teeth had the desired esthetic appearance.



**Figure 5:** The post-operative panoramic radiograph after restorations of all the erupted teeth



**Figure 6:** (a) The post-operative bitewing radiograph showing adaptation and quality of the margins of the preformed stainless steel and zirconia crowns in the right side. (b) The post-operative bitewing radiograph showing adaptation and quality of the margins of the preformed stainless steel and zirconia crowns in the left side



**Figure 7: (a) 6-month follow-up clinical picture showing intact restorations in the maxillary arch. (b) 6-month follow-up clinical picture showing intact restorations and heavy calculus accumulation in the mandibular arch. (c) 6-month follow-up clinical picture showing intact veneering composite with slightly inflamed gingiva and the laterals incisors were fully erupted in the frontal view**



**Figure 8: (a) 18-month follow-up clinical picture showing intact restorations. The left 1<sup>st</sup> premolar was erupted in the maxillary arch. (b) 18-month follow-up clinical picture showing intact restorations and calculus accumulation in the mandibular arch. (c) 18-month follow-up clinical picture showing intact veneering composite with slightly inflamed gingiva in the frontal view**

The biggest challenges in the management of this patient's oral health remain his diet and brushing habits. Despite that the patient and his parents were counseled on how to brush the patient's teeth and were advised that he should reduce his intake of sugary foods and drinks, his oral hygiene did not improve, and calculus accumulation and gingival inflammation remained a problem. Possible next steps in improving the patient's oral hygiene may include suggesting a reward system for brushing his teeth each day. The parents should also be counseled to take a more active role in brushing the child's teeth if he is unwilling to brush his own teeth.

If this does not improve his brushing habits, he may need to visit the dentist's office more frequently for prophylaxis.

## DISCUSSION

The patient was diagnosed with Type III AI, based on a review of the literature and of the patient's signs and symptoms. His treatment consisted of the application of SSCs, zirconia crowns, composite veneer, counseling on diet and oral hygiene, and a referral to an orthodontist.<sup>8</sup>

Cases of AI vary in type and severity, and it is important to assess each patient's case on an individual basis before deciding on the course of treatment. It is important to look after the patient's dental, periodontal, and orthodontic health as early as possible. AI tends to present in primary teeth, usually with caries and tooth sensitivity. It can adversely affect the child psychologically and socially, as the tooth sensitivity and orthodontic problems associated with AI can make chewing difficult. Children with AI may also be self-conscious about the abnormal appearance of their teeth. Some children with AI only eat soft or pureed foods, and in that case, restorative treatments and diet counseling should be geared toward introducing the child to a more age-appropriate diet.

It is necessary to consider social factors in deciding on a course of treatment for children with AI. Orthodontic treatments, restorative dental treatments such as crowns, and even frequent visits to the dentist can be expensive. Often, the most esthetically appealing treatments are not the most affordable ones. Dentists should discuss with parents regarding the various options for treatment of AI and what each option costs.

Restorative treatment for AI consists of crowns and veneers applied to primary and permanent teeth. If a tooth requires pulpal treatment, the pulpal treatment should be completed before any type of crown is applied. SSCs are appropriate for posterior teeth, especially primary posterior teeth. Materials used for crowns on permanent anterior teeth include porcelain and zirconia.<sup>9</sup>

Patients with AI are prone to orthodontic problems, especially loss of vertical dimension and complications that arise from it, such as temporomandibular joint (TMJ) problems. Malocclusion and delayed eruption of permanent teeth are also associated with AI. Restorative procedures can restore vertical dimension, but temporary bite-raising jigs can be used before the restorative treatments are done to help the pediatric patients' TMJ adapt to the new vertical dimension.<sup>10</sup>

## CONCLUSION

AI is an inherited condition that can be managed through restorative dental and orthodontic treatment. Patients who receive proper treatment to manage their AI have a good prognosis esthetically and in terms of dental function. SSCs, zirconia crowns, and composite veneers are an effective intervention and can be applied to early permanent dentition. As shown in this case report, management of oral hygiene in pediatric patients remains a challenge.

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# Unique Ailment, Unusual Affliction: Ross Syndrome

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## Abstract

Ross syndrome is a rare disorder characterized by Adie's syndrome and segmental anhidrosis. It was first described in 1958 by Ross. There is involvement of the autonomic innervation which causes loss of sweat thereby impairing heat dissipation. This can be attributed to the affection of postganglionic cholinergic parasympathetic and sympathetic fibers to the sweat glands. We present a variant case of Ross syndrome in which the patient presented with anhidrosis of left half of the body. Thermal imaging revealed hemi anhidrosis and ophthalmic examination showed Adie's pupil. Neurological examination elicited hyporeflexia of deep tendon reflexes of left side. 3T magnetic resonance imaging of sympathetic plexus showed no abnormality. This case is presented as a rare variant of Ross syndrome.

**Key words:** Adie's pupil, Anhidrosis, Ross, Thermal imaging

## INTRODUCTION

Ross syndrome is a rare disorder characterized by Adie's syndrome and segmental anhidrosis. It was first described in 1958 by Alexander Ross. Less than 50 cases have been reported till date.<sup>1</sup> In Ross syndrome, there is involvement of the autonomic innervation which causes loss of sweat thereby impairing heat dissipation. This can be attributed to the defect of postganglionic cholinergic parasympathetic and sympathetic fibers to the sweat glands. Adie's syndrome is characterized by Adie's pupil (tonic pupil with slow reaction to light) and absent or diminished deep tendon reflexes.<sup>2</sup> We present a rare variant of Ross syndrome in a young male.

## CASE REPORT

A 25 years male presented in our tertiary care center with complaints of loss of sweating in the left half of the body

noticed 3 months back. He noticed left half of the body was dry while the other half was sweating. There was no history of invasive procedures or trauma. There was no other significant positive history. He was an occasional alcoholic for 1.5 years.

On examination, vitals were stable. There was no evidence of postural blood pressure changes. The individual was subjected to mild exercise (brisk walk) in which anhidrosis of left half of the body was appreciated as shown in Figure 1. Ocular examination revealed visual acuity of 6/6 in the right eye and 6/9 in the left eye. Anterior segment examination showed no abnormalities in the right eye. Left eye showed dilated pupils of 5 mm with no reaction to both direct and indirect light reflex (Figures 2 and 3). Pilocarpine drops were instilled which confirmed Adie's tonic pupil of left eye. Posterior segment evaluation was normal.

Routine blood investigations were within normal limits. 3T magnetic resonance imaging of sympathetic plexus were done and showed no abnormalities. Thermal infrared imaging showed a significant rise in temperature of left half of the body due to loss of heat dissipation by sweating (Figures 4-6). Hence, we confirmed the diagnosis of Ross syndrome.

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Figure 1: Anhidrosis of left half of body after exercise

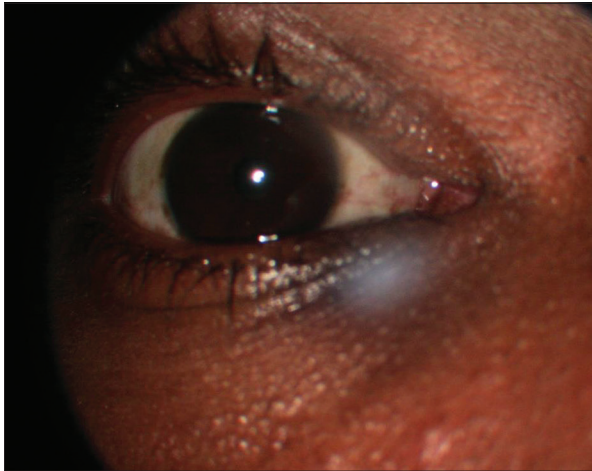


Figure 2: Normal pupil of right eye

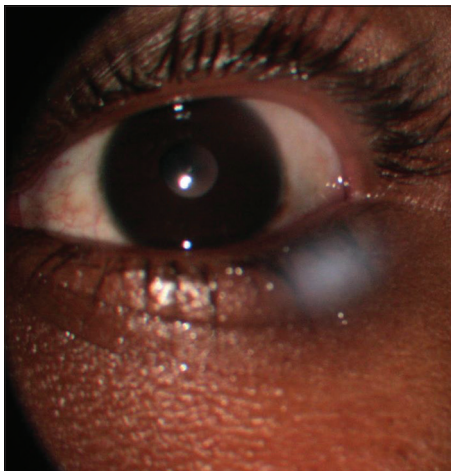


Figure 3: Dilated and nonreacting pupil of left eye

## DISCUSSION

Ross syndrome is a rare neurological disorder affecting both sexes with slight female predominance.<sup>3</sup> Previous literature described Ross syndrome as segmental anhidrosis with Adie's syndrome. In our case, there is anhidrosis of left side of face, neck, trunk extending till the medial aspect of the thigh along with tonic pupil and decreased deep tendon reflexes of same side. Decrease in deep

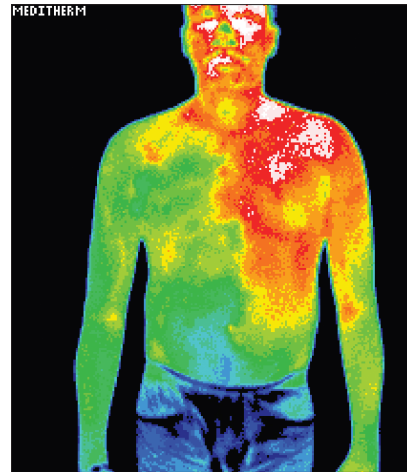


Figure 4: Thermal infrared imaging showing significant rise in temperature

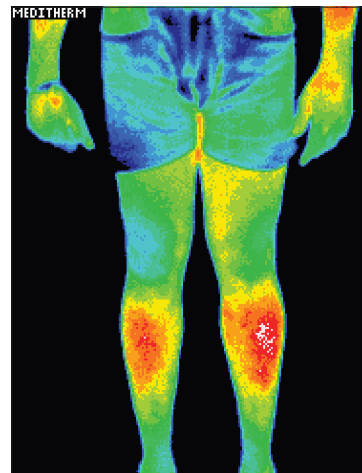


Figure 5: Thermal infrared imaging showing significant rise in temperature

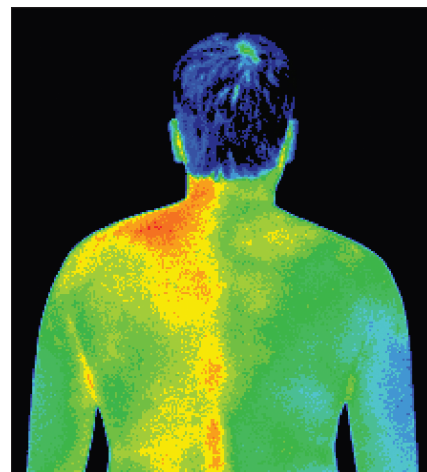


Figure 6: Thermal infrared imaging showing significant rise in temperature

tendon reflexes is due to damage of the dorsal root ganglia.<sup>4</sup> Anhidrosis is due to defective postganglionic cholinergic parasympathetic and sympathetic fibers to the

sweat glands whereas Adie's pupil results due to damage of the parasympathetic cholinergic fibers between the iris and ciliary ganglion.<sup>5</sup> Harlequin syndrome is a condition where there is asymmetric sweating and flushing of the upper thoracic region of the chest, neck, and face.<sup>6</sup> We excluded the diagnosis of Harlequin as there was pupillary involvement in our patient and decreased deep tendon reflexes. Defects in thermoregulation with anhidrosis can lead to hyperthermia of the affected side which can be life threatening.<sup>7</sup> Hyperthermia can be managed to some extent by wearing wet clothing during physical activity.<sup>8</sup> This case is presented for its rare variant of Ross syndrome.

## CONCLUSION

Ross syndrome is a rare neurological disorder affecting both sexes with slight female predominance. Previous literature described Ross syndrome as segmental anhidrosis with Adie's syndrome

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# Congenital Hemifacial Hyperplasia: Report of a Rare Case with Review of Literature

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## Abstract

Hemifacial hypertrophy is a developmental disorder which is characterized by facial asymmetry unilaterally. It is a congenital malformation usually seen at birth and progressively increases with age. Although etiology is unknown, various theories such as chromosomal abnormalities, heredity, atypical twinning, endocrine dysfunction, and altered intrauterine environment have also been proposed. A few cases have been reported in the literature. We herein report a case of true hemifacial hyperplasia in 65 years old male.

**Key words:** Congenital hemifacial hyperplasia, Facial asymmetry, Hemifacial hypertrophy

## INTRODUCTION

A minor asymmetry is acceptable characteristic of morphogenesis. However, asymmetry which is easily noticeable can affect esthetic, normal functioning and quality of life. A congenital developmental disturbances causing unilateral overdevelopment of tissues of face both hard and soft is seen in this rare disorder called hemifacial hypertrophy. In 1982, Hemihyperplasia was first described by Meckel.<sup>1</sup> Rowe in 1962 classified it as complex involving entire half of the body, simple involving one or both limbs, and hemifacial involving half of the face. The term hyperplasia is preferably used since an increase in number of cells is seen rather than increase in size of cells.<sup>2</sup> The aim of this report is to present a case of congenital hemifacial hyperplasia and to update the existing clinical knowledge.

## CASE REPORT

A 65-year-old male complained of inability to open his mouth since many years. He gave a history of enlarged right

side of face since birth which has gradually increased to the existing size. His parents, all his siblings, and children did not suffer from his disorder.

On extra oral examination, a gross facial asymmetry was seen on the right side of the face. The soft tissue on maxillary and mandibular region along with ear pinna and ala of nose was enlarged as compared to the left side of the face. Chin was deviated toward the left side of the face. The mass was soft and nontender on palpation (Figures 1 and 2).

On intraoral examination, enlargement of the maxillary and mandibular alveolar ridge, tongue and gingiva were seen on the affected side. Reduced mouth opening with intermaxillary distance of 1.5 cm was present. The absence of teeth was noticed on the affected side which had exfoliated 2 years back (Figure 3).

Orthopantomogram, lateral view of the skull and posterior anterior view of skull revealed the absence of teeth on the right side and enlarged body of the mandible unilaterally. There was an increased height of the ramus and body of the mandible on the right side in comparison to left side. An oversized right condyle and deviation of chin toward the unaffected side could be appreciated (Figures 4 and 5). Based on these clinical and radiologic examinations, a diagnosis of congenital hemifacial hyperplasia was concluded.

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**Figure 1: Profile of the patient showing gross asymmetry on right side of the face**



**Figure 2: Comparative profile of right and left side of the patient showing obvious asymmetry on right side**



**Figure 3: Intraoral examination showing absence of teeth and enlarged tongue on right side**

## DISCUSSION

Hemifacial hyperplasia is a rare congenital anomaly of hard and soft tissue where there is an enlargement of one half of the face. It is seen in 1 in 86000 live births and was first reported by Friedreich in 1863. Usually, it presents itself at birth with a male predominance. The right side of the face is more commonly affected.<sup>2</sup> This case was a male with right side of the face affected. The enlargement was present since birth and had then stabilized after 18 years of age.



**Figure 4: Orthopantomogram showing absence of teeth on the right side and enlarged body of the mandible and oversized right condyle unilaterally. Deviation of chin toward the unaffected side could be appreciated**



**Figure 5: Lateral view of the skull and posterior anterior view of skull showing increased height of the ramus and body of the mandible on the right side in comparison to left side**

Although etiology is unknown, few theories which have been proposed are hereditary, atypical twinning, anomalies in chromosome, altered environment in intrauterine life, endocrine dysfunctions, central nervous system disturbances and malformations of vascular or lymphatic systems. This etiological heterogeneity is a result of multisystem involvement.<sup>3</sup>

The integumentary, cardiovascular, neurological, genitourinary, musculoskeletal, respiratory, and endocrine systems are affected by this disorder. There is asymmetric growth and development of facial bones and dentition. Asymmetry is not a feature of deciduous dentition but early eruption of permanent dentitions seen.<sup>4</sup> In our case, we could not record the size of the dentition on the affected side as there was an early shedding of the permanent teeth.

Hemiatrophy or Parry Romberg syndrome which manifests as unilateral underdevelopment along with weakness of muscles and deficit of neurological entities can pose as a differential diagnosis. However, it manifests later in life between 5 to 15 years of age. Bony tumors, fibro osseous lesions do not



involve the soft tissues and dentition. Cutaneous lesions and vascular malformations are usually bilateral. All these lesions with an exception of hemiatrophy can be diagnosed histopathologically. Proteus syndrome, hyperpituitarism, epidermal nevus syndrome, Maffucci syndrome, Ollier's syndrome, Klippel-Trenaunay-Weber syndrome, Langer-Giedion syndrome, Russell Silver syndrome, McCune-Albright syndrome, and multiple exostosis syndrome can mimic hemifacial hypertrophy. Unilateral allocation of dental abnormalities and coinciding unilateral tongue enlargement are the striking features of hemifacial hypertrophy.<sup>2,4</sup>

## CONCLUSION

Hemifacial hypertrophy creates a diagnostic dilemma and needs a thorough clinical and radiological evaluation. It

requires a multidisciplinary approach of management because of its multisystem involvement. Unless there is a necessity for cosmetic correction, treatment is not indicated.

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# Pericardial Effusion in a Patient with Hypothyroidism Successfully Treated Without Pericardiocentesis

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## Abstract

Hypothyroidism presenting with pericardial effusion is commonly seen. Complete resolution of effusion without pericardiocentesis after thyroid hormone supplement is not reported in literature. We are reporting a case of 70-year-old female presented with breathlessness. She was diagnosed to have moderate pericardial effusion secondary to hypothyroidism. Her symptoms and pericardial effusion completely resolved after 1 month therapy of thyroid hormone without pericardiocentesis. Her QRS voltages on electrocardiogram improved with thyroid hormone supplement. There is no recurrence of symptoms and pericardial effusion after follow-up of 1 year.

**Key words:** Hypothyroidism, Pericardiocentesis, Pericardial effusion, QRS voltages, Thyroid hormone supplement

## INTRODUCTION

Hypothyroidism is the most common pathological hormone deficiency.<sup>1</sup> It is more common in women and its incidence increases with age. Common signs and symptoms of hypothyroidism include lethargy, cold intolerance, weight gain, constipation, dry skin, alopecia, hoarse voice, pedal edema weight gain, bradycardia and psychomotor retardation.<sup>2,3</sup> We are reporting a case of elderly female who presented with moderate pericardial effusion, the later turned to be secondary to hypothyroidism. Patient was treated with 100 mcg of thyroxine supplement after which pericardial effusion was resolved completely over a period of 1-month, evidenced by follow-up two-dimensional (2D) echocardiogram (ECHO) and Doppler study.

## CASE REPORT

A 70-year-old elderly female presented on August 24, 2015, with a history of breathlessness on exertion,

bilateral lower limb swelling, and hoarseness of voice of 15 days duration. Initially, she had dyspnea on heavy work which later progressed to dyspnea on routine work. On examination, she was conscious oriented, obeying verbal commands. Pulse was 60/min blood pressure - 120/80 mm of Hg, On auscultation heart sounds were muffled, ankle reflexes were delayed bilaterally, SpO<sub>2</sub> was 98 % without O<sub>2</sub>, electrocardiogram (ECG) showed low voltage complexes, chest radiogram showed marked cardiomegaly, arterial blood gas was normal, and 2D ECHO showed moderate pericardial effusion with no signs of cardiac tamponade.

All routine tests are done to rule out the cause of pericardial effusion. Keeping in mind her symptoms and signs and low voltages in ECG, thyroid function tests (TFTs) are also done and they found to be grossly abnormal which included T3 - 30 ng/dl, T4 - 2.0 µg/dl, and thyroid-stimulating hormone (TSH) - more than 40 mIU/L. which was indicative of hypothyroidism. The patient was put on tablet levothyroxine 100 µg OD. Patient felt symptomatically better and was discharged from hospital on August 31, 2015. Repeat 2D ECHO done on follow-up on October 07, 2015, suggestive of normal size cardiac chambers, no pericardial effusion with good left ventricle systolic function. TFT done after 3 months of discharge showing T3 - 140 ng/dl, T4 - 10.1 µg/dl, and TSH - 5.6 mIU/L. The patient is coming to follow-up and fine till now a

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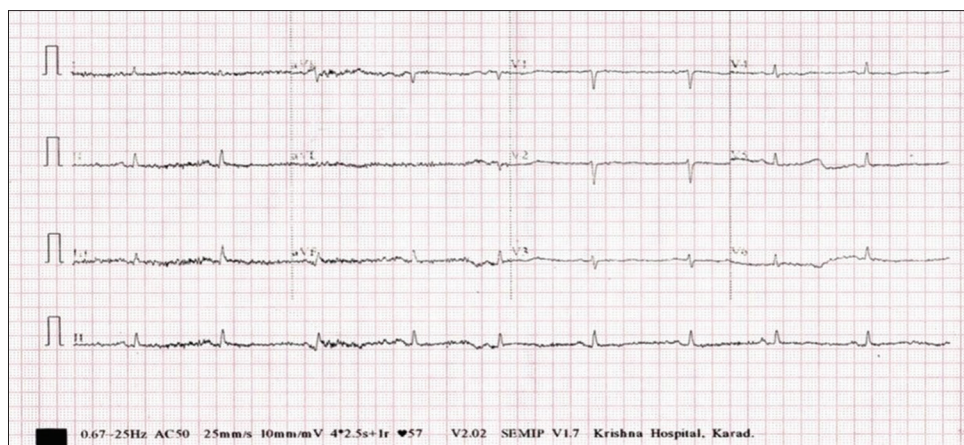


Figure 1: Electrocardiogram on admission

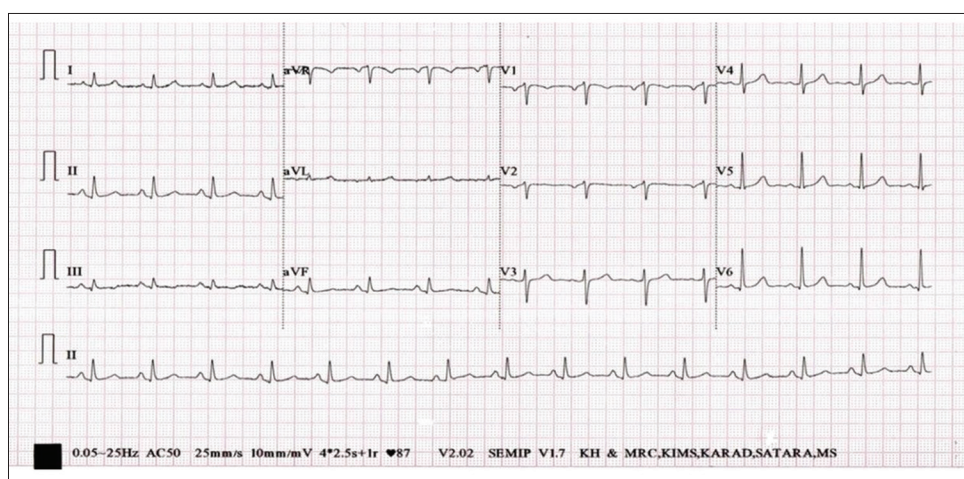


Figure 2: Electrocardiogram on discharge (with improved voltages)

**Table 1: Improvement in thyroid function**

TFT	August 25, 2015	November 25, 2015
T3	30	140
T4	2.0	10.1
TSH	>40	5.6

TSH: Thyroid-stimulating hormone, TFT: Thyroid function tests

follow-up 2D ECHO done after 1 year on August 27, 2016, which is also normal with no pericardial effusion (Table 1 and Figures 1-5).

## DISCUSSION

Any defect in hypothalamic-pituitary-thyroid axis may result in the development of hypothyroidism. Hypothyroidism is associated with some cardiovascular findings such as increased systemic vascular resistance, decreased cardiac contractility, decreased cardiac output, atherosclerosis, coronary artery disease, and pericardial effusion. Pericardial effusion can be detected in 25% of hypothyroid patients.<sup>4</sup> Hypothyroidism leads to

decreased synthesis of albumin. Increased permeability of capillaries results in loss of albumin in intravascular compartments through increased transcapillary escape rate of albumin, eventually leading to reduced plasma volume. Thus, the consequent increase in concentration of albumin in extravascular compartment causes increased interstitial fluid volume and impaired lymphatic drainage.<sup>5,6</sup>

Normally, there is 10-50 ml of fluid present between visceral and parietal layers of pericardium, which is produced by pericardium through ultrafiltration of plasma. The above-mentioned pathological mechanisms cause an increase in the volume of the pericardial fluid leading to moderate to severe pericardial effusion. As in our patient, the moderate to severe pericardial effusion can be completely cured without pericardiocentesis only with thyroid hormone supplement. Because of insidious and nonspecific characteristics of the signs and symptoms of hypothyroidism along with rare occurrence of moderate to severe pericardial effusion in some patients, the possibilities of hypothyroidism may be overlooked in the differential



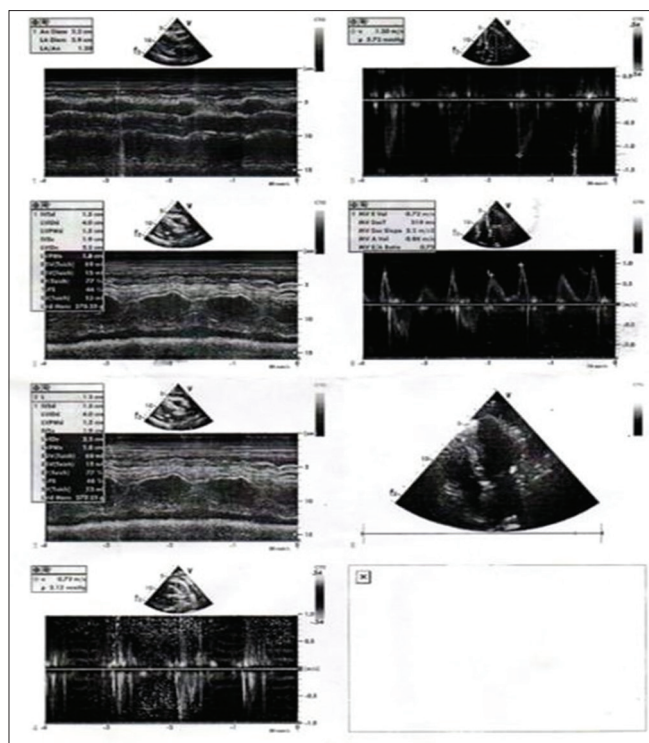


Figure 3: Two-dimensional echocardiogram on admission

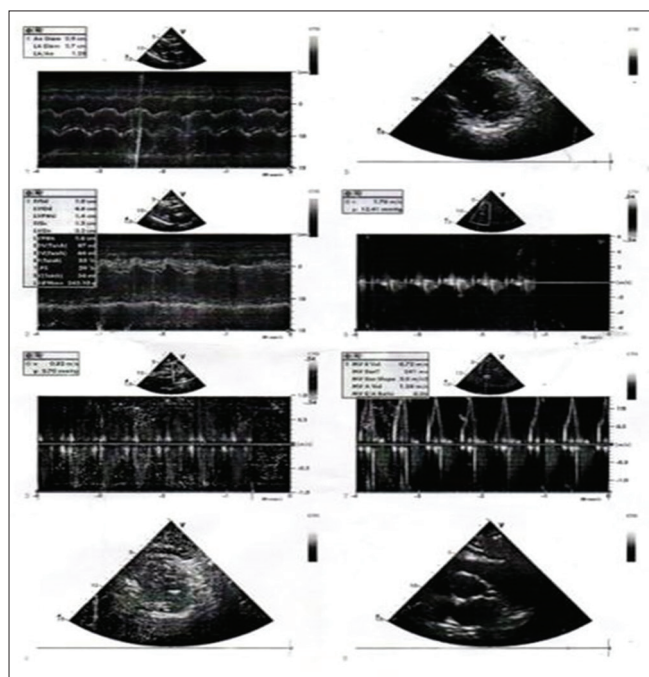


Figure 4: Two-dimensional echocardiogram on discharge

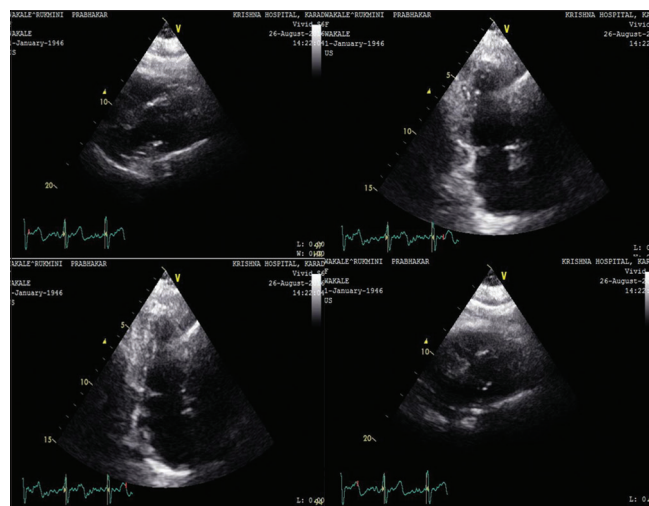


Figure 5: Two-dimensional echocardiogram later after 1 year (On August 26, 2016) – S/O No pericardial effusion with good left ventricle function

diagnosis of moderate to severe pericardial effusion. As hypothyroidism is treatable cause of moderate to severe pericardial effusion the diagnosis must be established and treatment should be promptly started.<sup>7</sup> In patients with unexplained pericardial effusion, TFTs and ECHO should always be performed. After obtaining euthyroid status with treatment, pericardial effusion slowly disappears, preventing unnecessary pericardiocentesis in these patients.<sup>8</sup>

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# Giant Gastric Wood Bezoar: An Unknown Occurrence in Pediatric Age

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## Abstract

Bezoars are masses or concretions of indigestible materials found in the gastrointestinal tract. Various materials have been the cause of the bezoar; however, wood has never been reported before in pediatric age group. Wood bezoars represent a therapeutic challenge as they are hard in consistency, large in size, and there is risk of damage to the endoscope during retrieval. We report a case of a 10-year-old boy with wood bezoar. Three attempts of endoscopic retrieval by the gastroenterologist were made. The last attempt resulted into gastric perforation. He underwent a laparotomy with gastrostomy and retrieval of large wood bezoar. The child recovered well and is under psychological treatment for wood consumption.

**Key words:** Gastric, Pediatric, Wood bezoar

## INTRODUCTION

Bezoars are collections of indigestible foreign material that accumulate and coalesce in the gastrointestinal (GI) tract. The overall reported incidence of bezoars is 0.4%.<sup>1</sup> In pediatric population, common types described are lactobezoars, phytobezoars, and trichobezoars.<sup>2</sup>

We report a case of 10-year-old boy with wood bezoar, which was managed successfully by surgical intervention following failure of three attempts of endoscopic retrieval. This is the first case to be reported in pediatric age group.

## CASE REPORT

A 10-year-old boy presented with a history of episodic abdominal pain for 1½ years, vomiting for 6 months,

generalized weakness and easy fatigability. He presented to the Gastroenterology Department for the same and was investigated. He habitually ingested broomsticks, matchsticks, wood flakes, and plywood scraps from his school desk since he was 2½ years old. He had a hard lump in the left hypochondrium about 5 cm × 5 cm in size. An X-ray abdomen erect showed radio-opaque shadow outlining the stomach wall. Ultrasound of abdomen showed echogenic material in stomach with thickened walls. Computed tomography scan of abdomen revealed hyperdense material with air specks within suggestive of bezoar with gastric mucosal folds hypertrophy and enhancement. Upper GI scopy (Figure 1) showed a wood bezoar. The patient underwent three attempts of retrieval of bezoar endoscopically by the gastroenterologists with the usage of Coca Cola® beverage, but very little of the bezoar could be extracted. After the third attempt of endoscopic retrieval, he presented with distended abdomen along with tenderness and guarding, suspicious of GI perforation. However, the X-ray abdomen did not reveal free gas under diaphragm. After adequate resuscitation, he underwent exploratory laparotomy. The stomach was distended with few pus flakes on the surface and a 0.5 cm × 0.5 cm perforation over the anterior wall. Anterior gastrotomy incorporating the perforation site was

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done along with en masse removal of the wood bezoar. The bezoar was 13 cm × 11 cm × 6 cm in dimension and weighed 200 g (Figure 2). There was marked hypertrophy of the gastric mucosal folds. The gastrotomy was closed in two layers. Postoperatively, he was counseled by the child psychologists and was started on fluoxetine. He has been regularly following up with the child guidance clinic and since surgery (1 year 4 months follow-up), he is alright and not eating wooden scrapes.

## DISCUSSION

Bezoar (from Persian word “bazahr” meaning antidote) is a mass found trapped in the GI system, usually the stomach, though it can occur in other locations.<sup>3</sup>

Bezoars can be of many types - Tricho (hair), phyto (plant), lacto (milk), litho (stone), trichophyton (hair and plant), paper bezoar, pharmacobezoar (medicines), cement bezoar, yeast bezoar, shellac bezoar, polybezoar (bezoars

composed of multiple objects, e.g., metallic, plastic), and chewing gum bezoars.<sup>4</sup> Rapunzel’s syndrome is rare and an unusual form of trichobezoar which extends into the small intestine to various extent. The term “Rapunzel’s syndrome is derived from the Grimm Brothers’ fairy tale of a 12-year-old princess who was shut into a tower with neither stairs nor doors by an enchantress who climbed up the tower’s walls with the help of Rapunzel’s long tresses.<sup>5</sup>

Wood bezoar is a very rare type of bezoar. After an extensive literature review, we could find only one case report about a wood bezoar in 20 years female with neuropsychiatric disorder and history of ingesting matchsticks and color pencils for over 4 years.<sup>6</sup> To the best of our knowledge, our case is the first case of wood bezoar in pediatric population.

Clinical manifestations of bezoar vary with its location; from being asymptomatic to complaints such as epigastric distention, abdominal pain, and acid regurgitation to lump to major complications of bezoars such as gastric ulceration, intestinal obstruction, and gastric perforation.<sup>7</sup>

Various treatment modalities are available for the management of bezoars. Bezoars can be treated by conservative modalities (gastric lavage), endoscopic treatment, conventional surgery as well as laparoscopic surgery.<sup>8</sup> Endoscopic management of bezoar can be done using NaHCO<sub>3</sub> which is mucolytic also CO<sub>2</sub> bubbles are released which penetrate into the bezoar and digest the fibers in the concretions. The use of Coca Cola® lavage has also been reported in a few studies.<sup>9</sup> In our case, three attempts were made for removal of wood bezoar by gastroenterology, but failed to retrieve it completely and had gastric perforation during the third attempt. In conventional surgery, bezoar removal is commonly done by gastrotomy and/or enterotomy depending on location and extent. If complicated by small bowel obstruction, gastric perforation or gastric hemorrhage, then gastric repair and/or intestinal resections may be needed.<sup>10</sup> Nowadays, laparoscopic approach has been used as well. When expertise is available, laparoscopy is safe and effective in the management and yields superior postoperative outcomes when compared with conventional open approach.

Wood bezoar is not been reported in pediatric age group, and only one report is available in adult population. It needs very high index of suspicion for diagnosis. Various modalities are available for the diagnosis; however, definitive diagnosis is only made by upper GI endoscopy. Endoscopic management is successful in managing bezoars to a various extent. Wood bezoars are relatively difficult to manage with endoscopy and may have complications such as gastric perforation and damage to endoscope. Hence,



**Figure 1: Upper gastrointestinal endoscopy showing wood bezoar**



**Figure 2: Bezoar was 13 cm × 11 cm × 6 cm in dimension and weighed 200 g**

primary surgical exploration and removal of wood bezoar are advisable.

## CONCLUSION

Wood bezoar is an extremely rare entity not yet reported in pediatric population. We recommend surgical removal of wood bezoar without endoscopic trial.

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