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# Comparison between Intra-articular and Intramuscular Depot Methylprednisolone Injection in Functional Improvement of Hand in Patients Suffering from Early Rheumatoid Arthritis

Swarnali Mandal<sup>1</sup>, Biswadip Ghosh<sup>2</sup>

<sup>1</sup>Assistant Professor, Department of Physical Medicine and Rehabilitation, Murshidabad Medical College, Berhampore, West Bengal, India,

<sup>2</sup>Associate Professor, Department of Rheumatology, IPGME&R and SSKM Hospital, Kolkata, West Bengal, India

## Abstract

**Objective:** The objective of this study was to compare the improvement in hand function and disease activity among patients receiving intra-articular with intramuscular depot methylprednisolone injections.

**Design:** A prospective cohort of 136 patients with rheumatoid arthritis were randomly allocated in two parallel groups (IA and IM) who were given depot methylprednisolone injection either intraarticularly or intramuscularly after assessment of wrist ROM, grip strength, CDAL and KFT scores on 1<sup>st</sup> visit and reassessed at 1 month and 3 months post-injection.

**Results:** Wrist flexion and extension, power grip and all pinch grips of both hands have shown statistically significant improvement over time between any two visits, except right wrist extension, right and left lateral pinch grip did not have statistically significant improvement between 2<sup>nd</sup> and 3<sup>rd</sup> visits. CDAL scores reduced and KFT scores improved in persistent manner more in IM group over time between any two visits which are statistically significant. It is also seen that with decrease in disease activity there is improvement of functional ability in the subjects.

**Conclusions:** Intra-articular injections have sustained effects throughout the study period in ROM improvement, and intramuscular injections have short-lived effects and are more effective in improving outcomes of functional status and disease activity.

**Key words:** Grip strength, Hand function, Intra-articular corticosteroid, Rheumatoid arthritis

## INTRODUCTION

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability.<sup>[1]</sup> We encounter a lot of patients in our hospital who have significant difficulties in performing activities of daily living due to hand deformities arising due to RA. The incidence of RA increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases.<sup>[2]</sup> As the disease affects people

of working age group, any deformity is likely to cause vocational loss. Thus, avoiding or reducing joint damage by appropriate rehabilitation in both early and established/late RA is very essential to maintain function.

Normal hand function is very important for every person in every aspect of their lives. In RA patients, hand function is severely impaired in basic activities in daily life, professional life and affects the patient physically, socioeconomically, and psychologically.

Both intra-articular and intramuscular corticosteroid injections are well-established methods to control inflammation in RA. Intra-articular corticosteroid injections are predominantly used for treating RA patients with mono or oligoarthritis. Intra-articular injections are performed by allocation of drugs in the intra-articular space aiming to control local inflammation and to promote atrophy of

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**Corresponding Author:** Dr. Biswadip Ghosh, Department of Rheumatology, Institute of Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital, 244 AJC Bose Road, Kolkata, India



the synovial “pannus”<sup>[3-5]</sup> There are a number of studies showing significant improvement in inflammatory process and reduction of pain in such RA patients. However, there is paucity of literature regarding effectiveness of intra-articular corticosteroid injection in functional improvement and reduction of disease activity of RA patients as compared to systemic steroid administration.

The major goal of treatment for RA is to eliminate articular inflammation, prevention of bone erosion and cartilage damage and, consequently, avoid irreversible functional disability.<sup>[6]</sup> Hence, it is our earnest endeavor to study the effectiveness of intra-articular versus intramuscular depot methylprednisolone injections in functional improvement of the hand of RA patients.

### Aims and Objectives of the Study

The study aimed to compare the improvement in hand function and disease activity among patients receiving intra-articular with intramuscular depot methyl prednisolone injections in patients suffering from early RA.

## MATERIALS AND METHODS

### Study Period

The study period was 18 months.

### Study Design

This was a open-label prospective parallel group observational study.

### Study Population

Patients with RA who are attending OPD of the Department of Physical Medicine and Rehabilitation and Department of Rheumatology, Institute of Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital, Kolkata, India.

### Inclusion Criteria

The following criteria were included in the study:

1. Diagnosis of RA as per ACR/EULAR 2010 classification criteria
2. Unilateral or bilateral inflamed wrist joints
3. Age between 18 years and 65 years
4. DMARDS naive newly diagnosed RA with disease duration less than 2 years

### Exclusion Criteria

The following criteria were excluded from the study:

1. Advanced RA with hand deformities
2. Uncontrolled diabetes, hypertension, bleeding diathesis, h/o leprosy or any other neuropathic disorder
3. Associated fracture or traumatic injury to tendons
4. Open wound or local skin infection

5. Overlap syndromes
6. Who have received intra-articular steroid earlier or is on systemic steroid at time of presentation.

## SAMPLE SIZE CALCULATION

The sample size for the study was calculated on the basis of Clinical Disease Activity Index (CDAI) score as primary outcome measure. It was calculated that minimum 31 subjects should be required per group to detect a difference of 5 in CDAI score between groups with 80% power and 5% probability of Type – 1 error. This calculation assumes a standard deviation of five for CDAI score and two-sided testing. Sample size calculation was done by nMaster 2.0 (Department of Biostatistics, CMC, Vellore, India) Software.

## LABORATORY INVESTIGATIONS

Routine baseline investigation reports including complete hemogram, fasting blood sugar, postprandial blood sugar, urea, creatinine, TSH, LFT, BT, and CT, reports of rheumatoid factor, anti-CCP antibody.

### Schedule of Data Collection

The patients with completed baseline investigation reports were given intra-articular or intramuscular depot methylprednisolone injections on day 1 and were re-assessed after intervals of 1 month and 3 months post-intervention.

### Parameters and the Procedures

- Parameters of objective are as follows:
  1. Range of motion of wrist joints
  2. Handgrip strength measurements
  3. Patient's disease activity assessment by CDAI
  4. Hand function assessment using Keitel Functional Test (KFT).
- Study tools
  1. Hand dynamometer, goniometer
  2. Injection depot methylprednisolone (40mg/ml), xylocaine chloride 2% (1 ml)
  3. 5cc and 2cc syringes, Band-aid.

### Methodology

Institutional Ethics Committee approval was received (Inst/IEC/523 dated 11<sup>th</sup> Jan 2014 of IPGME&R, Kolkata, India. Chairperson: Dr. Hemanta Majumder).

Informed consent from all patients was taken for this study.

For this study, patients with diagnosed RA as per ACR/EULAR 2010 criteria having disease duration of <2 years were first

selected according to inclusion and exclusion criteria of the study and who agreed to participate in the study. The routine baseline blood reports were investigated, and those who did not have any contraindications for receiving injections were finally selected.

The consent forms along with the prefixed pro forma were filled with detailed history, clinical examination (including handgrip strength and ROM assessment), CDAI scoring, and hand function assessment by KFT were done. Patients were then allocated randomly in intra-articular (IA) and intramuscular (IM) groups.

On 1<sup>st</sup> visit, all patients received methotrexate 10 mg weekly. They were taught ROM exercises and joint protection techniques. No other DMARDs were added until the end of follow-ups (i.e. 3 months). Patients in IA group were given intra-articular (IA) depot methylprednisolone injection in inflamed wrist joints (40 mg in each). Patients in IM group were given intramuscular (IM) depot methylprednisolone injection (80 mg) in the gluteal region on the 1<sup>st</sup> day and another dose of 80 mg on the same day of 3<sup>rd</sup> week. Patients were asked to follow-up after 1 month from the day of 1<sup>st</sup> visit and after 2 months from the day of 2<sup>nd</sup> visit (i.e., 3 months post-intervention). In both the follow-up visit, patients were assessed as per the study parameters.

#### **Range of motion assessment**

By goniometer for wrist flexion and extension, goniometry was performed on each follow-ups in each patient in both groups for assessing the improvement.

#### **Grip strength measurement**

Power and pinch grip strength was measured using Jamar Hand Dynamometer. Power grip measured with detachable handle at second position with dynamometer supported on a flat surface in erect position. Average of three trials in 10 min interval is recorded. Pinch grip (both palmer and lateral) is measured between thumb and index finger with weight of the dynamometer supported by examiner.

All these grip strengths were assessed on each follow-up to look for any improvement.

#### **Patient's disease activity assessment**

A thorough physical examination was performed on each patient to determine a total number of tender and swollen joints of the patient.

Patient's and providers global assessment (VAS) of disease activity was obtained on a 0–10 mm scale. CDAI score was then calculated by summation of above parameters to assess patient's disease activity ranging from 0 to 76.

This score was taken as the primary outcome measure and was calculated on each follow-ups in each patient in both groups for assessing the improvement.

#### **Hand function assessment**

KFT parameters 1–9 for hand function assessment of small joints of hand were taken and scoring done for both hands. The total score was taken for observing improvement in three follow-ups in each patient in both groups.

## **RESULTS AND ANALYSIS**

#### **Method for Statistical Analysis**

For statistical analysis the following software was used – Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001] and GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007].

The improvement between visits was calculated in percentages by taking the mean of the different parameters of the 1<sup>st</sup> visit as baseline data. The mean of subsequent visits was subtracted from baseline data, and the difference between the two means was calculated as percentage for each group. The main outcome measure of each parameter was taken, namely, range of motion of wrist joint in goniometry, power and pinch grip strengths, CDAI and KFT scores.

## **DEMOGRAPHIC PROFILE**

Out of 136 patients in the study, 70 were included in IA group and 66 in IM group.

#### **Sex**

Out of 136 patients, 108 (79%) were female and 28 (21%) were male. In IA group, out of 70 patients 58 (83%) were female and 12 (17%) were male. In IM group, out of 66 patients 50 (76%) were female and 16 (24%) were male. Evidently, there is female preponderance in the study population.

#### **Age**

In the total sample of 136 patients, age ranged from 23 to 62 years with mean age being 41.15 years. Mean age in IA group is 41 years (range 23–57 years) and in IM group 41.3 years (range 23–62 years). Therefore, most patients were middle-aged; maximum age in IA being 57 years and IM being 62 years.

## **DURATION OF DISEASE**

Duration of disease at the time of 1<sup>st</sup> visit varied from 3 months to 24 months. Mean duration in total sample



is 16.06 months, in IA group 1.74 months and IM group 17.45 months.

## CLINICAL PARAMETERS COMPARISON RESULTS

### Range of Motion

Wrist flexion and extension of both hands had statistically significant improvement overtime between any two visits ( $P < 0.05$ ) [Table 1], except improvement of right wrist extension between 2<sup>nd</sup> and 3<sup>rd</sup> visit, which is not statistically significant and the effect of intra-articular steroid is sustained until the 3<sup>rd</sup> month [Figure 1].

### Grip Strength

It is seen that power grip (Figure 2) and all pinch grips of both hands (Table 2) have shown.

## PINCH GRIPS

From Figures 1 and 2, it is seen that power grip and all pinch grips of both hands have shown statistically significant improvement overtime between any two visits ( $P < 0.05$ ), except improvement of the right and left lateral pinch grip between 2<sup>nd</sup> and 3<sup>rd</sup> visits.

### CDAI and KFT

From Figure 3, it is evident that CDAI scores reduced over time between any two visits, which is statistically significant, most significant reduction has occurred in the 1<sup>st</sup> month after intervention. The above figures also depict that KFT score improvement was statistically significant between any two visits in persistent manner. It is also seen that with decrease in disease activity there is improvement of functional ability in the subjects.

## DISCUSSION

In our prospective parallel-group randomized controlled study conducted at the Department of Physical Medicine and Rehabilitation and Department of Rheumatology, Institute of Post Graduate Medical Education and Research, Kolkata, India, over the period of 18 months, we tried to compare the functional

improvement of hand in RA patients between those who received intra-articular depot methylprednisolone injection with those receiving intramuscularly. There are a number of studies assessing improvement by either local or systemic steroid administration in these patients, but there is paucity of literature regarding any comparison between these groups pertaining to hand function evaluation and in DMARDS naïve newly diagnosed RA patients having disease duration <2 years,

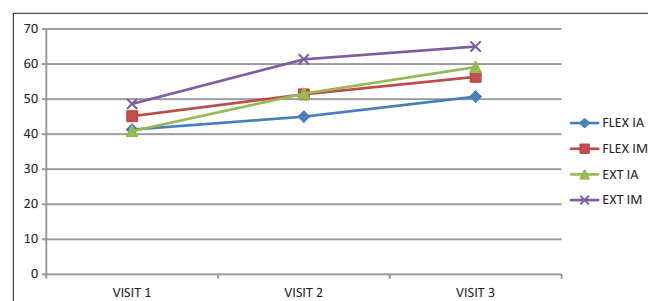


Figure 1: Improvement in range of motion of the right wrist joint in IA and IM groups overtime

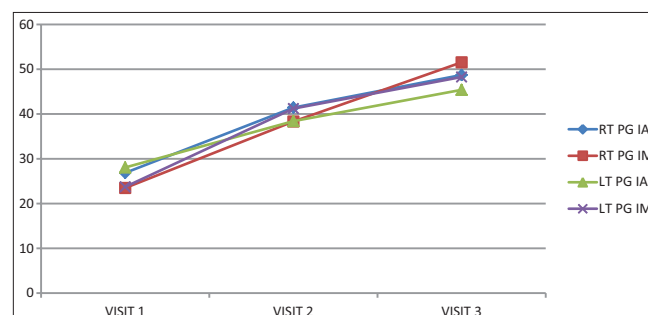


Figure 2: Improvement in power grip strength in IA and IM groups over time

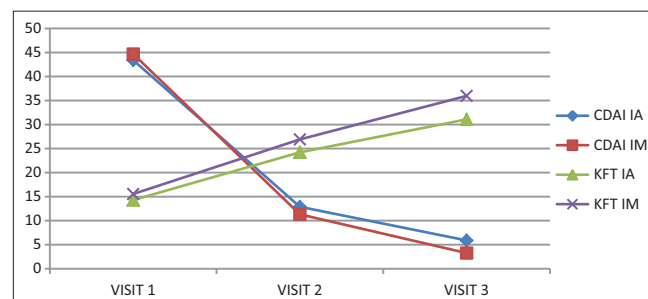


Figure 3: Improvement in CDAI and KFT in IA and IM groups overtime

Table 1: Comparison in % improvement between visits as a percentage for bilateral wrists

% improvement between visits	RT. wrist FLX.		RT. wrist EXT.		LT. wrist FLX.		LT. wrist EXT.	
	IA	IM	IA	IM	IA	IM	IA	IM
After 1 m	8.06	13.75	26.21	26.15	20.14	36.52	28.65	13.74
After 3 m	22.81	24.82	44.74	33.63	41.28	51.66	33.95	21.16
Between 1 and 3 m	14.75	11.07	18.53	7.48	21.14	15.14	5.30	7.42

**Table 2: Comparison in improvement between visits as a percentage for bilateral palmer and lateral pinch grip**

% improvement between visits	RT palmar pinch grip		LT. palmar pinch grip		RT lateral pinch grip		LT lateral pinch grip	
	IA	IM	IA	IM	IA	IM	IA	IM
After 1 m	43.77	33.17	28.23	51.02	11.12	31.23	11.20	45.55
After 3 m	51.33	63.32	36.49	84.42	21.02	42.64	21.74	60.21
Between 1 and 3 m	7.56	30.15	8.26	33.40	9.90	11.41	10.54	14.06

before the development of any hallmark deformity. Initially, we included 75 patients in each group for the study, but nine patients in IM group and five patients in IA group dropped out of subsequent visits. Hence, we concluded the study with 66 patients in IM group and 70 patients in IA group.

We used the blind technique for intra-articular injection as it was shown earlier by Joanna Cunningham *et al.*<sup>[7]</sup> in his study that although US guidance significantly improves the accuracy of joint injection but it did not improve the short-term outcome of joint injection. Furthermore, Lopes *et al.*<sup>[8]</sup> showed that blind IAs (intra-articular injections) in peripheral joints exhibit good accuracy when performed by good dexterity according to the anatomical landmarks with better accuracy in elbow, wrist, MCP joints, and knee joints and are associated with a satisfactory clinical response in RA.

In our study, there is clear female preponderance with 108 out of 136 patients being female and most of the patients were middle-aged, mean age being  $41.15 \pm 9.84$  years with maximum age being 62 years in IM group and 57 years in IA group. One hundred thirty-six patients were evaluated twice in two follow-up visits at 1 month and 3 months post-intervention in each group. They were assessed for improvement of wrist joint ROM, grip strengths, KFT, and CDAI scores.

It was seen by goniometric evaluation in our study that both groups showed statistically significant improvements in flexion and extension of both wrist joints ( $P < 0.001$  for both groups, intragroup analysis), except left wrist extension in IA group and right wrist extension in IM group did not show statistical significance between 2<sup>nd</sup> and 3<sup>rd</sup> visits.

Unfortunately, in our study, in intergroup comparison of wrist goniometry, the data could not be compared as it differed significantly between groups at baseline data (1<sup>st</sup> visit). Only in case of left wrist flexion, significant better improvement in IM group at 1 month post-intervention ( $P = 0.015$ ) with no difference in outcome at 3 months post-intervention ( $P = 0.320$ ) was noted. However, interestingly, when we calculated the

improvement in percentage among the visits, it revealed more improvement in intra-articular group at 3 months, more between 2<sup>nd</sup> and 3<sup>rd</sup> visits, as compared with intramuscular group [Table 1]. Konai *et al.*<sup>[9]</sup> supported this finding in their study by concluding that intra-articular glucocorticoids injection is superior to its systemic use for the management of monoarticular synovitis in rheumatoid patients but they intervened in knee joints who were on stable doses of oral corticosteroid for the past 30 days and stable doses of DMARDs for the past 3 months, whereas we excluded patients who were on any form of systemic steroid in past 3 months. Häkkinen *et al.*<sup>[10]</sup> (2003) also recorded range of motion large joints like us in their study, but their aim was to correlate joint mobility with health assessment questionnaire (HAQ). They found limited motion of wrist, shoulder, and knee joints are associated with increased disability (higher total HAQ scores). The possible explanation for this finding may be that the restriction of wrist ROM leading to poor hand function may be primarily due to synovitis and pain in early-stage which when resolved by the effect of local steroid, improves the ROM as well as functional capability. Therefore, the effect of intramuscular steroid was fast but short-lived in contrast to delayed but sustained benefit of intra-articular steroid.

Not only these, we also looked for improvement in handgrip strength in our study and found that in both IA and IM group, bilateral power grips and all pinch grips had statistically significant improvement over time between any two visits ( $P < 0.05$ ), except bilateral palmer pinch grip in IA group and bilateral lateral pinch grip in IM group did not any significant improvement between 2<sup>nd</sup> and 3<sup>rd</sup> visits. The findings of Skogh *et al.*<sup>[11]</sup> (2006) matched ours with respect to improvement pattern of the grip strength. They measured peak and average grip force over 10 s in the right and left hand by an electronic device and concluded it was profoundly affected at diagnosis, but improved significantly within 3 months.

While comparing these data between groups, it revealed that power and pinch grip strength in both groups improved equally well with no statistically significant difference ( $P > 0.05$ ), but then, calculation in terms of improvement percentage disclosed intramuscular group

had better results [Figure 2 and Table 2]. There is evidence from several other studies that grip strength correlates well with disease activity and improves with time as disease activity diminishes. Shipham *et al.*<sup>[12]</sup> (2003) and Häkkinen *et al.*<sup>[10]</sup> (2003) further inferred from their studies that highest correlation exists between grip strength and difficulty in ADL and decreased grip strength was associated with increased disability as reflected by higher total HAQ scores. On the contrary, Poulisa *et al.*<sup>[13]</sup> (2003) concluded from their study that there are no statistical differences in grip and pinch strength between healthy persons and early RA patients, but our patients had at least 2 years of disease duration. Hence, the general ability and well-being of the patient is reflected by the grip strength also,<sup>[14]</sup> which might not merely be a measure of hand function, as it showed more improvement in systemic steroid rather than local steroid.

Further, in our study, it was also shown that both routes of administration of steroid were equally effective in reducing disease activity reflected by CDAI score reduction and also had significant improvement in both groups between follow-ups. Similarly, we found almost identical improvement percentages in both groups [Figure 3]. A study by Pereira *et al.*<sup>[15]</sup> also patients showed marked improvement of CDAI scores following injection ( $P < 0.001$ ) although they intervened in wrist with painful refractory synovitis of RA patients. In the CIMESTRA study,<sup>[16]</sup> Hetland and Hørslev-Petersen although assessed disease activity by ACR outcome measures but their conclusion goes with ours that at 1 year, 85% of patients achieved ACR 20, 68% ACR50, and 59% ACR 70 in combination group receiving methotrexate and intra-articular injections of glucocorticoids. Both the studies came to the same conclusion that steroid retards joint damage and induces higher remission rate in early RA patients with decreased disease activity which was our finding too.

To evaluate the functional status of our patients, we applied the KFT in our study. KFT improved significantly in either group in both follow-up visits ( $P < 0.001$ ). Not only intergroup comparison revealed that the patients were functionally impaired in 1<sup>st</sup> visit in both groups equally but also in the follow-up visit there is more improvement in IM group than IA group which is significant statistically ( $P = 0.046$  in 2<sup>nd</sup> visit, and 0.000 in 3<sup>rd</sup>). The percentage improvement in IM group was more prominent between 1<sup>st</sup> and 3<sup>rd</sup> month whereas it is equitable at 1 month in both groups [Figure 3]. This trend is assumed to be due to the overall reduction of disease activity by the higher systemic dose of IM steroid that improved the functional scores consequently. After thorough search of literature, we found only one study by

Dellhag and Bjelle<sup>[17]</sup> in 1999 that used KFT as functional parameter in RA patients, but their objective was to follow the fate of hand function with ADL capacity over a period of 5 years in their study. They showed that hand function deteriorated during a 5-year period in female RA patient's more than male patients.

In our study, all the study parameters have improved significantly in both IA and IM group. Although statistical analysis exhibited that KFT has shown more improvement in IM group than IA group while grip strength and CDAI improved equally in both groups and incomparable data on goniometry, but on percentage improvement calculation, we found that in grip strength; KFT and CDAI, improvement was more in IM group. On the other hand, wrist ROM improved better in IA group. Therefore, it can be assumed that for functional improvement of hand in RA patients with disease duration  $< 24$  months, intra-articular injections might be considered when local effects are sought for, and intramuscular corticosteroid can be given if systemic improvement appertains to disease activity is the target of treatment. But keeping in mind the higher side effect profile and abuse potential of the systemic steroid, intra-articular administration might be preferred when applicable.

Therefore, we conclude that all the study parameters have significant improvement concerning hand function and disease activity in IA and IM group, but when compared between IA and IM groups, grip strength and CDAI scores revealed no difference in improvement pattern whereas KFT showed better results in IM group. The percentage improvement calculations revealed that wrist goniometry had better results in IA group whereas grip strength, CDAI, and KFT had better results in IM group.

Finally, to summarize, intra-articular injections have sustained effects throughout the study period in the range of motion improvement, and intramuscular injections have short-lived effects and are more effective in improving outcomes of functional status and disease activity. Thus, in short term, intra-articular injections have more prominent local effects whereas intramuscular injections improve the systemic parameters more.

## DISCLOSURE STATEMENT

This study was not funded by any governmental or non-governmental organization or any pharmaceutical company. And no financial or other benefit was related to this study, and no commitment or agreement was there to provide such benefit from a commercial entity.

### What is known?

Intra-articular corticosteroid injections (IACSI) are predominantly used for treating RA patients with refractory and persistent mono or oligoarthritis. IACSI show significant improvement in inflammatory process and reduction of pain in such RA patients. In most studies, IACSI are given in knee joints of RA patients. Systemic corticosteroids are predominantly used for control of pain and inflammation in case of RA flare and at initiation of DMARDS as bridging therapy. Grip strength is used as a measure of hand function.

### What is new?

Intra-articular injections have sustained effects throughout the study period in range of motion improvement whereas intramuscular injections have short-lived effects and are more effective in improving outcomes of functional status and disease activity. Grip strength is a measure of disease activity along with hand function. There is improvement of functional ability in patients with decrease in disease activity.

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# A Study of the Effect of Cigarette Smoking on Lipid Profile of People of Kolhan Region

Kumari Rekha<sup>1</sup>, Neelam Choudhary<sup>2</sup>

<sup>1</sup>Tutor, Department of physiology, Mahatma Gandhi Memorial Medical College and Hospital, Jamshedpur, Jharkhand, India, <sup>2</sup>Professor, Department of physiology, Mahatma Gandhi Memorial Medical College and Hospital, Jamshedpur, Jharkhand, India

## Abstract

**Introduction:** Cigarette smoking is an important and independent risk factor of atherosclerosis, coronary artery disease, and peripheral vascular disorders. It adversely affects the concentration of the plasma lipids and lipoprotein levels.

**Materials and Methods:** The present study was conducted in the Department of Physiology, Mahatma Gandhi Memorial Medical College and Hospital, Jamshedpur. Sixty healthy cigarette smokers were compared with forty healthy age-matched, non-obese, non-smokers. Participants in both the groups were in the age range of 25–35 years having no history of alcohol abuse or diseases such as diabetes mellitus and hypertension.

**Conclusion:** Total cholesterol and low-density lipoprotein (LDL) showed a highly significant upper range in smokers with  $P < 0.001$ . High-density lipoprotein and very LDL were also increased to a partially significant level in smokers with  $P < 0.1$ .

**Key words:** Coronary artery disease, High-density lipoprotein, Low-density lipoprotein, Total cholesterol, Triglyceride, Very low-density lipoprotein

## INTRODUCTION

Smoking is one of the most potent and prevalent addictive, influencing behaviors of human beings for over four centuries. It in different forms is a major risk factor for atherosclerosis and coronary heart disease.<sup>[1]</sup> There is a dose–response relationship between the number of cigarette/bidi smoked and cardiovascular morbidity and mortality.<sup>[2,3]</sup> Smoking leads to increase in the concentration of serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), very LDL-C (VLDL-C), and fall in the level of antiatherogenic high-density lipoprotein-cholesterol (HDL-C) as reported by various workers.<sup>[4]</sup> Various mechanisms leading to lipid alteration by smoking are as follows:

- Nicotine stimulates a sympathetic, adrenal system leading to increased secretion of catecholamines

resulting in lipolysis and increased concentration of plasma-free fatty acids (FFAs), which further results in increased secretion of hepatic FFAs and hepatic TG along with VLDL-C in the blood stream<sup>[2,3]</sup>

- Fall in estrogen levels occurs due to smoking, which further leads to decreased HDL-C<sup>[5]</sup>
- Presence of hyperinsulinemia in smokers leads to increased cholesterol, LDL-C, VLDL-C, and TGs due to decreased activity of lipoprotein lipase<sup>[6]</sup>
- Consumption of a diet rich in fat and cholesterol as well as a diet low in fiber and cereal content by smokers as compared to non-smokers.<sup>[7]</sup>

## MATERIALS AND METHODS

Blood samples were obtained after an overnight fast. About 5 ml of blood was collected from the left antecubital vein, of which about 2 ml is transferred into an overfast vial and mixed well and centrifuged at a speed of 3000 revolutions per minute for 10 min to separate the plasma, which was used for biochemical analysis. Rest 3 ml of blood is transferred to the test tube, and this blood was allowed to clot to get serum. This serum was separated in a centrifuge tube at 3000 revolutions per min to get a clear

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**Corresponding Author:** Dr. Kumari Rekha, C- 126, Harmu Housing Colony, Near Sahjanand Chawk, P.O. – Argora, Ranchi - 834 002, Jharkhand, India.

sample of serum. This clear supernatant serum was used for biochemical investigation.

### Estimation of Serum TC

Method – Enzymatic colorimetric Trinder end point.

The reagents were allowed to attain room temperature prior to use.

Pipette into tube marked	Blank (μL)	Standard (μL)	Sample (μL)
Reagent R	1000	1000	1000
Standard	-----	10	-----
Sample	-----	-----	10

They were incubated for 5 min at 37°C; the reading was done against blank at 500 nm, and calculation was made. The concentration of cholesterol in the sample is directly proportional to the intensity of red complex (red Quinone), which was measured at 500 nm.

Calculation

$$\text{Cholesterol} = \frac{\text{Absorbance of sample}}{\text{absorbance of standard}} \times \text{Concentration of standard.}$$

### Estimation of Serum TG

Method – Enzymatic colorimetric method.

Contents were mixed and incubated for 5 min at 37°C. The reading was done against blank at 546 nm.

Pipette into tube marked	Blank (μL)	Standard (μL)	Sample (μL)
Reagent R	1000	1000	1000
Standard	-----	10	-----
Sample	-----	-----	10

Calculation

$$\text{Serum TG} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times n.$$

n = Standard concentration

Reference values: >150 mg/dl.

### Estimation of HDL-C

Method – Phosphotungstate method.

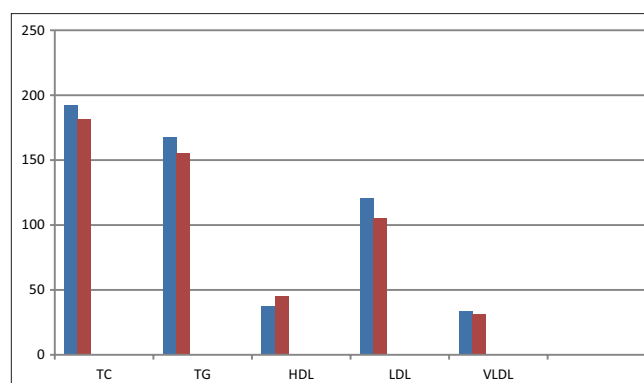
Principle – chylomicrons, LDL, and VLDL are precipitated by addition of phosphotungstic acid and magnesium chloride. After centrifugation, the HDL fraction remains in the supernatant, which is determined with CHOD-PAP method.

Reference value: >40 mg/dl.

**Table 1: Lipid-level variation among smokers and non-smokers (mean±SD) in mg/dl**

Types of lipids	Smokers (n=60)	Non-smokers (n=40)	t	P	Significance
TC	192.51±18.94	181.29±19.20	4.01	<0.0001	HS
TG	167.49±16.74	155.14±15.41	5.17	<0.001	HS
HDL	37.66±3.35	45.36±7.18	2.78	<0.1	PS
LDL	120.94±18.18	104.88±19.56	5.85	<0.001	HS
VLDL	33.50±3.35	31.03±3.08	1.08	<0.1	PS

TC, TG, and LDL showed a highly significant upper range in smokers. HDL and VLDL were also increased to a partially significant level in smokers. TC: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein



**Figure 1: Lipid-level variations among smokers and non-smokers (mean in mg/dl)**

Calculation of LDL and VLDL by Friedewald's Formula:

$$\text{LDL} = \text{TC} - (\text{HDL} + \text{VLDL}),$$

$$\text{VLDL} = \text{TG}/5,$$

Reference value:

LDL = Up to 190 mg/dl

VLDL = 14–31.8 mg/dl.

## RESULT AND OBSERVATION

Table 1 and Figure 1 shows lipid level variations among smoker and non- smoker. Definitely smokers show highly significant variations in lipid levels from non- smoker. Smokers have higher level of TC, TG and LDL while HDL and VLDL is partially significant.

## CONCLUSION

Our study clearly shows a strong relationship between elevation of serum lipids and cigarette smoking. It is revealed that Total cholesterol, triglyceride and LDL were significantly higher in smokers as compared to non-smokers. Smoking generates oxidised platelet activity



factor derivatives. These stimulate interaction between platelets- leucocytes and endothelial cell and thus augment inflammation and thrombosis.<sup>[8]</sup> A high level of LDL-C, TG, and TC is strongly associated with development of coronary artery disease, whereas a low level of HDL remains a significant independent predictor of coronary artery disease.<sup>[9,10]</sup>

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# Clinical Evidence of Hearing Loss in Patients Treated with Cisplatin for Head-and-Neck Squamous Cell Carcinomas

M Ravikumar<sup>1</sup>, Benhur Benraj Kommu<sup>2</sup>

<sup>1</sup>Associate Professor, Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, India, <sup>2</sup>Junior Resident, Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, India

## Abstract

**Background:** Cisplatin is a chemotherapeutic agent that is widely used to treat a variety of malignant tumors. Serious dose-limiting side effects such as ototoxicity, nephrotoxicity, and neurotoxicity are likely to occur with its use.

**Aim of the study:** The aim of the study was to do audiological evaluation of patients on cisplatin before and after chemotherapy for squamous cell carcinomas of head and neck and analyze for hearing loss (HL).

**Materials and Methods:** A total of 46 patients undergoing cisplatin administration were included in the study. History taking, preliminary ENT examination, and audiological evaluation with pure-tone audiometry were done. A pure-tone average (PTA) was calculated using the speech frequencies (500, 1000, and 1500 kHz). High-frequency pure-tone audiometry was also done in all patients to know the basal auditory threshold before starting cisplatin therapy. Baseline audiometry was done Prior to Chemotherapy or at least 24 h after administration of Cisplatin. Monitoring audiometry was done before each cycle of Cisplatin therapy. Follow-up audiometry was done 1, 3, and 6 months after chemotherapy. Dosage of cisplatin ranged from 50 mg to 115 mg with cumulative dose ranging from 250 mg to 850 mg in all the patients. All the data were analyzed using standard statistical methods.

**Observations and Results:** Among 46 patients, there were 33 males and 13 females (28.26%) with a male-to-female ratio of 2.53:1. Patients were aged between 45 years and 70 years and the mean age was  $55.35 \pm 2.70$  years. 22/46 (47.82%) patients were in the range of 55–65 years age group followed by 15/46 (32.60%) patients who were in the 45–55 years age group. 9/46 (19.56%) patients were in the 65–75 years age group. Patients of all age groups showed high-frequency (3000 kHz–12,000 kHz) HL in the study group. The thresholds were found to be increasing from 35 dB to 59 dB with increasing frequencies from 3000 kHz to 12,000 kHz.

**Conclusions:** In this study, all the patients showed significant evidence of severe mixed type of HL. The HL was significant in all the age groups and in both the genders. Six months follow-up showed no recovery of HL presumable resulting in permanent HL. Very few patients showed vestibular involvement. Audiometric monitoring may help to provide early evidence of decreased hearing ability, leading to the possible limitation of the severity of ototoxicity.

**Key words:** Cisplatin, Cochlea, Ototoxicity, Sensorineural Loss and Pure-tone Audiometry

## INTRODUCTION

Hearing loss (HL) observed after the usage of cisplatin chemotherapy appears to be varying with different patients. It appears to be dose related and also depends on age, noise

exposure, nutritional status, anemia, low serum albumin, and concurrent radiation to head-and-neck region.<sup>[1-3]</sup> HL is usually permanent and bilaterally symmetrical.<sup>[1]</sup> Apart from HL patients also complain of pain in the ear and tinnitus.<sup>[4]</sup> The prevalence of tinnitus among cisplatin used patients was 2–36% in the study by Reddel *et al.*<sup>[4]</sup> High-frequency thresholds are usually affected first followed by middle frequencies when doses in excess of 100 mg/m<sup>2</sup> are used.<sup>[2]</sup> Reports of dose-related HL in 20% of men in whom cisplatin was used for testicular carcinomas are available in literature.<sup>[1]</sup> Very high doses of cisplatin >400 mg/m<sup>2</sup> were found to be associated with permanent HL.<sup>[1]</sup> Patients with

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**Corresponding Author:** Dr. M Ravikumar, Associate Professor, Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, India.

nasopharyngeal carcinoma appear to be very susceptible to the interaction of cisplatin chemotherapy with cochlear irradiation. Radiation doses greater than 48 Gy increased the HL in these patients.<sup>[5]</sup> However, radiation therapy to the head-and-neck region with intensity-modulated radiation therapy as for brain tumors, such as medulloblastoma, can be modified using to reduce the doses of radiation to the cochlea.<sup>[6]</sup> A recent study showed that patients receiving <40 Gy radiations for head-and-neck malignancies did not suffer from HL, but when these patients received additional cisplatin as chemotherapy high-frequency HL was noted. At the end of the therapy, only 5% of patients showed HL on audiograms, but follow-up of these patients for more than 2 years revealed HL in more than 44% of the patients.<sup>[7]</sup> Additional follow-up for 6–44 months showed mild further progression of HL of 10–15 dB after completion of therapy.<sup>[8]</sup> The American Speech–Language–Hearing Association<sup>[9]</sup> recommends cost-effective ototoxicity identification for any population receiving ototoxic medication. The following should be considered: “(1) The patient’s level of alertness or ability to respond reliably; (2) the most appropriate times during the treatment protocol for test administration; and (3) the test should comprise the baseline, monitoring, and post-treatment evaluations.”<sup>[10]</sup> In this context, a clinical study was undertaken by conducting audiological evaluation of patients undergoing combined or adjuvant chemotherapy using cisplatin for the treatment of head-and-neck squamous cell carcinomas.

## MATERIALS AND METHODS

A cross-sectional prospective and analytical study was conducted by including 46 patients who were undergoing cisplatin administration used as concurrent to radiotherapy or adjuvant chemotherapy in a tertiary teaching hospital of Telangana. An institutional ethical committee clearance was obtained before the commencement of the study. An ethical committee cleared consent letter was used for the study.

### Inclusion Criteria

(1) Patients who were diagnosed as squamous cell carcinoma of head-and-neck region were included. (2) Patients receiving cisplatin as one of the drugs in chemotherapy were only included. (3) Patients undergoing concurrent radiotherapy were included. (4) Patients undergoing adjuvant chemotherapy were included.

### Exclusion Criteria

(1) Patients who are debilitated with malignancy were excluded. (2) Patients with earlier ear pathology were excluded. Patients with sensorineural deafness were excluded. (3) Patients with uncontrolled diabetes mellitus, hypothyroidism, and renal failure were excluded. All the patients were subjected to thorough history taking, preliminary ENT examination, and audiological evaluation with pure-tone audiometry which were done. The patients were questioned about hearing impairment; tinnitus or vertigo before and after chemotherapy, and a record was created. A pure-tone average (PTA) was calculated using the speech frequencies (500, 1000, and 1500 kHz). High-frequency pure-tone audiometry was also done in all patients to know the basal auditory threshold before starting cisplatin therapy. The pure-tone audiometry was repeated after every cycle of chemotherapy with cisplatin that is at the end of the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> cycles. An appropriate time interval for audiological assessments depending on the frequency and dose of cisplatin was undertaken. Baseline audiometry was done Prior to Chemotherapy or at least 24 h after administration of Cisplatin. Monitoring audiometry was done before each cycle of Cisplatin therapy. Follow-up audiometry was done 1, 3, and 6 months after chemotherapy. Dosage of cisplatin ranged from 50 mg to 115 mg with cumulative dose ranging from 250 mg to 850 mg in all the patients. All the data were analyzed using standard statistical methods.

## OBSERVATION AND RESULTS

A total of 46 patients who were undergoing cisplatin administration used as concurrent to radiotherapy or adjuvant chemotherapy in a tertiary teaching hospital of Telangana. Among the 46 (71.73%) patients, there were 33 males and 13 females (28.26%) with a male-to-female ratio of 2.53:1. Patients were aged between 45 years and 70 years and the mean age was  $55.35 \pm 2.70$  years. 22/46 (47.82%) patients were in the range of 55–65 years age group followed by 15/46 (32.60%) patients who were in the 45–55 years age group. 9/46 (19.56%) patients were in the 65–75 years age group [Table 1].

Patients in the age group of 65–75 years showed HL with mean PTA values of  $55.65 \pm 2.20$  when compared to basal audiometry values of  $34.50 \pm 2.85$  dB which was

**Table 1: The age, gender incidence, and basal audiometry (PTA) findings of the study group (n=46)**

Age group in years (%)	Male–33 (71.73%)	Female–13 (28.26%)	Basal audiometry (mean and SD of PTA)
45–55–15 (47.82)	11 (23.91)	4 (8.69)	22.45±2.15 dB
55–65–22 (32.60)	16 (34.78)	6 (13.04)	26.30±2.10 dB
65–75–9 (19.56)	6 (13.04)	3 (6.52)	33.45±2.85 dB

SD: Standard deviation, PTA: Pure-tone average

statistically significant with  $P = 0.012$  ( $P < 0.05$ ). Patients in the age group of 55–65 years showed HL with mean PTA values of  $50.25 \pm 4.30$  when compared to basal audiometry values of  $25.60 \pm 2.10$  dB which was statistically significant with  $P = 0.035$  ( $P < 0.05$ ). Patients in the age group of 45–55 years showed HL with mean PTA values of  $45.25 \pm 2.15$  when compared to basal audiometry values of  $24.35 \pm 2.15$  dB which was statistically significant with  $P = 0.041$  ( $P < 0.05$ ) [Table 2].

Patients of all age groups showed high-frequency (3000 kHz–12,000 kHz) HL in the study group. The thresholds were found to be increasing from 35 dB to 59 dB with increasing frequencies from 3000 kHz to 12,000 kHz. The actual mean air conduction values are shown in Table 3.

Among the 46 patients, three patients complained of tinnitus after the 1<sup>st</sup> cycle of cisplatin therapy. Two patients complained of vertigo after the 2<sup>nd</sup> cycle that was treated with medical management. The cumulative dose of cisplatin was ranging from 225 mg to 800 mg/m<sup>2</sup>.

## DISCUSSION

Ototoxicity due to cisplatin is well recorded in literature but neglected by both the patients and the physicians unless the severity of HL impairs the daily activities of the patient. The HL is of bilateral nature and involves both the speech frequencies and high frequencies equally. The HL is also permanent in nature.<sup>[11,12]</sup> The high-frequency loss may be due to susceptibility of basal turn of cochlea to cumulative concentration of the drug cisplatin.<sup>[1]</sup> It is postulated that initially the higher frequencies are affected first; later, progressively, the speech frequencies are affected resulting in the subject's hearing capabilities.<sup>[13]</sup> Rise in thresholds of speech frequencies results in difficulty in discriminating the consonant sounds of the speech, especially in

ambient noise.<sup>[14]</sup> HL in speech frequencies would result in clinical, behavioral, and psychological disorders resulting in impairment in functional status, cognitive status, depressive symptomatology, and disability.<sup>[13]</sup> There are many studies in literature revealing the high incidence of permanent, and irreversible high-frequency bilateral symmetrical loss in patients administered cisplatin for various malignancies.<sup>[4,7-10]</sup> In the present study, patients in the age group of 65–75 years showed HL with mean PTA values of  $55.65 \pm 2.20$  when compared to basal audiometry values of  $34.50 \pm 2.85$  dB which was statistically significant with  $P = 0.012$  ( $P < 0.05$ ). Patients in the age group of 55–65 years showed HL with mean PTA values of  $50.25 \pm 4.30$  when compared to basal audiometry values of  $25.60 \pm 2.10$  dB which was statistically significant with  $P = 0.035$  ( $P < 0.05$ ). Patients in the age group of 45–55 years showed HL with mean PTA values of  $45.25 \pm 2.15$  when compared to basal audiometry values of  $24.35 \pm 2.15$  dB which was statistically significant with  $P = 0.041$  ( $P < 0.05$ ). Patients of all age groups showed high-frequency (3000 kHz–12,000 kHz) HL in the study group. The thresholds were found to be increasing from 35 dB to 59 dB with increasing frequencies from 3000 kHz to 12,000 kHz. Literature also shows that the vestibular end-organ degeneration following the use of cisplatin,<sup>[4,15]</sup> but in this study, there only three patients who complained of tinnitus and two patients who complained of vertigo. Tinnitus is reported to occur in a progressive and dose-dependent manner.<sup>[11,12]</sup> In the present study, it was observed that patients who were diagnosed as carcinoma nasopharynx and underwent concurrent radiotherapy were administered high doses of cisplatin  $>640$  mg/m had severe HL when compared to other malignancies. This can be explained as the same patients were subjected to curative doses of radiotherapy also resulting in severe HL. Audiometric monitoring may help to provide early evidence of decreased hearing ability, leading to the possible limitation of the severity of ototoxicity. Moreover, for some patients, it is possible that

**Table 2: The audiological evaluation before and after cisplatin chemotherapy (n=46)**

Age group	Basal audiometry (mean and SD of PTA)	Audiometry after the 1 <sup>st</sup> month cycle: Mean and SD PTA	Audiometry after the 3 <sup>rd</sup> month cycle: Mean and SD PTA	Audiometry after the 6 <sup>th</sup> month cycle: Mean and SD PTA	P-value
45–55 years	24.35±2.15 dB	31.55±3.25	39.42±3.30	45.25±4.10	0.041
55–65 years	25.60±2.10 dB	39.10±4.15	42.75±3.55	50.25±4.30	0.035
65–75 years	34.50±2.85 dB	46.25±4.20	51.40±4.60	55.65±2.20	0.012

PTA: Pure-tone average

**Table 3: The mean air conduction thresholds of high frequencies on audiometry (n=46)**

Age group	3000 kHz	4000 kHz	5000 kHz	6000 kHz	8000 kHz	10,000 kHz	12,000 kHz
45–55 years	35.30±2.10	38.20±2.15	42.30±2.85	48.55±3.10	50.45±2.60	52.35±2.30	55.30±1.75
55–65 years	38.10±1.30	44.55±3.65	49.45±3.90	53.30±1.85	54.20±1.35	56.35±2.25	58.95±2.30
65–75 years	40.50±1.70	45.30±2.85	51.50±2.80	55.20±2.95	56.20±3.10	57.10±1.50	59.10±3.05

the drug dosage may be modified. Despite these efforts, ototoxicity will still occur after cisplatin administration.

## CONCLUSIONS

In this study, all the patients showed significant evidence of severe mixed type of HL. The HL was significant in all the age groups and in both the genders. Six months follow-up showed no recovery of HL presumable resulting in permanent HL. Very few patients showed vestibular involvement. Audiometric monitoring may help to provide early evidence of decreased hearing ability, leading to the possible limitation of the severity of ototoxicity.

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# Perinatal Outcome of the Second Twin with Respect to Mode of Delivery – A Prospective Analysis

Sneha Singh<sup>1</sup>, Priyanka Priyadarshini<sup>2</sup>, Hiralal Konar<sup>3</sup>, Lovely Agarwal<sup>4</sup>

<sup>1</sup>Junior Resident, Department of Obstetrics and Gynaecology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India, <sup>2</sup>Senior Resident, Department of Obstetrics and Gynaecology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India, <sup>3</sup>Professor and Head, Department of Obstetrics and Gynaecology, Agartala Government Medical College, Agartala, Tripura, India, <sup>4</sup>Resident Medical Officer Cum Tutor, Department of Obstetrics and Gynaecology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India

## Abstract

**Aims and Objectives:** The aim of the study was to study the perinatal outcome of the second twin with respect to mode of delivery.

**Materials and Methods:** Consecutive pregnant women having twin pregnancies beyond 28 weeks of gestation admitted to the department of the institute during the period from April 2016–May 2017 were included in the study.

**Results:** A total of 50 cases were enrolled in the study. Vaginal, ventouse/forceps, and lower segment cesarean section (LSCS) were the different modes of delivery consisting of 48%, 2%, and 50% of cases, respectively. Perinatal loss of the second twins was higher in LSCS group consisting of 61.11% of cases. Perinatal loss of the second twins was 100% for monochorionic monoamniotic pregnancies whereas 33.33% for monochorionic diamniotic and 29.03% for dichorionic diamniotic pregnancies. The delivery time interval of <10 min between the first and second twin had the higher second twin perinatal loss, i.e., 37.14% and less poor APGAR score, i.e., 57.14% in comparison to time interval of 10–30 and >30 min groups but statistically insignificant. For second twin, vertex presentation had higher poor APGAR score compared to non-vertex presentation, i.e., 65.63% versus 55.56%. Poor APGAR score was found to be higher in cesarean section, outlet forceps and vaginal mode of deliveries consisting of 60%, 100%, and 62.5%, respectively. In overall, 64% of second twins and 84% of first twins were alive, and the difference had  $P = 0.034$ . About 62% of second twins and 34% of first twins were having poor APGAR score of <7, and the difference had  $P = 0.005$ . About 67.44% and 76.92% of second twins were found to be alive higher in maternal age group of  $\geq 20$  years and multigravida group, respectively, having  $P < 0.05$ . About 64.52% and 100% of second twins were alive higher in <37 weeks gestational age group and birth weight of second twin  $\geq 2500$  kg groups, respectively, with  $P < 0.05$ . Second twins were having higher alive in vertex-non-vertex presentation, vaginal mode of delivery for both the twins, DCDA group and intertwin delivery interval of 10–30 min groups consisting of 71.43%, 72%, 70.97%, and 77.78%, respectively, with  $P > 0.05$ .

**Conclusion:** The perinatal mortality of 2<sup>nd</sup> twin is higher than that of 1<sup>st</sup> twin in terms of monochorionic, prematurity, and low birth weight. Intensive labor monitoring, safe delivery, and improved neonatal care facilities appear to be the major areas to improve the perinatal outcome.

**Key words:** Mode of delivery, Perinatal outcome, Second twin

## INTRODUCTION

Multiple pregnancies are a high-risk situation because of its inherent risks to mother and the fetus. Twin or multiple

pregnancies are gaining importance worldwide because of the attributable rise in treatment of infertility including assisted reproductive technologies.

Twin gestations comprise 3.3% of all pregnancies.<sup>[1]</sup> Twin pregnancies are associated with increased fetal loss, prematurity, structural abnormalities, and fetal growth restriction. Complications associated with twin pregnancy result from exaggerated physiological response, overdistension of uterus, hyperplacental, and unique problems posed by monochorionic placentation. Intrapartum complications include preterm labor, dysfunctional labor,

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\*Corresponding Author: Dr. Priyanka Priyadarshini, Department Obstetrics and Gynaecology, Calcutta National Medical College and Hospital, Kolkata - 700 014, West Bengal, India.



malpresentation, operative vaginal delivery, and cesarean section. Postpartum complications are high such as postpartum hemorrhage, sepsis, and failure of lactation. The conduct of a twin delivery remains one of the most challenging events in the current obstetric practice.

Besides a higher incidence of prematurity and low birth weight (birth weight < 2500 g) in twins, many other factors such as discordant growth, route of delivery, inter-twin delivery time interval, birth order, and gender have been reported to influence neonatal outcome adversely. Second twins delivered at term are at increased risk of delivery-related perinatal death.<sup>[2]</sup> The second twins are more vulnerable to adverse perinatal outcome than first twin due to separation of placenta, cord compression, cord prolapse, delay in delivery, and uterine dysfunction.<sup>[3]</sup> The second twin is at added risk of respiratory distress syndrome (RDS).<sup>[4]</sup> This outcome of the second twin is mostly related to discordant growth and also due to preterm birth. However, data related to twins born in the Southeast Asian region is sparse.

A woman having twin pregnancy should undergo determination of the type of placenta, followed by adequate counseling regarding extra calorie intake, frequent antenatal visits for early identification of maternal morbidities and ultrasound for monitoring the fetal growth to detect any anomalies, intrauterine growth retardation (IUGR) and discordancy at the earlier onset.

The obstetrician should advise woman to take adequate bed rest, antenatal steroids and should plan for the best mode of delivery in each case to prevent preterm birth.<sup>[5]</sup> A multidisciplinary approach involving skilled obstetrician, anesthesiologists, and neonatologists is necessary for handling women bearing twin pregnancies to get a successful pregnancy outcome with less fetal and maternal morbidity.<sup>[6]</sup>

The present study has been designed to determine the clinico-epidemiological profile and perinatal outcome of second twin deliveries at a tertiary care hospital in India.

## MATERIALS AND METHODS

The present study was a prospective observational one conducted in the department of obstetrics and gynecology of a tertiary care teaching institute during the period from May 2016 to April 2017. Consecutive pregnant women having twin gestation beyond 28 weeks of gestation admitted through antenatal clinic and emergency department of the institute and giving consent to participate were included in the study.

A detailed history including the age, parity, booking status and socioeconomic status, last menstrual period (LMP), obstetric history, history of twin pregnancy, family history of twin pregnancy, history of ovulation induction or other artificial reproductive techniques measures were taken. A detailed history in each trimester regarding any complaints in the antenatal period such as excessive vomiting, anemia, and urinary tract infections, history of adequate calorie intake during each trimester, intake of tocolytics, or antenatal steroids.

The routine examination consisted of looking for features of anemia, position and presentation of fetuses, and fetal parts and fetal heart sounds. Ultrasonography was done to confirm the diagnosis, presentation of the fetuses, any anomalies, birth weight discordancy, etc. Routine investigations were done. In patients admitted with labor pains, gestational age was calculated from day 1 of the LMP. Factors such as premature rupture of membranes, preterm premature rupture of membranes, preterm labor, abruption, presentation of fetuses, mode of delivery, time interval, APGAR scores, and complications of 3<sup>rd</sup> stage labor in the mother were noted. The placenta was examined postnatally and the chorionicity noted. APGAR score of second twin at 5 min, need of nursery or sick newborn care units (SNCU) admission assessed.

The perinatal outcome was measured in terms of number of babies admitted to the neonatal intensive care unit, and the final outcome of the babies, in terms of whether discharged in good condition or expired during the neonatal period. Neonatal morbidity was further defined based on the causes such as RDS, septicemia, IUGR, neonatal hyperbilirubinemia, hypoglycemia, and neonatal seizures (NNS). Causes of death were termed as due to birth asphyxia, sepsis, cord prolapse, prematurity and its complication, fetal growth restriction, NNS, and intrauterine death.

The outcome of the second twin with respect to gestational age, mode of delivery, and birth weight recorded, plotted and significance calculated using statistical analysis.

## RESULTS

A total of 50 consecutive pregnant women having twin gestation beyond 28 weeks of gestation attaining our institute during the study period were included in the study. Sociodemographic profile of multiple pregnancies is mentioned in Table 1. Multiple pregnancies were highest in the maternal age group of 21–30 years consisting of 58% and were more prevalent in primigravida consisting of 48%. Preterm pregnancies and frequency of booked cases had

**Table 1: Sociodemographic profile**

Parameters	Frequency with %
Age (years)	
≤20	15 (30)
21–30	29 (58)
31–40	5 (10)
41–50	1 (2)
Parit	
P0+0	24 (48)
P0+1	1 (2)
P1+0	15 (30)
P1+1	3 (6)
P2+0	6 (12)
P2+1	1 (2)
Socioeconomic status	
Low	22 (44)
Middle	28 (56)
Gestational age (weeks)	
≥37	19 (38)
34 <sup>0/7</sup> –36 <sup>6/7</sup>	29 (58)
28–34	2 (4)
Antenatal visits	
Booked	44 (88)
Unbooked	6 (12)
Admission route	
Emergency	34 (68)
OPD	16 (32)
Ovulation	
Induced	3 (6)
Spontaneous	47 (94)

P: Parity, OPD: Outpatient door

higher incidence consisting of 62% and 88%, respectively. The higher number of admission was from emergency, i.e., 68% of the cases. Only 6% of the pregnancies were result of ovulation induction.

Incidence of dichorionic diamniotic (DCDA) pregnancy was higher followed by monochorionic diamniotic (MCDA) and monochorionic monoamniotic (MCMA) with the incidence of 62%, 30%, and 8%, respectively. The most common presentation of both babies was vertex-vertex being 44% followed by vertex–breech and others [Table 2].

With respect to chorionicity, the median gestational age was higher in dichorionic twin being 37.7 weeks with compared to monochorionic twin where it was 33.4 weeks for MCDA and 36 weeks for MCMA twins. Furthermore, average birth weight was more in dichorionic twin (2.07 kg for first twin and 2.05 for second twin) than monochorionic twin.

Perinatal loss of both the twins was higher in birth weight group of 1–<1.5 kg, i.e., 50% for twin 1 and 100% for twin 2. According to mode of delivery, perinatal loss of both the twins was higher in LSCS group consisting of 21.74% and 44% of cases for twin 1 and twin 2, respectively [Table 3]. Perinatal loss of both the twins was higher in monochorionic pregnancies in comparison

**Table 2: Chorionicity and presentation of both babies**

Parameters	Number of cases with %
Chorionicity	
DCDA	31 (62)
MCDA	15 (30)
MCMA	4 (08)
Presentation	
Vertex-vertex	22 (44)
Vertex–breech	11 (22)
Breech-vertex	9 (18)
Breech-breech	4 (08)
Vertex-transverse	2 (04)
Transverse-vertex	1 (02)
Breech-transverse	1 (02)

DCDA: Dichorionic diamniotic, MCDA: Monochorionic diamniotic, MCMA: Monochorionic monoamniotic

**Table 3: Perinatal loss with respect to birth weight and mode of delivery**

Parameters	First twin		Second twin	
	Total number of cases	Perinatal loss %	Total number of cases	Perinatal loss %
Birth weight (kg)				
<1	0	0 (0)	0	0 (0)
1–<1.5	6	3 (50)	7	7 (100)
1.5–<2.5	35	5 (14.2)	35	10 (28.5)
2.5–4	9	0 (0)	8	0 (0)
Mode of delivery				
Vaginal	27	3 (11.11)	24	7 (29.17)
Ventouse/	0	0	1	0
Forceps				
LSCS	23	5 (21.74)	25	11 (44)

LSCS: Lower segment cesarean section

to dichorionic pregnancies and the value was 100% for MCMA pregnancies [Table 4]. Delivery time interval of >10 min between the first and second twin had the higher second twin perinatal loss of 37.14% in comparison to time interval of 10–30 and >30 min groups [Table 5].

The mean and median APGAR score was less in second twins with compared to first twin, i.e., twin 1 with mean of 6.92, median of 7.00, and twin 2 with mean of 6.06, median of 6.00. Monochorionic twins have poor APGAR score in relation to dichorionic twins. For the second twin, lower APGAR score was found to be slightly higher in both sex groups than the score of ≥7. Vertex presentation of second twin had higher poor APGAR score compared to non-vertex presentation, i.e., 42% versus 20%, respectively [Table 6]. Intertwin delivery interval is not an influencing factor for poor APGAR score of the second twin, i.e., interval of <10 min had lower APGAR score in 40% and score of ≥7 in 30% [Table 7].

Seventeen cases of first twins and 34 cases of second twins were admitted under SNCU/NICU [Table 8]. For perinatal

**Table 4: The perinatal outcome with respect to chorionicity**

Parameters	DCDA (%)	MCDA (%)	MCMA (%)
Total number of cases	31	15	4
Perinatal loss			
First twin	1 (3.23)	3 (20)	4 (100)
Second twin	9 (29.03)	5 (33.33)	4 (100)

**Table 5: Delivery time interval between the babies and the perinatal outcome of the second twin**

Minutes	Total number of cases	Perinatal loss in percentage to total cases
<10	35	13 (37.14)
10–30	9	2 (22.22)
>30	6	2 (33.33)

**Table 6: APGAR score of first and second twins with respect to chorionicity, presentation, mode of delivery, and sex distribution**

Parameters	APGAR score			
	First twin		Second twin	
	<7	≥7	<7	≥7
Chorionicity				
DCDA	4	27	18	13
MCDA	9	6	9	6
MCMA	4	0	4	0
Presentation				
Nonvertex	6	9	10	8
Vertex	11	24	21	11
Mode of delivery				
Cesarean section	9	14	15	10
Outlet forceps	0	0	1	0
Vaginal	8	19	15	9
Gender				
Boy	11	15	18	10
Girl	6	18	13	9

DCDA: Dichorionic diamniotic, MCDA: Monochorionic diamniotic, MCMA: Monochorionic monoamniotic

outcome, 84% of first twins were alive whereas 64% of second twins were alive and the difference was statistical significant with the  $P = 0.034$ . About 62% of second twins had low APGAR score compared to first twins where it was 34%, and the difference was statistically significant with  $P = 0.005$  [Table 9]. Perinatal morbidity and mortality are comparatively high in the second twin.

Death of the second twins was more in delivery by cesarean section and vaginal mode of delivery consisting of 44% and 25% in comparison to death of first twins with the corresponding value of 21.74% and 7.41%, respectively [Table 10]. However, mode of delivery is found to have no significant influence on the perinatal outcome of both the first and second twins with  $P = 0.225$  and  $0.321$ , respectively.

**Table 7: APGAR SCORE of the second twin with respect to intertwin delivery time interval**

Intertwin delivery interval	APGAR score of the second twin	
	<7	≥7
<10	20	15
10–30	5	4
≥30	6	0

**Table 8: SNCU/NICU admission**

NICU/SNCU	Twins		Total	P value
	First twin	Second twin		
Mother	32 (65.31)	14 (29.17)	46 (47.42)	0.002
NICU	8 (16.33)	16 (33.33)	24 (24.74)	
SNCU	9 (18.37)	18 (37.5)	27 (27.84)	
Total	49 (100)	48 (100)	97 (100)	

NICU: Neonatal intensive care units, SNCU: Sick newborn care units

**Table 9: Perinatal outcome and APGAR score of the second twin compared to the first twin**

Parameters	Twins		P value
	First twin (%)	Second twin (%)	
Outcome			0.034
Alive	42 (84)	32 (64)	
Dead	7 (14)	17 (34)	
Stillborn	1 (2)	1 (2)	0.005
APGAR score			
<7	17 (34)	31 (62)	
≥7	33 (66)	19 (38)	

**Table 10: Comparison of outcome of both twins in relation to mode of delivery**

Outcomes	Mode of delivery					
	Cesarean section		Outlet forceps		Vaginal	
	T1 (%)	T2 (%)	T1 (%)	T2 (%)	T1 (%)	T2 (%)
Alive	18 (78.26)	14 (56)	0	1 (100)	24 (88.89)	17 (70.83)
Dead	5 (21.74)	11 (44)	0	0	2 (7.41)	6 (25)
Stillborn	0	0	0	0	1 (3.70)	1 (4.17)

According to maternal characteristics, the perinatal outcome of second twins in terms of alive was higher in maternal age group of  $\geq 20$  years and multigravida group consisting of 67.44% and 76.92%, respectively, in comparison to that in maternal of  $>20$  years group and primigravida group where it was 42.86% and 50%, respectively. The data were statistically significant having  $P < 0.05$  [Table 11]. According to neonatal characteristics, perinatal outcome of second twins in terms of alive was higher in  $<37$  weeks gestational age group and birth weight of second twin  $\geq 2500$  kg groups consisting of 64.52% and 100%, respectively, with the statistically  $P < 0.05$ . According

to neonatal characteristics, perinatal outcome of second twins in terms of alive was higher in vertex-non-vertex presentation, vaginal mode of delivery for both the twins, DCDA group and intertwin delivery interval of 10–30 min groups consisting of 71.43%, 72%, 70.97%, and 77.78%, respectively, with the statistically  $P > 0.05$  [Table 12].

## DISCUSSION

In our study, the majority of twin pregnancies were seen in the age group of 21–30 years consisting of 58% which was supported by Konar *et al.* where they found the incidence of 65.71% in the age group of 20–29 years.<sup>[7]</sup> In present study, incidence of twin pregnancy in primigravida was 50%, whereas in the study of Kwon *et al.* they found

the incidence of 67.1% in the primigravida women.<sup>[8]</sup> In contrast, Konar *et al.* found higher incidence, i.e., 70% in multigravida.<sup>[7]</sup> The most common presentation in our study was vertex-vertex followed by vertex-breech presentation which was supported by the studies done by Konar *et al.* and Chittacharoen *et al.*<sup>[7,9]</sup> In our study, majority of the cases delivered at preterm, i.e., <37 weeks consisting of 62% cases which were supported by Dera *et al.* where 62.5% of cases delivered at <37 weeks,<sup>[10]</sup> whereas Konar *et al.* observed per-term deliveries in 44.2% cases.<sup>[7]</sup>

In our study, the median gestational age was higher in dichorionic twin being 37.7 weeks with compared to monochorionic twin, and it implies preterm delivery to be more common with monochorionic twin pregnancies than dichorionic twin pregnancies. Continuing pregnancy >37 weeks in monochorionic pregnancies had higher mortality when compared with dichorionic pregnancies. Hack *et al.* in their study found six neonatal deaths in monochorionic pregnancies after 32 weeks of gestation. Perinatal mortality was 7/1000 births in those who delivered >37 weeks. Hence, they concluded that mortality at term was higher in monochorionic twin pregnancies than in dichorionic twin pregnancies, hence, waiting for spontaneous onset of labor after 37 weeks is not justified.<sup>[11]</sup> Planned elective delivery between 36 and 37 weeks should be considered, which avoids the respiratory disorders in the neonate due to preterm delivery. Furthermore, 1% risk of IUD after 37 weeks can be avoided. This does not warrant elective cesarean section in all cases and does not have significant impact on the neonatal outcome. Few studies suggested that most of the monochorionic pregnancies complicated by discordancy and twin-twin transfusion syndrome ends up in preterm births and intrauterine fetal death. In the absence of such complications, elective preterm delivery is not indicated.<sup>[12]</sup> Uncomplicated twin pregnancies delivered electively by 37 weeks had lesser incidence of adverse outcomes in the neonate compared with those pregnancies with >37 weeks with awaited spontaneous onset of labor.

In the present study, 54% of first twin babies and 48% of the second twin babies delivered vaginally, two of the second twin delivered by cesarean followed by vaginal delivery of the first twin due to indications such as cord prolapse and fetal distress. The perinatal loss of the second twin was not influenced by the mode of delivery. It was similar to study of Caukwell *et al.* where they found that the presentation and mode of delivery of the second twin were not associated with significant difference in any of the outcome variables.<sup>[13]</sup> Konar *et al.*, in their study, found perinatal mortality less in both the twins undergoing cesarean section compared to that undergoing vaginal delivery in the same geographic area.<sup>[7]</sup>

**Table 11: Perinatal outcome of the second twin according to maternal characteristics**

Maternal characteristics	Total number	Alive (%)	Dead (%)	P value
Maternal age (years)				
<20	7	3 (42.86)	4 (57.14)	<0.05
≥20	43	29 (67.44)	14 (32.56)	
Gravidity				
Primigravida	24	12 (50)	12 (50)	<0.05
Multigravida	26	20 (76.92)	6 (23.08)	

**Table 12: Perinatal outcome of the second twin according to neonatal characteristics**

Neonatal characteristics	Total number	Alive	Dead	P value
Gestational age at birth (weeks)				
<37	31	20 (64.52)	11 (35.48)	<0.05
≥37	19	2 (10.53)	17 (89.47)	
Fetal presentation				
Vertex-vertex	22	15 (68.18)	7 (31.82)	>0.05
Vertex-nonvertex	14	10 (71.43)	4 (28.57)	
Non-vertex-others	14	7 (50)	7 (50)	
Mode of delivery				
Both vaginal (v-v)	25	18 (72)	7 (28)	>0.05
Both cs (c-c)	23	12 (52.17)	11 (47.83)	
First vaginal second cs	2	0	2 (100)	
Birth weight of second twin (gm)				
<2500	42	25 (59.52)	17 (40.48)	<0.05
≥2500	8	8 (100)	0	
Chorionicity: DCDA	31	22 (70.97)	9 (29.03)	>0.05
MCDA	15	10 (66.67)	5 (33.33)	
MCMA	4	0	4 (100)	
Birth weight difference between first and second twin				
<20% nondiscordant	27	16 (59.26)	11 (40.74)	>0.05
>20% discordant	13	7 (53.85)	6 (46.15)	
Gender				
Boy	28	18 (64.29)	10 (35.71)	>0.05
Girl	22	15 (68.18)	7 (31.82)	
Intertwin delivery interval (minutes)				
<10	35	22 (62.86)	13 (37.14)	>0.05
10–30	9	7 (77.78)	2 (22.22)	
>30	6	4 (66.67)	2 (33.33)	



Bjelic-Radisic *et al.*, in a study, stated that low APGAR was found maximum in those cases delivered by V-CS (vaginal-1<sup>st</sup> twin and cesarean section of 2<sup>nd</sup> twin) followed by V-V and then CS-CS. They found higher mortality in non-vertex 2<sup>nd</sup> twin supporting our data.<sup>[14]</sup> In our study, vaginal delivery had higher low APGAR score with compared to CS but, data were statistically insignificant. The high CS rate in V/NV presentation and the significantly worse perinatal short-term outcome of NV second twins underlines that randomized studies are necessary to evaluate the best delivery mode for V/NV twins.

A study by Dera *et al.* suggested that the mode of delivery had no influence on the morbidity and mortality of the non-cephalic second twin of weight >1.5 kg.<sup>[10]</sup> Steins Bisschop *et al.* suggested that there is no consensus regarding the ideal route of delivery for non-vertex twins. They stated that it is ideal to do LSCS for non-vertex first twin since the phenomena of interlocking twins are seen with breech/vertex twins.<sup>[15]</sup> Yang *et al.* stated that vaginal delivery causes more morbidity to the second twin than caesarean section of both the twins.<sup>[16]</sup> American College of Obstetricians and Gynecologists Committee on practice bulletin does not give a clear cut conclusion regarding the mode of delivery.<sup>[17]</sup>

Cochrane systematic review regarding this issue stated that delivery of non-vertex second twins by vaginal route is associated with increased maternal morbidity and also does not improve the neonatal outcome; hence, further trials are needed to conclude regarding opting for LSCS.<sup>[18]</sup> Hack *et al.* stated regarding MCDA pregnancies that perinatal mortality was similar between all modes of delivery groups.<sup>[11]</sup>

The second twin is in a state of chronic distress (hypoxia) compared to the first twin. Irrespective of mode of delivery second twin was born with low mean APGAR score (<7) compared to first twin in the present study.

In the present study, intertwin delivery interval was not found to be an influential factor in the perinatal outcome of the second twin. This was supported by the study of Cukeirman *et al.* who found that composite adverse outcome of the second twin and NICU admission was not significantly influenced by intertwin delivery interval.<sup>[19]</sup> Similar observation was quoted by Algeri *et al.* that intertwin delivery time was not an influencing factor. Hence, in line with this result, in their clinical practice, they did not use a fixed time in which baby should be delivered.<sup>[20]</sup> Kwon *et al.* observed a better neonatal outcome when the inter twin delivery time interval was <10 min.<sup>[8]</sup>

In the present study, fetal monitoring of twin in all cases during the intrapartum period could not be done due to

non-availability of twin transducers, intrapartum period needs to be observed.

It is a known fact that birth weight <2500 g has a poorer outcome in terms of morbidity and mortality of both the twins. In the present study, the perinatal mortality was highest in the birth weight of <2.5 kg, and it was statistically significant with  $P < 0.05$ . This was similar to Konar *et al.* who observed perinatal outcome of the second twin was unfavorable among low birth weight.<sup>[7]</sup>

Average birth weight in kg in dichorionic and monochorionic pregnancies was 2.1 and 1.9, respectively. The average birth weight was approximately 100 g higher in dichorionic twins than in monochorionic twins. Hack *et al.* compared monochorionic and dichorionic twins in 651 pairs and observed that the birth weight of dichorionic twins was 288 g higher than monochorionic twins.<sup>[11]</sup>

In the present study, discordancy was found higher in monochorionic twin pregnancies than in dichorionic twin pregnancies, with the loss of 22.2% for first twin babies and 46.17% for second twin babies. Moreover, the mortality for the discordant second twin in a monochorionic pregnancy was still higher, i.e., 50% versus 33.3% in dichorionic twin pregnancies.  $P > 0.05$ ; hence, the difference was not statistically significant. Percentages of discordant babies were in equal in both monochorionic and dichorionic twin pregnancies. However, the mortality was higher for monochorionic pregnancies (33.3%) than di-chorionic (15.7%) pregnancies in the study of Hack *et al.*<sup>[11]</sup>

In the present study, the outcome of the second twin baby has been judged based on values of APGAR score of both twin babies. There were 34% of first twin babies and 62% of second twin babies with APGAR score of <7. Numbers of NICU/SNCU admissions were high for second twin babies, i.e., 34 versus 17 of first twin babies and the difference is statistically significant with  $P < 0.05$ .

In the present study, mortality for the second twin is higher, i.e., 340/1000 births than the first twin, i.e., 140/1000 births. In our study, 84% of first twin babies were discharged alive whereas 64% of second twin babies discharged alive. We found higher perinatal loss in the second twin with compared to first twin, and our results were similar to Santana *et al.*<sup>[21]</sup>

## CONCLUSION

With the increased age of motherhood and with the increased number of mothers seeking infertility treatments, assisted reproductive technologies are been used widespread, leading onto the increased incidence

of twin gestations. Any patient with multiple gestations should be clinically managed as a high-risk pregnancy. The multidisciplinary team should be led by an obstetrician and should include midwives, sonologist, neonatologist, and anesthetist. Such a service would provide a structured plan that will enable early detection, appropriate management, and effective use of the resources for the antenatal, intrapartum, and postnatal needs of the patients.

Perinatal/Neonatal morbidity and mortality are significantly higher in multiple gestations than singleton pregnancies. Out of the perinatal mortality of the twins, the perinatal mortality of 2<sup>nd</sup> of the twin is higher than that of 1<sup>st</sup> twin in terms of prematurity and low birth weight. Immediate neonatal problems detected were prematurity and birth asphyxia. The outcome was poorer for monochorionic twins than in dichorionic twins. Furthermore, the chorionicity is important in assessing the perinatal outcome of the twins than the zygosity, which can only be determined using genetic testing. Providing optimum antenatal checkup to all mothers having multiple gestations could not improve perinatal outcome. All patients with multiple gestations should have a thorough first- and second-trimester ultrasonography to assess chorionicity, amnionity, individual fetal growth, and congenital malformations. The presentation of each fetus must be sonographically verified as soon as the patient with multiple pregnancies presents in labor. Intensive labor monitoring, safe delivery, and improved neonatal care facilities appear to be the major areas to improve the perinatal outcome.

However, the present study suffers from the limitation of sample size and self-imposed restrictions in case selection and sparse studies.

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# Attenuation of Extubation Response in Patients Undergoing Abdominal and Lower-Limb Surgeries under General Anesthesia – A Comparative Study between Dexmedetomidine and Esmolol

Rahul Mamde<sup>1</sup>, Vinay P Chhallani<sup>2</sup>, Ashutosh Vijay Jaiswal<sup>3</sup>

<sup>1</sup>Assistant Professor, Department of Anesthesiology, Vikhe Patil Medical College, Ahmednagar, Maharashtra, India, <sup>2</sup>Consultant Cardiac Anesthesiologist, Anand Rishiji Hospital and Medical Research Centre, Ahmednagar, Maharashtra, India, <sup>3</sup>Assistant Professor, Department of Anesthesiology, Government Medical College and Superspeciality Hospital, Nagpur, Maharashtra, India

## Abstract

**Introduction:** Laryngoscopy and tracheal intubation cause significant changes in the hemodynamics of patients. Many pharmacological methods have been devised to reduce the extent of hemodynamic events. This study compares the efficacy of two such agents, dexmedetomidine and esmolol, for the attenuation of response to extubation.

**Materials and Methods:** This study was carried out on 100 patients aged 18–60 years, belonging to the American Society of Anesthesiologists Grades I and II, having no major systemic comorbidities, and undergoing abdominal or lower-limb surgeries under general anesthesia. They were randomly divided into two groups: Group D (dexmedetomidine) and Group E (esmolol). Pre-operative, intraoperative, and post-operative vitals and side effects were monitored.

**Results:** Both the groups were comparable in terms of demographic variables, physical attributes, and baseline vital parameters. It was observed that dexmedetomidine is better at controlling heart rate and systolic, diastolic, and mean blood pressures during extubation than esmolol. There was no significant respiratory depression. No significant side effects were observed.

**Conclusion:** Dexmedetomidine is an effective and safe drug to provide stable hemodynamics and protects against the stress response to extubation in patients undergoing abdominal and lower-limb surgeries under general anesthesia.

**Key words:** Cardiovascular effects, Dexmedetomidine, Esmolol, Extubation, Laryngoscopy, Tracheal intubation

## INTRODUCTION

Laryngoscopy and tracheal intubation cause significant changes in the hemodynamics of patients. A similar set of hemodynamic derangements have been noticed by various workers during tracheal extubation.<sup>[1]</sup> Direct laryngoscopy and endotracheal intubation are almost always associated with hemodynamic changes caused by epipharyngeal and laryngopharyngeal stimulation.<sup>[1]</sup> This increases

sympathoadrenal activity resulting in hypertension, tachycardia, and arrhythmias.<sup>[1]</sup> This increase in blood pressure (BP) and heart rate (HR) is usually transitory, variable, and unpredictable. Hypertensive patients are more prone to have a significant increase in BP.<sup>[2]</sup> Transitory hypertension and tachycardia may be hazardous to those with hypertension, myocardial insufficiency, and cerebrovascular diseases.

Many pharmacological methods have been devised to reduce the extent of hemodynamic events with a high dose of opioids, local anesthetics such as lignocaine,<sup>[3]</sup> alpha<sup>[4]</sup>- and beta<sup>[5]</sup>-adrenergic drugs, and vasodilator drugs such as nitroglycerine.<sup>[6]</sup>

Dexmedetomidine<sup>[7]</sup> is a selective  $\alpha_2$ -adrenergic receptor agonist which is known to produce sedation<sup>[8]</sup> and analgesia

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**Corresponding Author:** Dr. Ashutosh Vijay Jaiswal, C/o Adv. C. J. Jaiswal, Plot No. 17–B, Nandanvan, Nagpur - 440 024, Maharashtra, India

and also has sympatholytic, anesthetic-sparing,<sup>[9]</sup> and hemodynamic-stabilizing properties without significant respiratory depression. Its sympatholytic effect<sup>[10,11]</sup> decreases mean arterial pressure and HR by reducing norepinephrine release and hence improves hemodynamic stability during extubation. It has also been documented to decrease post-operative nausea and vomiting<sup>[12]</sup> after surgery.

Esmolol is an ultra-short-acting  $\beta_1$ -adrenoceptor antagonist without any partial agonistic action or local anesthetic action which is known to produce hemodynamic stability during laryngoscopy, intubation, and extubation. It selectively blocks  $\beta_1$ -adrenoceptors and competitively reduces receptor occupancy by catecholamines and other  $\beta$ -adrenergic agonists. It has been shown to blunt hemodynamic responses to perioperative noxious stimuli. It also decreases the need for opioids during surgery and recovery.

The present study evaluates the comparative effect of dexmedetomidine and esmolol on the hemodynamic response to extubation in patients undergoing abdominal and lower-limb surgeries.

## MATERIALS AND METHODS

This was a prospective, randomized, open-label, double-blind study. Prior approval of the Institutional Ethics Committee was taken. A total of 100 patients aged 18–60 years, belonging to the American Society of Anesthesiologists (ASA) Grades I and II, and undergoing abdominal or lower-limb surgeries under general anesthesia were included in the study. Any patient refusing to give consent, pregnant and lactating women, morbidly obese patients or patients having any systemic comorbidity (uncontrolled asthma or chronic obstructive pulmonary disease despite treatment, acute cholecystitis, and severe hepatic and renal diseases), and patients on beta-blockers were excluded from the study. Written informed consent was taken from all the patients.

Preoperatively, the patients were kept nil by the mouth for the last 10–12 h prior to surgery. All the necessary pre-operative investigations such as complete blood count, serum biochemistry, random blood sugar, and urine tests were done as per standard protocol.

The patients were, then, randomly divided into two groups as (CONSORT 2010 Flow Diagram):

- Group “D”: In this group, patients will receive an intravenous bolus of 0.5  $\mu\text{g/kg}$  dexmedetomidine starting 10 min before extubation.

- Group “E”: In this group, patients will receive an intravenous bolus of 1 mg/kg esmolol starting 2 min before extubation.

Pre-operative vitals were recorded in the form of baseline pulse, electrocardiogram,  $\text{SpO}_2$  and BP. Venous cannulation was done. Premedications were given. All patients received 500 ml of lactated Ringer’s solution prior to induction. Induction was done with propofol, and vecuronium was used as a muscle relaxant. Patients were intubated with appropriate-sized polyvinyl chloride endotracheal tubes. Anesthesia was maintained by nitrous oxide in oxygen 50:50, and HR was maintained at a rate of 60–90 beats/min and systolic BP at 110–140 mmHg and diastolic BP at 70–100 mmHg. Any decrease in HR ( $<45$  beats/min) was treated with injection atropine 0.001 mg/kg and injection glycopyrrolate 0.004 mg/kg. Anesthesia was reversed with injection Neostigmine 0.05 mg/kg and injection glycopyrrolate 0.008 mg/kg.

HR, systolic and diastolic BPs, respiratory rate, and  $\text{SpO}_2$  were monitored preoperatively, at the time of bolus dose (10 min before extubation for Group D and 2 min before extubation for Group E), at extubation and up to 15 min after extubation. Patients were also observed for any complication.

## Statistical Analysis

The analysis was done by SPSS. Quantitative data were analyzed using Student’s *t*-test, and qualitative data were analyzed using Chi-square test. *P*-value of  $<0.05$  was considered statistically significant.

## RESULTS

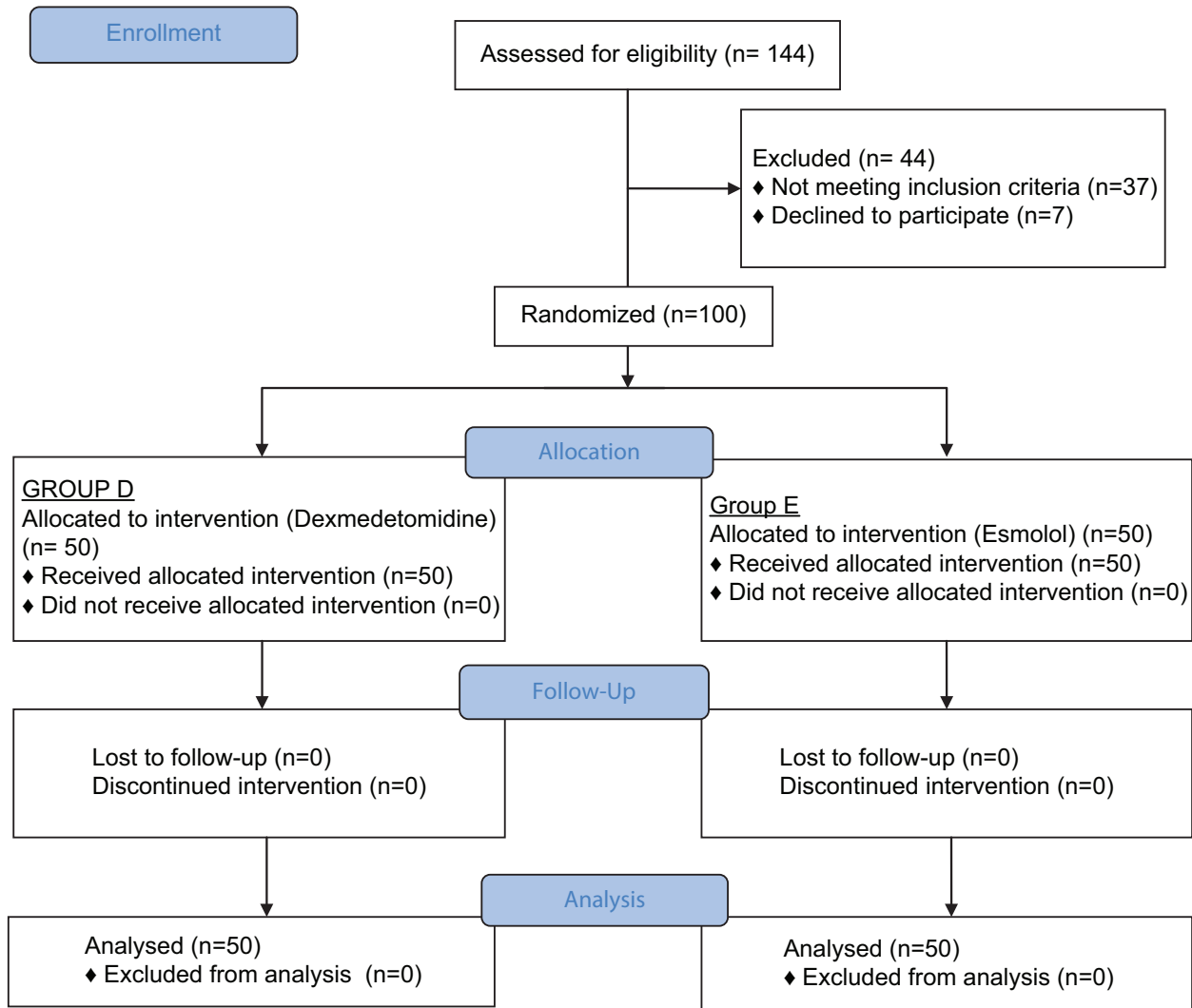
Both the groups were comparable in terms of demographic variables (age and gender), physical attributes such as weight, ASA grade, and  $\text{SpO}_2$ .

There was also no statistically significant difference in the baseline HRs of both the groups. However, there was a statistically significant but clinically insignificant decrease (compared to baseline) in HR after extubation. However, HR remained more in Group E than Group D, even after 15 min [Table 1].

Similar were the trends of systolic BP [Table 2], diastolic BP [Table 3], and mean arterial pressure [Table 4]. All of these parameters remained higher in Group E than Group D from extubation till after 15 min, and this difference was statistically significant ( $P < 0.05$ ).

The incidence of side effects (hypotension and bradycardia) is as per Table 5. The incidence and difference were not statistically significant ( $P = 0.14$ ).

## CONSORT 2010 Flow Diagram

**Table 1: Comparison of heart rate in Group D and Group E**

Event	Mean heart rate (beats/min)		P-value	Significance
	Group D	Group E		
Pre-operative	78.60±9.861	80.880±6.997	0.201	Not significant
At the time of bolus dose	87.52±10.62	90.60±9.26	0.12	Not significant
At extubation	76.60±8.48	81.020±9.52	0.016	Significant
1 min	70.74±9.46	76.6±9.83	0.03	Significant
3 min	66.82±9.94	74.52±8.28	<0.001	Significant
5 min	65.30±8.28	73.46±6.73	<0.0001	Significant
10 min	63.78±5.68	71.94±6.94	<0.0001	Significant
15 min	62.32±4.37	70.64±5.92	<0.0001	Significant

**Table 2: Comparison of systolic blood pressure in Group D and Group E**

Event	Mean systolic blood pressure (mmHg)		P-value	Significance
	Group D	Group E		
Pre-operative	123.74±12.57	123.74±11.79	0.82	Not significant
At the time of bolus dose	125.62±10.45	129.02±9.42	0.09	Not significant
At extubation	110.58±6.89	117.92±8.04	<0.001	Significant
1 min	103.92±7.001	114.64±7.13	<0.0001	Significant
3 min	99.62±7.94	112.48±6.12	<0.0001	Significant
5 min	99.98±6.50	110.14±6.207	<0.0001	Significant
10 min	98.82±4.66	109.62±6.25	<0.0001	Significant
15 min	96.84±4.04	108.28±6.76	<0.0001	Significant

**DISCUSSION**

Significant hemodynamic fluctuations can occur during laryngoscopy and during intubation and extubation which

can especially be detrimental in patients with reduced cardiopulmonary reserve. Various pharmacological agents have been studied to counteract these adverse hemodynamic changes during tracheal extubation.

**Table 3: Comparison of diastolic blood pressure in Group D and Group E**

Event	Mean diastolic blood pressure (mmHg)		P-value	Significance
	Group D	Group E		
Pre-operative	75.76±8.19	76.28±8.39	0.761	Not significant
At the time of bolus dose	79.12±10.14	78.74±9.80	0.849	Not significant
At extubation	68.88±5.72	73.88±6.46	<0.001	Significant
1 min	62.80±6.99	71.92±6.68	<0.0001	Significant
3 min	60.50±7.23	70.46±6.24	<0.0001	Significant
5 min	60.04±5.41	67.88±7.003	<0.0001	Significant
10 min	58.58±4.94	67.62±6.88	<0.0001	Significant
15 min	57.82±4.78	67.440±6.50	<0.0001	Significant

**Table 4: Comparison of mean arterial pressures in Group D and Group E**

Event	Mean arterial pressure (mmHg)		P-value	Significance
	Group D	Group E		
Pre-operative	91.78±9.24	91.98±9.29	0.914	Not significant
At the time of bolus dose	94.66±9.23	95.52±9.00	0.638	Not significant
At extubation	82.76±5.65	88.627±6.74	<0.0001	Significant
1 min	76.52±6.65	86.34±6.39	<0.0001	Significant
3 min	73.56±7.05	84.44±5.78	<0.0001	Significant
5 min	73.36±5.36	81.94±6.29	<0.0001	Significant
10 min	72.08±4.31	81.500±6.31	<0.0001	Significant
15 min	70.80±3.902	81.08±6.24	<0.0001	Significant

**Table 5: Comparison of adverse effects**

Event	Group D (%)	Group E (%)	P-value	Statistical significance
Hypotension	3 (6)	2 (6.66)	0.14	Not significant
Bradycardia	2 (4)	0		

In the present study, two such agents were studied: Dexmedetomidine and esmolol.

Both the groups were comparable in terms of demographic variables, physical attributes, ASA grades, and SpO<sub>2</sub>. The baseline values of HR and BP (systolic, diastolic, and mean) were also comparable in both the groups.

### HR

During extubation, HRs were higher in Group E than in Group D, which were statistically significant. This difference in HRs during extubation could be attributed to the termination of action of esmolol due to its very short half-life.

There was also a clinically insignificant decrease in HRs in both the groups after extubation. However, HRs remained more in Group E compared to Group D, which were statistically significant.

This difference could be attributed to the early start of dexmedetomidine bolus (10 min before extubation) as the bolus has to be administered over 10 min; whereas, esmolol is administered over 2 min before extubation.

Thus, the control of HR was significantly better in Group D than in Group E from extubation to 15 min after extubation.

### BP

The trend of systolic BP, diastolic BP, and mean arterial pressure followed similar trends as discussed with HR above.

Thus, the control of BP (systolic BP, diastolic BP, and mean arterial pressure) was significantly better in Group D than in Group E from extubation to 15 min after extubation.

The cardiovascular effects of dexmedetomidine may be attributed to stimulation post-synaptic alpha-receptors leading to direct vasoconstriction and nitric oxide-mediated vasodilation.<sup>[13]</sup> Central sympatholysis also leads to hypotension and bradycardia.<sup>[14]</sup> There is a considerable decrease in myocardial work and myocardial O<sub>2</sub> consumption, and it has been found to decrease adverse cardiac events perioperatively.<sup>[15]</sup>

These results were in accordance with the study by Ghodki *et al.*,<sup>[16]</sup> an observational study on dexmedetomidine as an anesthetic adjuvant in laparoscopic surgery using entropy monitoring, which observed that extubation was smooth in all patients with minimal change in hemodynamics. Furthermore, in the study by Ornstein *et al.*,<sup>[17]</sup> demonstrating the effect of esmolol on HR, mean arterial pressure, and plasma renin activity, it was found that the control of mean arterial pressure was delayed, which may, in part, be related to the gradual decline in the plasma renin activity.

In another study by Uysal *et al.*,<sup>[18]</sup> comparing the effects of dexmedetomidine, esmolol, and sufentanyl, the hemodynamic responses to extubation were suppressed in the dexmedetomidine group. It was hypothesized to be due to dexmedetomidine being a highly selective alpha-2-agonist.

In another study, Ibraheim *et al.*,<sup>[19]</sup> found that both esmolol and dexmedetomidine, when added to anesthetic regimen, provided an effective and well-tolerated method to reduce the amount of blood loss in patients undergoing scoliosis surgery, which may be attributed to attenuated hemodynamic responses.

Similarly, in the study by Kol *et al.*,<sup>[20]</sup> it was concluded that both esmolol and dexmedetomidine, combined



with desflurane, provided an effective and well-tolerated method of achieving controlled hypotension to limit the amount of blood in the surgical field in these adult patients undergoing tympanoplasty. Another study by Shams *et al.*,<sup>[21]</sup> comparing dexmedetomidine and esmolol with sevoflurane for induction of hypotension for functional endoscopic sinus surgery, had a similar conclusion. They concluded that both dexmedetomidine and esmolol with sevoflurane were safe agents for controlled hypotension and were effective in providing ideal surgical field during functional endoscopic sinus surgery.

### Adverse Effects

In the present study, two patients (4%) had bradycardia (HR < 45 bpm) in Group D while no patients in Group E had bradycardia (statistically insignificant). However, clinically significant hypotension (defined as <20% of basal map sustained for 2 or more readings) was found in 3 (6%) patients in Group D and 2 (6.66%) patients in Group E.

This was similar to the study by Wiest,<sup>[22]</sup> which studied the therapeutic efficacy and pharmacokinetic characteristics of esmolol. The principal adverse effect of esmolol was noted to be hypotension (incidence of 0 to 50%), which was frequently accompanied by diaphoresis. The incidence of hypotension appeared to increase with doses exceeding 150 µg/kg/min and in patients with low baseline BP. Hypotension infrequently required any intervention other than decreasing the dose or discontinuing the infusion. Symptoms generally resolved within 30 min after discontinuing the drug. They concluded that in surgical and critical care settings, the pharmacokinetic profile of esmolol allows the drug to provide rapid pharmacological control and minimizes the potential for serious adverse effects.

In another study, Aho *et al.*<sup>[7]</sup> showed that dexmedetomidine causes bradycardia at a dose of >2.4 mcg/kg. Wiest,<sup>[22]</sup> in the study, demonstrated that esmolol causes bradycardia at a dose of 150 mcg/kg/min.

### Limitations

The study was limited to the outpatient department attendance and indoor admission of the patients undergoing abdominal or lower-limb surgeries under general anesthesia. Therefore, the results may not be generalized.

## CONCLUSION

It can be effectively concluded that although both, dexmedetomidine and esmolol, are safe and efficacious in attenuating the hemodynamic stress response during extubation, dexmedetomidine is better at controlling HR

and systolic, diastolic, and mean BPs during extubation than esmolol. Thus, dexmedetomidine is an effective and safe drug to provide stable hemodynamics and protects against the stress response to extubation in patients undergoing abdominal and lower-limb surgeries under general anesthesia.

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# Incidence of Tympanosclerosis in Chronic Suppurative Otitis Media Patients in a Tertiary Care Hospital

K Arumugam

Assistant Professor, Department of Otorhinolaryngology, Government Medical College, Pudukkottai, Tamil Nadu, India

## Abstract

**Introduction:** Tympanosclerosis is an anatomoclinical entity which causes thickening and fusion of collagenous fibers into a homogenous mass with final deposition of scattered intracellular and extracellular calcium and phosphate crystals in the subepithelial tissue of tympanic membrane and middle ear structure.

**Aim:** This study aims to study the incidence of tympanosclerosis in chronic suppurative otitis media (CSOM) patients.

**Materials and Methods:** Patients with CSOM admitted for surgery were subjected to detailed ENT examination and investigation which included otoscopy, tuning fork tests with 256, 512, and 1024 Hz, free-field hearing, pure tone audiometry, X-ray mastoids, and computed tomography (CT) temporal bone. CT temporal bone can be used to determine the extent of disease in the middle ear and ossicles fixation.

**Results:** In 62 patients with CSOM, the incidence of tympanosclerosis was found to be 17.7% (11 cases). In patients with tympanosclerosis, the lesions were confined to tympanic membrane alone in 72% (8 cases) while the involvement of both tympanic membrane and middle ear was found in 18% (2 cases). In tympanosclerosis, 9% (1 case) had an AB gap of <20 dB, 63.6% (7 cases).

**Conclusion:** Tympanosclerosis is long-term sequelae of CSOM. The hearing loss associated with tympanosclerosis was of the conductive type in the majority of cases.

**Key words:** Chronic suppurative otitis media, Hearing loss, Tympanosclerosis

## INTRODUCTION

Tympanosclerosis is irreversible pathological sequelae of chronic inflammation of middle ear cleft and signifies the end result of simultaneously operating healing process. The exact etiology of tympanosclerosis is not extensively understood. The possible following long-term otitis media and insertion of tympanostomy tube of tympanosclerotic plaques (TSPs) essentially consist of white chalky calcareous deposits beneath the lining epithelium. This is caused by thickening and fusion of

collagenous fibers into a homogeneous mass interspersed with intra- and extra-cellular deposition of calcium and phosphate crystals followed by ossification to a variable extent. The clinical significance of the TSP depends on the anatomical disposition. It may present as isolated deposit in the tympanic membrane and middle ear or extend to ossicular ligaments, ossicles, interosseous joints, muscles, tendons, and submucosal space, leading to a varying degree of immobility of ossicular chain. Tympanosclerosis clinically has been rarely found in active ears and with cholesteatoma.<sup>[1,2]</sup> This has not been supported by pathological temporal bone specimens.<sup>[3]</sup> TSP depending on its size, site, and involvement of ossicular chain affects severely the sound transfer mechanism, and hearing restoration results in the following tympanoplasty. Clinically significant tympanosclerosis has been defined as requiring direct surgical removal to affect hearing improvement. It has been found to be present in less than half of those patients manifesting any degree of tympanosclerosis.<sup>[4]</sup>

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**Corresponding Author:** K Arumugam, Department of Otorhinolaryngology, Government Medical College, Pudukkottai, Tamil Nadu, India.

Thus, significant TSP will necessitate surgical intervention in such ears during tympanoplasty procedure to make it functionally effective and rewarding.

### Aim

This study aims to study the incidence of tympanosclerosis in chronic suppurative otitis media (CSOM) patients.

## MATERIALS AND METHODS

This prospective observational study, patients of CSOM admitted for surgery, was examined. All the patients presented with a history of deafness and/or otorrhea of varying duration. They were subjected to detailed ENT examination and investigation which included otoscopy, tuning fork tests with 256, 512, and 1024 Hz, free-field hearing, pure tone audiometry, and X-ray mastoids. Pure tone averages of 0.5, 1, 2, and 3 KHz were taken to assess the hearing level pre- and post-operatively. The presence of tympanosclerosis was observed by otoscopic and/or microscopic examination. Intratympanic tympanosclerosis has been subdivided into “open” and “closed” varieties, depending on the integrity of the tympanic membrane. The tympanosclerotic aggregations can vary in size, ranging from small isolated deposits to huge masses which may completely submerge the ossicles and obscure normal landmarks. Preoperatively, the ossicular mobility, middle ear mucosa, and degree of tympanosclerosis in the tympanic membrane and middle ear were noted. The removal of tympanosclerosis was decided intraoperatively. The majority of TSP are of rubbery consistency and have a lamellar structure so that they can be readily separated into a series of concentric onion layers. Less commonly, the plaques are densely hard and adherent to the underlying bone. Data were presented as frequency and percentage. Damage to inner ear as a result surgical procedure is possible and serious concern results in the form of sensory neural hearing loss.

## RESULTS

In this study, 62 patients with CSOM were included. The incidence of tympanosclerosis in our study was found to be 17.7% (11 cases of 62 patients of CSOM). In this study, six female patients and five male patients were included [Figure 1]. About 45.4% (5 cases) of patients with tympanosclerosis were greater than the age of 21 years [Figure 2].

On analysis of intraoperative findings in patients with tympanosclerosis, the lesions were confined to tympanic membrane alone in 72% (8 cases) while the involvement of both tympanic membrane and middle ear was found in 18% (2 cases) [Figure 3].

About 63.6% (7 cases) had a dry ear at the time of presentation which was confirmed intraoperatively. On the other hand, 18.1% (2 cases) had a discharging ear at the time of presentation. Peroperatively, 9% (1 case) had edematous middle ear mucosa with glue and 9% (1 case) had an associated cholesteatoma of these two discharging ears. On examination of the ossicular chain, 63.6% (7 cases) had a mobile chain, 18% (2 cases) had a fixed chain while 9% (1 case) showed erosion of the ossicular chain. On analysis of the audiometric data of 11 patients with tympanosclerosis, 9% (1 case) had an AB gap of <20 dB, 63.6% (7 cases) had an AB gap of 20–40 dB while 27.2% (3 cases) had an AB gap of more than 40 dB [Figure 4]. When the AB gap was correlated with the site of tympanosclerosis, 71.4% (5 of 7 cases) had an AB gap of <40 dB when tympanosclerosis was confined only to the tympanic membrane. On the other hand, 50% (1 of 2 cases) had an AB gap of more than 40 dB when tympanosclerosis involved both the tympanic membrane and middle ear.

## DISCUSSION

Intratympanic tympanosclerosis is an insidious condition, which may take years to become manifest clinically. It is, therefore, difficult to determine its true incidence. Most of the statistics quoted in literature are based on clinical or operative data and fail to take account of cases in the early asymptomatic category.<sup>[5,6]</sup>

Tympanosclerosis developed in 13% of ears with secretory otitis media treated with paracentesis compared with 59% with grommet tube insertion. Kay *et al.* in the meta-analysis of 134 studies regarding sequelae of tympanostomy tube insertion revealed 32% incidence of post-intubation tympanosclerosis compared with 10% of controls.<sup>[7]</sup>

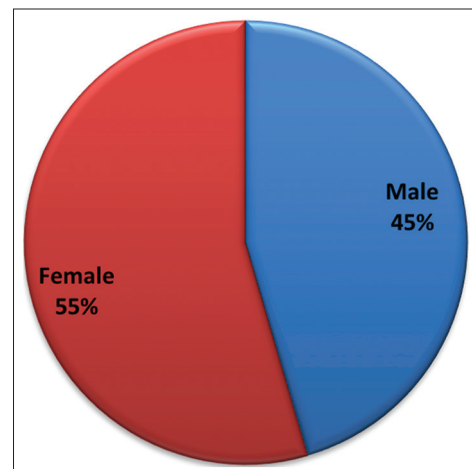


Figure 1: Distribution of gender

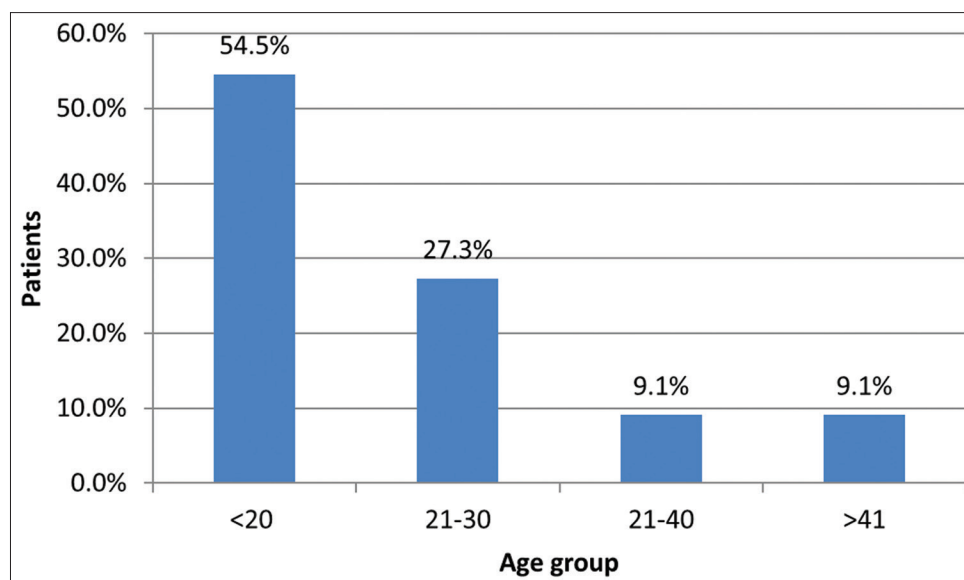


Figure 2: Distribution of age group

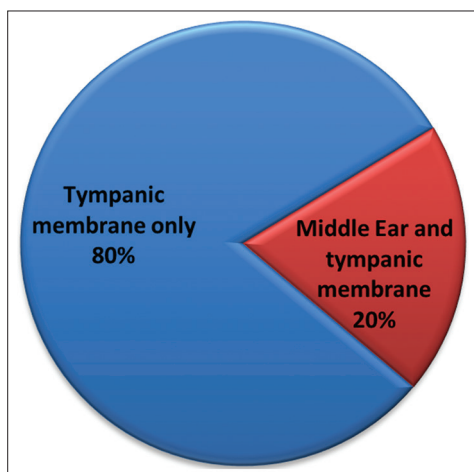


Figure 3: Distribution of site in intraoperative findings

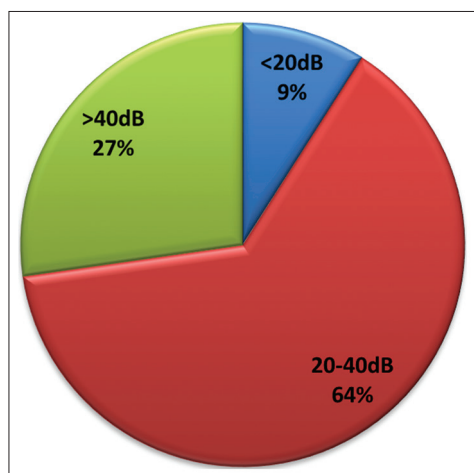


Figure 4: Distribution of degree of hearing loss

This suspicion is underlined by several histological studies, in which a number of subclinical cases were

uncovered on routine biopsy. Indeed, Friedmann<sup>[8]</sup> reported that of 60 histologically confirmed cases, only 32 were diagnosed clinically. In a review of over a 1000 operations performed for all types of middle ear disease, Austin<sup>[4]</sup> reported the presence of tympanosclerosis in the tympanic membrane or middle ear to be 32% irrespective of its clinical significance. Tympanosclerosis can be bilateral in 40–60% of cases.<sup>[9]</sup> However, the existence of the condition does not necessarily equate with its clinical importance.

Myringosclerosis was more common in children following grommet insertion hearing loss which was minimal or nil. Tympanosclerosis was more common in adults following chronic otitis media or hearing loss depends on the size and extent of involvement of ossicles or fixation.

Clinically, tympanosclerosis can either be myringosclerosis or intratympanic. Myringosclerosis occurs when the disease affects only the tympanic membrane and appears as white “chalky patches.” In most cases, it is asymptomatic or has little effect on hearing (Tos *et al.*, 1983),<sup>[10]</sup> but if the plaques involve large areas of tympanic membrane or if they are adherent to the bony annulus, handle of malleus, or promontory, the mobility of the drum will be greatly reduced resulting in marked hearing loss (Wielinga and Kerr, 1993).<sup>[11]</sup> It might be either open (80%) with tympanic membrane perforation or closed (20%) with the intact drumhead. The incidence of tympanosclerosis following the previous history of otitis media ranges from 14% to 43% in different clinical series. In the review, Tos and Stangerup demonstrated an association between ventilation tube placement and tympanosclerosis. Tympanosclerosis developed 13% of ear with secretory

otitis media treated with paracentesis, compared with 59% treated with grommet tube insertion. In addition, Kay *et al.*'s recent meta-analysis of 134 studies regarding sequelae tympanostomy tube insertion revealed 32% incidence of post-intubation tympanosclerosis compared with 10% of controls. The intratympanic type is frequently associated with marked conductive or mixed hearing loss. The degree of hearing loss depends on the extent of tympanosclerotic involvement of the ossicular chain (Kamal, 1997).<sup>[12]</sup>

## CONCLUSION

Tympanosclerosis is long-term sequelae of CSOM. The incidence varies widely in literature between 7% and 33% of all patients with a chronic middle ear infection. The degree and extent of tympanosclerosis plaques will eventually determine the severity of hearing loss.

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# A Comparative Study between Intranasal Midazolam and Ketamine as Premedication in Pediatric Patients

Medha Bapat<sup>1</sup>, Ashutosh Vijay Jaiswal<sup>2</sup>

<sup>1</sup>Anesthesia Consultant, Narayana Nethralaya 2, Banerghatta, Bangalore, India, <sup>2</sup>Assistant Professor, Department of Anesthesiology, Government Medical College and Super specialty Hospital, Nagpur, Maharashtra, India

## Abstract

**Introduction:** Surgery and anesthesia can be a traumatic experience for a child. Stormy induction of anesthesia in children can lead to an increased incidence of post-operative behavioral problems. Thus, sedative premedication may be used in children to aid smooth induction of anesthesia. Hence, this study was conducted to compare the preanesthetic sedative effects of intranasal midazolam and ketamine.

**Materials and Methods:** This study was carried out on 60 ASA Grades I and II pediatric patients aged 2–5 years undergoing emergency or elective surgery lasting for 30 min–2 h. The exclusion criteria were established. Patients were included after written informed consent of the parent/guardian. They were randomly divided into two groups: Group M and Group K. Pre-operative, intraoperative, and post-operative parameters were observed.

**Results:** Statistically significant tachycardia and increased blood pressure (BP) (both clinically insignificant) were observed in both the groups (more persistent in the ketamine group). The sedation by both the drugs was adequate in terms of parental separation score, acceptance of facemask and response to venipuncture with no statistically significant difference. There were also no significant side effects (namely, respiratory depression, increased secretions or emergence reaction).

**Conclusion:** Both the drugs midazolam and ketamine provide adequate preanesthetic sedation through intranasal route and are safe to use in pediatric patients without any significant side effects.

**Key words:** Cardiorespiratory depression, Emergence reaction, Intranasal, Ketamine, Midazolam, Parental separation, Pediatric, Preanesthetic, Sedation

## INTRODUCTION

Hospitalization introduces a new set of circumstances for which the child is unprepared. Surgery and anesthesia can be a traumatic experience for a child. Stormy induction of anesthesia in children can lead to an increased incidence of post-operative behavioral problems.<sup>[1]</sup> These problems can be reduced to some extent by psychological preparation of the child and parents. However, pharmacological adjunct may be more

reliable and better suited in case of preschool children. Thus, sedative premedication may be used in children to aid the smooth induction of anesthesia.<sup>[2]</sup> It is desirable that these premedications have ease of application, rapid onset, short duration of action, and free from significant side effects.

Out of the various routes of administration, the intranasal route is one of the recently studied routes of drug administration. It has certain advantages. Due to high mucosal vascularity, intranasal route offers rapid and virtually complete absorption within 1–2 h into systemic circulation.

As midazolam<sup>[3]</sup> and ketamine<sup>[4]</sup> have high hepatic clearance, avoidance of hepatic first-pass metabolism offers greater systemic bioavailability. Therefore, intranasal administration has faster onset than oral or rectal route.

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**Corresponding Author:** Dr. Ashutosh Vijay Jaiswal, C/o Adv. C. J. Jaiswal, Plot No. 17 – B, Nandanvan, Nagpur - 440024, Maharashtra, India.



In accordance with this, the current study was undertaken to evaluate the efficacy and safety of intranasal midazolam versus intranasal ketamine for preanesthetic sedation in pediatric patients, including assessment of sedation in the post-operative period and side effects, if any.

## MATERIALS AND METHODS

This was a randomized, double-blind, and prospective study undertaken after approval from the Institutional Ethics Committee. The study was carried out in 60 pediatric patients aged 2–5 years, ASA Grade I or II and scheduled for elective or emergency surgery lasting for 30 min–2 h. Patients having any upper respiratory infection, allergies or systemic comorbidities (hepatic or renal derangements or congenital anomalies) were excluded from the study. Written informed consent was taken from the parent/guardian. Thorough pre-operative assessment including detailed history taking, clinical examination, and laboratory investigations, was done.

The patients were randomly assigned to either of the two groups:

- Midazolam group (Group M): Received intranasal midazolam 0.2 mg/kg as premedication (5 mg/ml nasal spray)
- Ketamine group (Group K): Received intranasal ketamine 3 mg/kg as premedication (50 mg/ml vial).

Midazolam was administered by a nasal spray, whereas ketamine was administered by a syringe. This took 1–2 min. Patients' vitals were examined before administering premedication and at 5 min intervals after installation.

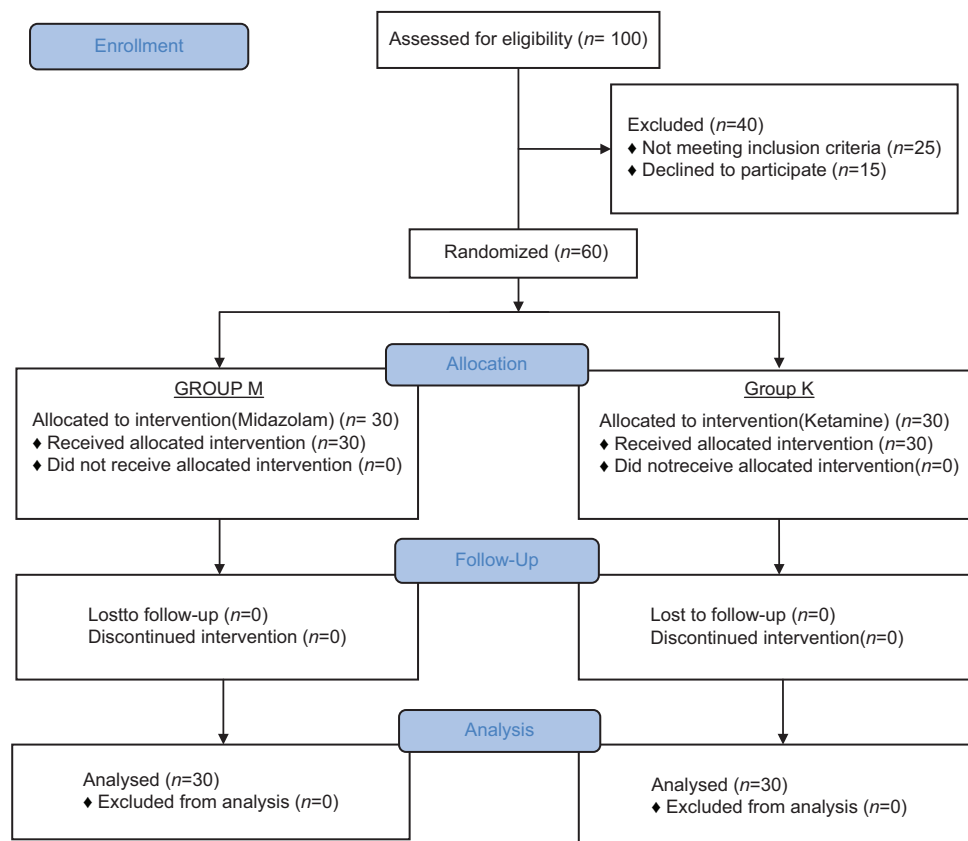
After observation for 20 min, the patient was shifted to the operation theater. Response to separation from parents was observed.

Degree of sedation was assessed using a five-point scale<sup>[5]</sup>:

1. Agitated: Patient clinging to parents and/or crying
2. Alert: Patient aware but not clinging to parents; may whimper but does not cry
3. Calm: Sitting or lying comfortably with spontaneous eye-opening
4. Drowsy: Sitting or lying comfortably with eyes closed, but responding to minor stimulation
5. Asleep: Eyes closed, arousable but does not respond to minor stimulation.

Preoxygenation was done by facemask, and the response was assessed similar to the above score as follows:

1. Agitated: Previous criteria and/or refuses mask
2. Alert: Previous criteria and/or initially refuses mask, but accepts after persuasion
3. Calm: Previous criteria and accepts mask
4. Drowsy: Previous criteria and accepts mask
5. Asleep: Previous criteria and accepts mask.



I.V. line was secured. Response to it was assessed. Degree of sedation was assessed using a five-point scale similar to the previous one.

1. Agitated: Previous criteria and/or refuses venepuncture
2. Alert: Previous criteria and/or initially refuses venepuncture, but allows after persuasion
3. Calm: Previous criteria and allows venepuncture
4. Drowsy: Previous criteria and allows venepuncture
5. Asleep: Previous criteria and allows venepuncture

Premedications were given. General anesthesia was induced, and intubation was done as per the standard protocols. At the end, after the reversal of neuromuscular blockade and extubation, post-operative sedation was assessed within 10 min of extubation with a three-point scale<sup>[6]</sup> as follows:  
 0: spontaneous eye opening,  
 1: eye opening to speech,  
 2: eye opening in response to physical stimulation.

Patients were observed in the recovery unit for 6 h, for any side effects.

### Statistical Analysis

The data were analyzed by SPSS software using appropriate statistical tests (Paired and Unpaired *t*-test for quantitative data and Chi-square test for qualitative data).  $P < 0.05$  was considered significant.

## RESULTS

Both the groups were similar in terms of demographic variable (namely, age and gender), physical attributes (weight), and type and duration of surgery.

In each group, the majority (80%) of the patients had a parental separation score of three or more. This shows that most of the children separated well. The difference between scores of both the groups was statistically and clinically not significant ( $P = 0.94$ ).

In each of the groups, the majority (80%) of the patients had a facemask acceptance score of three or more. This shows that most of the children accepted the facemask well. The response in both the groups was similar, and

the difference in response to facemask was statistically and clinically nonsignificant ( $P = 0.93$ ).

In Group M, 80% patients and 77% patients in Group K had a response to venepuncture scores of three or more. This shows that most of the children allowed venepuncture to be done peacefully. There was no statistically significant difference between the groups ( $P = 0.93$ ).

Tachycardia (clinically insignificant) was observed in both the groups, which returned to baseline at 10 min in Group M and at 15 min in Group K. Although the tachycardia was statistically significant within the group, the difference in tachycardia between the groups was significant up to 10 min only [Tables 1 and 2].

Similarly, there was a slight increase in blood pressure (BP) (clinically insignificant) both the groups [Table 3]. However, the difference of increase in BP between the groups was statistically significant up to 10 min only [Table 4].

No respiratory depression (Rate and  $SpO_2$ ) was noted in any group, and the difference was statistically insignificant ( $P > 0.05$ ).

After the surgical procedure was over, the patients were reversed and extubated after fulfilling all the extubation criteria. Regarding the post-operative sedation, 43% of the patients in Group M and 50% in Group K had spontaneous eye opening after surgery, within 10 min of extubation. The levels of sedation were found to be similar in both the groups ( $P = 0.87$ ).

Vomiting was the only side effect noted in both the groups (one case in Group M and two cases in Group K). However, the difference was not statistically significant ( $P = 0.17$ ).

## DISCUSSION

The sedative premedications administered to the children before surgery to lessen the trauma. There are various routes of administration, each having its own advantages and disadvantages. Needles inculcate bad memories and negative psychological effects. Rectal administration

**Table 1: Comparison of trends of pulse rate in Groups M and K (within group)**

Parameter	Group M				Group K			
	Mean pulse rate in group A	Paired <i>t</i> -value	<i>P</i> -value	Statistical significance	Mean pulse rate in group B	Paired <i>t</i> -value	<i>P</i> -value	Statistical significance
0 min	100.80	-	-	-	99.87	-	-	-
5 min	106.80	8.4	<0.001	Significant	110.67	15	<0.001	Significant
10 min	99.73	2.2	0.03	Significant	103.93	18	<0.001	Significant
15 min	99.53	2.6	0.012	Significant	98.87	2	0.045	Significant
20 min	98.33	5.2	<0.001	Significant	97.67	4.6	<0.001	Significant

leads to psychiatric embarrassment in older children and unreliable absorption, especially if the rectum is full of feces. Oral route has low bioavailability (15–27%)<sup>[7]</sup> due to high first-pass metabolism, so a higher dose (0.5–1 mg/kg) is required, and the peak effect is also delayed.<sup>[8,9]</sup> The bitter taste is also a limiting factor and cause for rejection as well as low compliance. Sublingual administration requires the drug to be held under the tongue for at least 30 s<sup>[10]</sup> which requires cooperation that is difficult to achieve in preschool children.

The nasal route has certain advantages. Due to high nasal vascularity, there is rapid and nearly complete absorption in 1–2 h into the systemic circulation.<sup>[11]</sup> It has a faster onset than oral or rectal route as well as time to reach maximal sedation.<sup>[12]</sup>

Therefore, in this study, the effects of intranasal midazolam with intranasal ketamine were compared, as preanesthetic sedation in children.

Both the groups were comparable in terms of demographic variables, physical attributes, type, and duration of surgery.

### Pulse Rate

In both the groups, there was an initial increase (clinically insignificant) in pulse rate, which later settled to the baseline. However, the settling back was delayed in Group K (by 20 min) than in Group M (by 10 min). Furthermore, the rise was significantly more in Group K than Group M. This

was comparable to the study by Narendra *et al.*,<sup>[13]</sup> where the tachycardia was more and persistent in the ketamine group. This may be due to absorption of ketamine and its sympathomimetic effects and not merely due to agitation of the patients.

### BP

There was a small decrease in BP in Group M, which was not clinically significant. The BP in Group K showed a statistically significant (clinically insignificant) rise up to 5 min and reached the baseline value by 15 min. At 5 and 10 min, the rise in BP in case of ketamine group is significantly more than that in midazolam group. This was similar to the study by Garcia-Velasco *et al.*,<sup>[14]</sup> where it was observed that the systolic arterial pressure was higher in the ketamine group as compared to midazolam group 20 min after administration of the drug and up on arrival in the operating theater.

### Respiration

Midazolam in a bolus dose of 0.15 mg/kg can cause transient apnea. Ketamine relatively preserves the ventilatory drive.

In this study, no significant respiratory depression was noted (respiratory rate and SpO<sub>2</sub>).

This was similar to the study by Niall *et al.*,<sup>[5]</sup> by Narendra *et al.*,<sup>[13]</sup> by Abhishek *et al.*,<sup>[15]</sup> and by Khatavkar and Bakhshi *et al.*<sup>[16]</sup>

### Parental Separation Scores

In each group, the majority (80%) of the patients had a score of three or more. This shows that most of the children separated well. However, the difference between scores of both the groups was statistically and clinically not significant.

The results are in accordance with Bhakta *et al.*,<sup>[17]</sup> where they found that 80% patients receiving intranasal midazolam had scores of three or more and that they separated easily from their parents. This was also similar to the study by Abhishek *et al.*<sup>[15]</sup> and Khatavkar and Bakhshi *et al.*<sup>[16]</sup>

**Table 2: Comparison of effects on pulse rate in Groups M and K (between groups)**

Time	Group	Mean±Standard deviation	P-value	Statistical significance
0 min	M	100.80±4.944	0.43	Not significant
	K	99.87±4.100		
5 min	M	106.80±5.671	0.005	Significant
	K	110.67±4.49		
10 min	M	99.73±3.886	<0.001	Significant
	K	103.93±2.95		
15 min	M	99.53±4.058	0.47	Not significant
	K	98.87±3.048		
20 min	M	98.33±3.968	0.48	Not significant
	K	97.67±3.198		

**Table 3: Comparison of trends of BP in Groups M and K (Within group)**

Parameter	Group M				Group K			
	Mean BP in group A	Paired t-value	P-value	Statistical significance	Mean BP in group B	Paired t-value	P-value	Statistical significance
0 min	77.67	-	-	-	78.00	-	-	-
5 min	78.27	1.96	0.059	Not Significant	84.47	21.67	<0.001	Significant
10 min	78.27	1.96	0.059	Not Significant	80.47	8.27	<0.001	Significant
15 min	76.60	2.72	0.011	Significant	76.73	3.90	0.001	Significant
20 min	76.60	2.72	0.011	Significant	77.00	2.47	0.019	Significant

BP: Blood pressure

**Table 4: Comparison of effects on blood pressure in Groups M and K (between groups)**

Time	Group	Mean±Standard deviation	P value	Statistical significance
0 min	M	77.67±2.928	0.65	Not significant
	K	78.00±2.678		
5 min	M	78.27±2.559	<0.001	Significant
	K	84.47±2.446		
10 min	M	78.27±2.559	0.001	Significant
	K	80.47±2.446		
15 min	M	76.13±3.636	0.50	Not significant
	K	76.73±3.258		
20 min	M	76.13±3.636	0.34	Not significant
	K	77.00±3.353		

### Response to Facemask

In each of the groups, the majority (80%) of the patients had a score of three or more. This shows that most of the children accepted the facemask well. The response in both the groups was similar, and the difference in response to facemask was statistically and clinically non-significant.

This is comparable to the study by Weksler *et al.*,<sup>[18]</sup> where the mask acceptance rate was 78% (67 out of 86) and rated as either excellent or adequate. The results were also comparable to the study by Narendra *et al.*<sup>[13]</sup> and Khatavkar and Bakhshi *et al.*<sup>[16]</sup>

### Post-operative Sedation Score

After the surgical procedure was over, the patients were reversed and extubated after fulfilling all the extubation criteria. They were monitored for post-operative sedation in the recovery room for a period of 6 h. The level of sedation was rated on a three-point scale.<sup>[6]</sup> About 43% of the patients in midazolam group and 50% in ketamine group had spontaneous eye opening after surgery, within 10 min of extubation. This was similar to the study by Narendra *et al.*<sup>[13]</sup>

### Side Effects

Despite the inherent side effects of both the drugs, the only side effect observed in both the groups was vomiting. Emergence reactions, though common with ketamine, were not observed in this study. This is in accordance with the study by Weksler *et al.*<sup>[18]</sup> and Khatavkar and Bakhshi *et al.*<sup>[16]</sup>

### Limitations

The study is limited by the OPD attendance of the patients undergoing surgeries. Therefore, the results may not be generalized. The non-pharmacological interventions might have been confounding factor, which were eliminated by randomization.

## CONCLUSION

It can be effectively concluded from the study that both midazolam and ketamine provide adequate preanesthetic sedation (parental separation, facemask acceptance, and response to venepuncture) through the intranasal route. Apart from clinically insignificant tachycardia (more persistent in the ketamine group), no side effects including respiratory depression and post-operative sedation were observed. Therefore, both the drugs are safe for preanesthetic sedation in pediatric population.

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# Comparison of the Effects of Magnesium Sulfate versus Clonidine as an Adjunct to Epidural 0.5% Ropivacaine in Lower Limb Surgeries in Adult Patients – A Prospective Double-blinded, Randomized, Controlled Study

Gudala Prasanna Kumar<sup>1</sup>, Krupakanth Gorle<sup>2</sup>

<sup>1</sup>Associate Professor, Department of Anaesthesiology, Rangaraya Medical College, NTR University of Health Sciences, Kakinada, Andhra Pradesh, India, <sup>2</sup>Consultant, Department of Anaesthesiology, NTR University of Health Sciences, Hope International Hospital, Kakinada, Andhra Pradesh, India

## Abstract

**Introduction:** Regional anesthesia is currently the most effective method of reducing the stress response and thereby pain, especially in patients with surgical procedures involving the lower body. Ropivacaine was studied both for surgical anesthesia and acute pain management. The aim of this study is to compare the effects of magnesium sulfate (50 mg) versus clonidine (150 mcg) as an adjunct to epidural 0.5% ropivacaine in lower limb surgeries in adult patients posted for lower limb procedures.

**Materials and Methods:** After institutional ethical committee approval and written, informed consent from the patient attendants, 75 patients undergoing elective surgeries under epidural anesthesia, aged 18–60 years of either gender, belonging to ASA Grades I and II were randomized for this study. Group N (Control): Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of normal saline epidurally. Group M: Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of magnesium sulfate (50 mg) epidurally. Group C: Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of clonidine (150 mcg) epidurally. Groups were assessed for characteristics of sensory and motor blockade, hemodynamics, and side effects. Data were analyzed statistically.

**Observations and Results:** The duration of post-operative analgesia (time to the first request of pain relief) was significantly prolonged and highest in the clonidine group followed by magnesium group than the control group (Group C  $278 \pm 5.26$  min vs. Group M  $251 \pm 5.65$  min vs. Group N  $233.00 \pm 4.48$  min [ $P < 0.001$ ]).

**Conclusion:** Hence, magnesium sulfate has been proved to be a promising alternative as an adjuvant to regional analgesia in the perioperative period.

**Key words:** Analgesia, Clonidine, Epidural anesthesia, Magnesium sulfate, Ropivacaine

## INTRODUCTION

Pain during surgery is often underestimated and undertreated. Being purely subjective, pain and its intensity vary widely among patients. Regional anesthesia is currently the most

effective method of reducing the stress response and thereby pain, especially in patients with surgical procedures involving the lower body.<sup>[1]</sup> Ropivacaine the recently introduced propyl homolog of bupivacaine in a pure S (-) enantiomeric form associated with a reduced incidence of both cardiovascular and central nervous system toxicity, a concern with racemic bupivacaine.<sup>[2]</sup> In view of the wider application of regional anesthetic procedure in modern anesthesia practice, there is a need for local anesthetic with desirable properties such as longer duration of sensory blockade and lesser duration of motor paralysis. Ropivacaine was studied both for surgical anesthesia and acute pain management.<sup>[3,4]</sup> The onset, intensity, and duration of sensory block are, in general,

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**Corresponding Author:** Dr. Krupakanth Gorle, Department of Anaesthesiology, NTR University of Health Sciences, Hope International Hospital, ADB Road, Near Achampeta Junction, Kakinada - 533 005, Andhra Pradesh, India.



similar to bupivacaine, but the depth and duration of motor block are less than with bupivacaine.<sup>[5,6]</sup> Various adjuvants such as fentanyl, morphine, clonidine, dexmedetomidine, and magnesium sulfate were added to ropivacaine in clinical trials to prolong the duration and improve the quality of pain relief.<sup>[7,8]</sup>

The aim of this study is to compare the effects of magnesium sulfate (50 mg) versus clonidine (150 mcg) as an adjunct to epidural 0.5% ropivacaine in lower limb surgeries in adult patients posted for lower limb procedures.

## MATERIALS AND METHODS

After institutional ethical committee approval and written, informed consent from the patient attendants, 75 patients undergoing elective surgeries under epidural anesthesia, aged 18–60 years of either gender, belonging to ASA Grades I and II were randomized for this prospective and controlled study. Randomization was done using computer-generated random numbers into three groups of 25 each.

All patients were subjected to epidural catheterization with 16/18 G size and given epidural anesthesia according to group allocation.

Group N (Control): Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of normal saline epidurally.

Group M: Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of magnesium sulfate (50 mg) epidurally.

Group C: Patients were administered 19 ml of 0.5% ropivacaine with 1 ml of clonidine 150 mcg) epidurally.

### Inclusion Criteria

ASA Grades I and II physical status, aged between 18 and 60 years, belonging to both the sexes undergoing lower limb surgeries.

### Exclusion Criteria

The following criteria were excluded from the study:

- Patients not willing to participate in the study
- Patients with ASA Grades III, IV, and V
- Patients with contraindication to regional anesthesia
- Those with known sensitivity to local anesthetics
- Patients with local infection at the site of injection
- Non-cooperative patients.

### Method

#### Pre-anesthetic evaluation

During pre-operative visit, patients' detailed history, general physical examination, and systemic examination

were carried out. Basic demographic data such as age, sex, height, and weight were recorded.

During pre-anesthetic check-up, the linear visual analog scale (VAS) was explained to all patients using 10 cm scale. Informed consent was obtained from all the 75 patients after the detailed explanation of the procedure to be performed. On the day of surgery, all patients were premedicated with 0.05–0.1 mg/kg of midazolam intramuscularly 45–60 minutes prior to the procedure. Baseline parameters of heart rate, blood pressure, respiratory rate, and SpO<sub>2</sub> were recorded before starting the case. Peripheral venous cannulation was done with 18G IV cannula and all the patients were preloaded with 500 ml Ringer's lactate solution. The patients were placed in the left lateral position and under strict aseptic precautions, after local infiltration with 1% xylocaine in the epidural space was identified with an 18G Tuohy needle at L3-L4 interspace, by "loss of resistance" technique. 18G epidural catheter was threaded through the needle into the epidural space for 4–5 cm and secured with adhesive tapes to the back. After negative aspiration for blood and cerebrospinal fluid, 3 ml of 1.5% lignocaine with 15 µg of adrenaline was given as test dose was given and the patient was turned to supine position. After 5 min, if there is no adverse reaction for the test dose, intravascular and intrathecal placement were ruled out, and the study and control drugs were administered as per the group allocation. The principal investigator loaded the study drugs as per group allocation and provided to the investigator who administered anesthesia just before administering epidural anesthesia in sealed covers.

Group N,  $n = 25$ , was given 19 ml of 0.5% ropivacaine and 1 ml of normal saline epidurally. Group M,  $n = 25$ , was given 19 ml of 0.5% ropivacaine and 1 ml of magnesium sulfate (50 mg) epidurally. Group C,  $n = 25$ , was given 19 ml of 0.5% ropivacaine and 1 ml of 150 mcg of clonidine epidurally.

In all the three groups, the onset of sensory blockade, onset of motor blockade, duration of analgesia, onset of two-segment regression, hemodynamic stability, and side effects are noted, systematically tabulated and statistically analyzed.

The level of sensory block was assessed by pinprick and the onset of blockade was noted. In all three groups, the time of injection was recorded as 0 h and onset of blockade, level (dermatomal) of sensory blockade, quality of motor blockade by modified Bromage scale [Table 1], two-segment regression time, and the time at which rescue analgesic given were noted. Continuously SpO<sub>2</sub> was monitored and pulse rate, respiratory rate, and blood pressure (non-invasive blood pressure) were

recorded every 5 min and urine output monitoring was done in both the groups and noted in the pro forma. Side effects such as nausea, vomiting, bradycardia, hypotension, respiratory depression, and shivering were noted in all the three groups.

Modified Bromage scale for the onset of motor blockade proposed by Bromage and modified by Logan-Wild Smith.

If the surgical procedure was long and patients required, the protocol was to administer further 10–12 ml of 0.5% bupivacaine by epidural route as top up. However, none of the patients required additional top up intraoperatively. Patients were administered rescue doses of 0.125% bupivacaine 10–12 ml if VAS  $\geq 4$  in the post-operative period. At the end of the surgery, the patients were shifted to post-operative ward, they were monitored for every 30 min for the first 6 h and thereafter every hour for 24 h period.

The time to first request analgesia (duration of post-operative analgesia) was recorded when the VAS reached 4 or more or when the patient complained of moderate-to-severe pain.

### Statistical Analysis

At the end of the study, all the data are compiled and statistically analyzed using:

- Descriptive data presented as mean  $\pm$  SD
- Continuous data analyzed by paired or unpaired *t*-test
- ANOVA after *t*-test for comparisons between groups and within groups.

## OBSERVATION AND RESULTS

All the 75 patients completed the study. The three groups were statistically comparable with respect to demographic data such as age, weight, height, male-to-female ratio, ASA grading, and duration of surgery as represented in Table 2. The types of lower limb procedures are presented in Table 3.

**Table 1: Bromage scale**

Scale	Criteria	Degree of block
0	Free movement of legs, feet with ability to raise extended leg	None
1	Inability to raise extended leg and knee flexion is decreased, but full extension of feet and ankles is present	Partial 33%
2	Inability to raise leg or flex knees; flexion of ankle and feet present	Partial 66%
3	Inability to raise leg, flex knee or ankle, or move toes	Complete paralysis

### Onset of Sensory Blockade

The mean time of onset of sensory block in Group N was  $12.38 \pm 0.88$  min, in Group M was  $5.96 \pm 0.73$  min, and in Group C was  $8.64 \pm 0.89$  min. The statistical analysis by ANOVA test showed that there was a statistically significant difference ( $P < 0.005$ ) between all the three groups, presented in Table 4.

### Two-Segment Regression Time

The two-segment regression time in Group N was  $106.24 \pm 2.47$  min, in Group M was  $113.28 \pm 1.92$  min, and in Group C was  $117.20 \pm 1.68$  min. The statistical analyses by ANOVA test showed that there was a statistically significant difference ( $P < 0.005$ ) between the three groups, presented in Table 4.

### Duration of Sensory Blockade

The mean duration of sensory blockade in Group N was  $215.92 \pm 5.21$  min, in Group M was  $236.00 \pm 5.68$  min, and in Group C was  $262.56 \pm 5.11$  min. the statistical analysis by ANOVA test showed that there is a statistically significant difference ( $P < 0.05$ ) in all the three groups, presented in Table 4.

### Onset of Motor Blockade

The mean duration of onset of motor blockade in Group N was  $24.58 \pm 1.77$  min, in Group M was  $13.26 \pm 1.28$  min, and in Group C was  $17.92 \pm 2.32$  min.

The statistical analysis by ANOVA test showed that there is a statistically significant difference ( $P < 0.05$ ) in all the three groups, presented in Table 4.

**Table 2: Demographic data**

Variable	Group N Mean/SD n=25	Group M Mean/SD n=25	Group C Mean/SD n=25	P value
Age in years	47/5.0	52/3.5	54/6.8	0.56
Weight in kg	58.96	53.28	56.94	0.44
Height in cm	155.76	155.32	155.48	0.34
Gender				
M:F ratio	12/13	13/12	14/11	
ASA grading				
I/II	14/11	15/10	13/12	
Duration of surgery	147/8	158/4	160/6	0.68

$P < 0.05$  considered not statistically significant. Data expressed as mean and standard deviation. Fisher's exact test

**Table 3: Types of surgeries**

Type of surgery	Group N n=25	Group M n=25	Group C n=25
IL nailing tibia	6	8	7
Tibial plating	6	6	5
ORIF femur	5	5	4
Dynamic hip screw	3	3	4
Adam Moore prosthesis	3	2	2
Total knee replacement	2	1	3

Data expressed in absolute numbers. ORIF: Open reduction and internal fixation

**Table 4: Characteristics of sensory and motor blockade**

Variable (time in min)	Group N Mean/SD n=25	Group M Mean/SD n=25	Group C Mean/SD n=25	ANOVA between groups (sum of squares)	Sig.
Mean onset of sensory block	12.38/0.88	5.95/0.73	8.64/0.89	519.88	0.01
Two-segment regression time	106.24/2.47	113.28/1.92	117.20/1.68	1542.08	0.001
Mean onset of motor block	24.55/1.77	13.26/1.28	17.92/2.32	1618.71	0.001
Duration of sensory block	215.92/5.21	236.00/5.68	262.56/5.11	27366.08	0.001
Duration of motor block	164.28/2.8	175.32/3.38	192.76/19.95	10309.54	0.001
Time to the first request analgesia	233/4.48	251/5.65	278/5.26	25657.14	0.01

Data expressed as mean and standard deviation

**Table 5: Intensity of motor blockade (modified Bromage scale)**

Grade	Group N n=25	Group M n=25	Group C n=25
0	2	1	2
1	20	21	19
2	3	3	4
3	0	0	0

Data expressed as absolute numbers

**Table 6: Intraoperative hemodynamics**

Groups	Mean PR	SD	Mean BP	SD	Mean RR	SD	Mean SpO <sub>2</sub>	SD
Group N	74	2	110	15	14	1.9	98	0.8
Group M	73	3	100	20	14	1.8	99	0.8
Group C	72	5	100	15	12	10.4	99	0.8

P&gt;0.05

**Duration of Motor Blockade**

The mean duration of motor blockade in Group N was  $164.28 \pm 2.80$  min, in Group M was  $175.32 \pm 3.38$  min, and in Group C was  $192.76 \pm 19.95$  min. the statistical analyses by ANOVA test showed that there is a statistically significant difference ( $P < 0.005$ ) between the three groups, presented in Table 4.

**Intensity of Motor Blockade**

The intensity of motor blockade evaluated by Bromage scale showed similar degree of block level of Grade 2 in all the three groups. The statistical analyses by Chi-square test showed that there was no statistical difference ( $P > 0.05$ ) between the three groups, presented in Table 5 and Figure 1.

**Intraoperative Hemodynamics**

In all the groups, there is no statistically significant difference in the hemodynamic variables. Mean systolic blood pressures and mean heart rates are represented in Table 6 and Figures 2 and 3.

**Duration of Post-operative Analgesia**

The duration of post-operative analgesia (time to the first request of pain relief) was significantly prolonged and highest in the clonidine group followed by magnesium

group than the control group. Group C  $278 \pm 5.26$  min versus Group M  $251 \pm 5.65$  min versus Group N  $233.00 \pm 4.48$  ( $P < 0.001$ ) are represented in Table 4 and Figure 4.

**Side Effects**

There were no statistical differences between clonidine group, magnesium group, and control group with respect to side effects such as hypotension, bradycardia, and shivering. About 40% of patients in clonidine group had sedation which is statistically significant when compared to other two groups, represented in Figure 5.

**DISCUSSION**

This study was undertaken to evaluate the effect of magnesium sulfate versus clonidine as an adjuvant to epidural ropivacaine compared with plain ropivacaine alone for lower limb surgeries.

Most of the previous studies proved that magnesium sulfate and clonidine have been associated with lesser analgesic requirements and less discomfort in the post-operative period when used systemically and also as adjuvants to regional anesthesia.<sup>[9,10]</sup> Recently, intrathecal and epidural administration of magnesium sulfate as an adjuvant to local anesthetics such as lignocaine, bupivacaine, levobupivacaine, and ropivacaine has been reported to produce effective and prolonged analgesia.<sup>[11,12]</sup>

N-methyl-D-aspartate (NMDA) receptor signaling may be important in determining the duration and intensity of acute post-operative pain. Magnesium sulfate is a competitive NMDA receptor antagonist and plays an important role in the prevention of central sensitization of pain in response to prolonged nociceptive stimuli.<sup>[13]</sup> Clonidine is an alpha-2 agonist, which induces dose-dependent antinociception at spinal level mainly through the stimulation of alpha-2 adrenoceptors in the dorsal horn.<sup>[14]</sup>

In our study, the mean time of the onset of sensory blockade in magnesium Group C is significantly less than clonidine group and control group

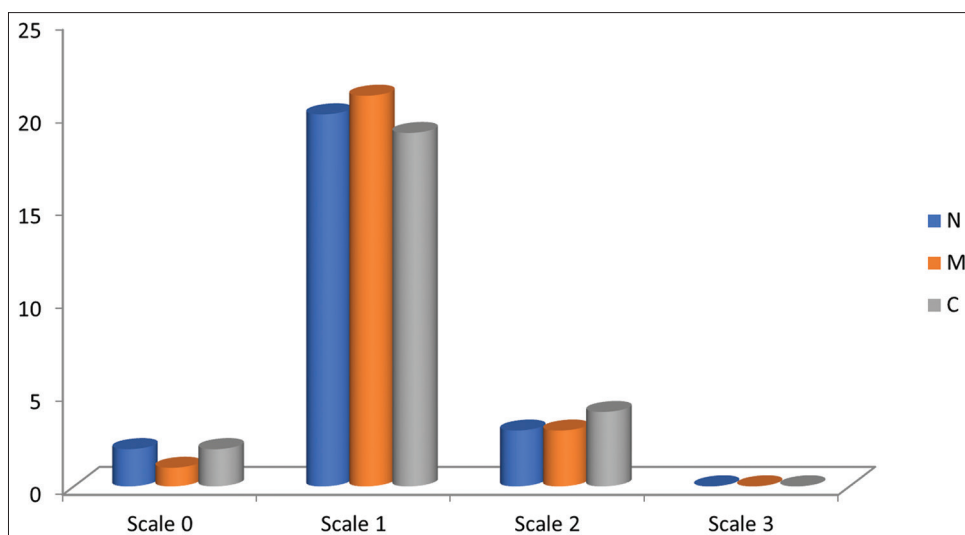


Figure 1: Intensity of motor blockade according to modified Bromage scale

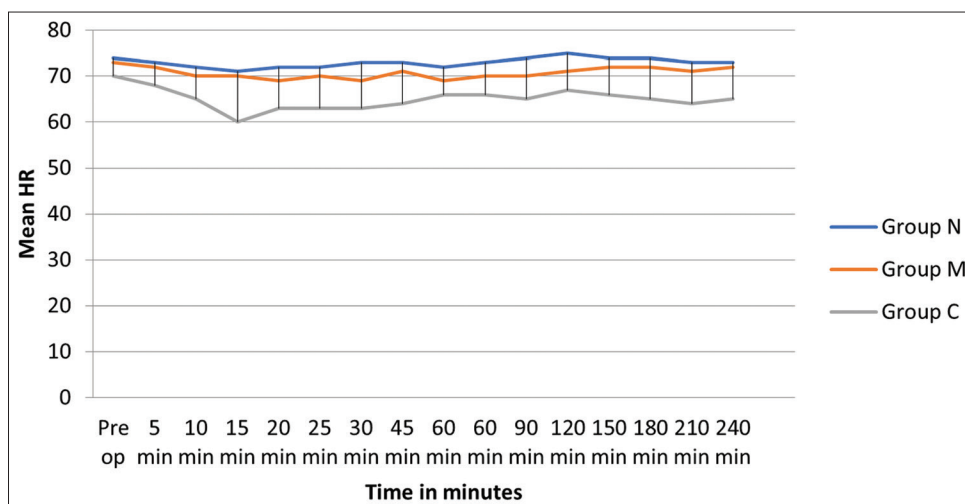


Figure 2: Intraoperative heart rate ( $P > 0.05$ )

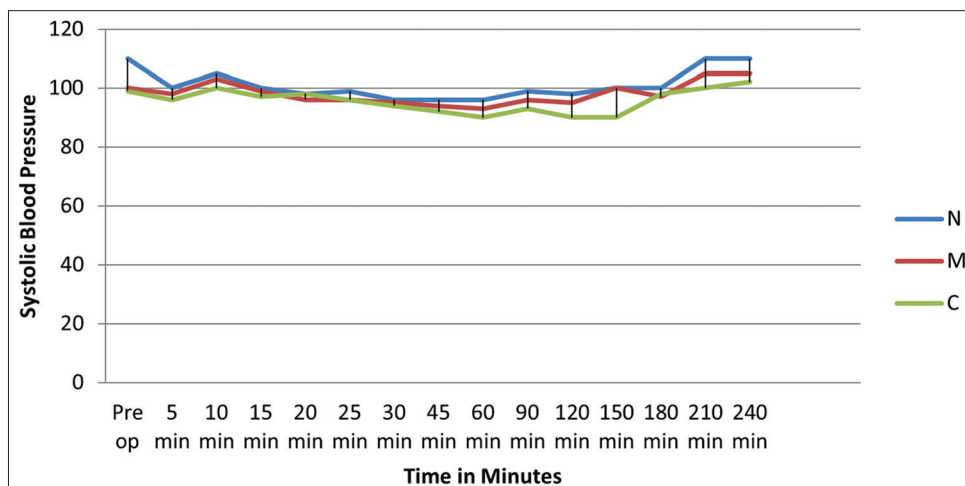


Figure 3: Systolic blood pressure ( $P > 0.05$ )

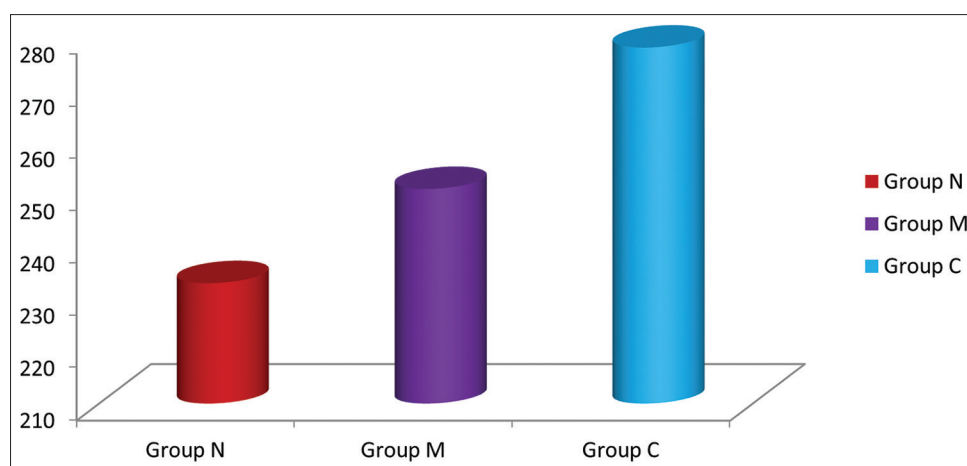


Figure 4: Time to the first request analgesia

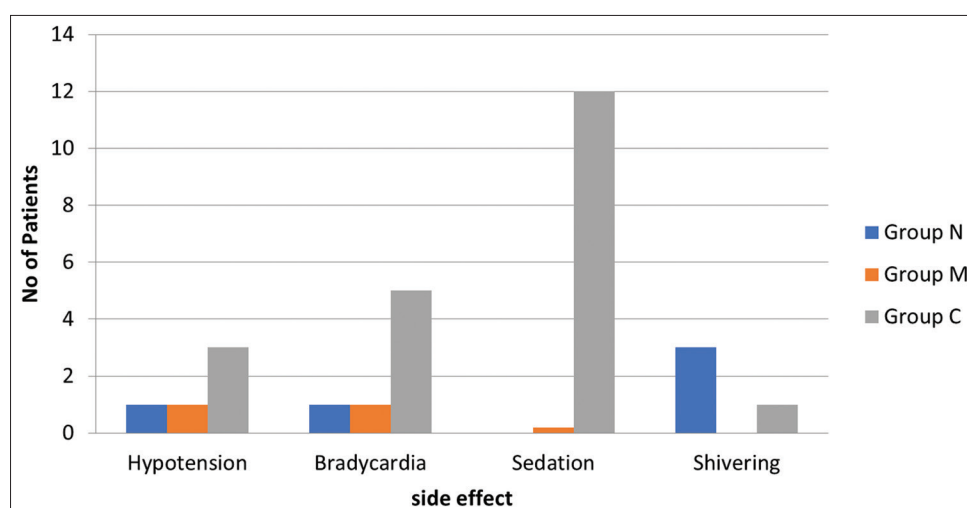


Figure 5: Incidence of side effects

(Group M  $5.96 \pm 0.73$  min vs. Group C  $8.64 \pm 0.89$  min vs. Group N  $12.38 \pm 0.88$  min,  $P < 0.005$ ).

In a study conducted by Ghatak *et al.*, epidural magnesium sulfate versus clonidine with bupivacaine showed that mean time of onset to T6 level for magnesium sulfate  $11.80 \pm 3.21$  min versus clonidine  $16.93 \pm 3.43$  min versus plain ropivacaine  $18.73 \pm 2.79$  min, ( $P < 0.001$ ), they correlated with the observations of this study.<sup>[15]</sup>

In our study, the two-segment regression time in magnesium group was significantly less than clonidine group but higher than control group (Group M  $113.28 \pm 1.92$  min vs. Group C  $117.20 \pm 1.68$  min vs. Group N  $106.24 \pm 2.47$  min [ $P < 0.001$ ]).

This finding also correlated with the above-mentioned study by Ghatak *et al.* (magnesium sulfate  $130.33 \pm 33.94$  min vs. clonidine  $145.33 \pm 27.74$  min vs. plain bupivacaine  $123.00 \pm 28.03$  min [ $P < 0.001$ ]).

The mean duration of sensory blockade in our study was significantly higher with clonidine group than magnesium and control groups (Group C  $262.56 \pm 5.11$  min vs. Group M  $236.00 \pm 5.68$  min vs. Group N  $215.92 \pm 5.21$  min [ $P < 0.001$ ]).

Mohammed *et al.* evaluated the efficacy and safety of epidural magnesium sulfate and clonidine as adjuvants to bupivacaine for post-thoracotomy pain relief and concluded that thoracic epidural analgesia using bupivacaine with clonidine is an efficient therapeutic modality for post-thoracotomy pain. Magnesium as an adjuvant provided quality post-operative analgesia decreasing the need for post-operative rescue analgesia and incidence of post-operative shivering without causing sedation.<sup>[16]</sup> The duration of post-operative analgesia is significantly prolonged in clonidine group in their study compared to magnesium and control groups comparable to the present study.

In a study conducted by Khalili *et al.*, who compared magnesium sulfate with bupivacaine versus plain



bupivacaine for lower extremity surgeries concluded that the duration of sensory blockade was significantly longer with magnesium sulfate group than in the control group (magnesium sulfate 106.5 min vs. control group 85.5 min [ $P < 0.001$ ]) which finding also is similar to this study.<sup>[17]</sup>

The mean time to onset of motor blockade in the present study was significantly less in magnesium group than clonidine group than control group (Group M  $13.26 \pm 1.28$  min vs. Group C  $17.92 \pm 2.32$  min vs. Group N  $24.58 \pm 1.77$  min [ $P < 0.001$ ]).

Similarly, the duration of motor blockade was significantly high in clonidine group than magnesium group and control group (Group C  $192.76 \pm 19.95$  min vs. Group M  $175.32 \pm 3.38$  min vs. Group N  $164.28 \pm 2.8$  min [ $P < 0.001$ ]).

The duration of post-operative analgesia (time to the first request of pain relief) was significantly prolonged and highest in the clonidine group followed by magnesium group than the control group (Group C  $278 \pm 5.26$  min vs. Group M  $251 \pm 5.65$  min vs. Group N  $233.00 \pm 4.48$  min [ $P < 0.001$ ]).

Shahi *et al.* did a comparative study on magnesium sulfate versus dexmedetomidine as adjuncts to epidural bupivacaine in lower limb surgeries and concluded that magnesium sulfate, administered epidurally, also prolongs the duration of analgesia, but less than epidural dexmedetomidine.<sup>[18]</sup> They reported that dexmedetomidine produced prolonged analgesia with arousable sedation.

Pradhan *et al.* conducted a comparative study on clonidine versus magnesium sulfate as adjuncts to epidural bupivacaine and concluded that magnesium sulfate was a better alternative to clonidine as an adjuvant to bupivacaine in epidural anesthesia in orthopedic lower limb surgeries for rapid onset of action, but clonidine has prolonged duration of action.<sup>[19]</sup> The observations of their study were comparable to the present study (Group M  $5.96 \pm 0.73$  min vs. Group C  $8.64 \pm 0.89$  min vs. Group N  $12.38 \pm 0.88$  min,  $P < 0.005$ , in the present study).

In our study, the intraoperative hemodynamic variables were more or less comparable in all the three groups except a few cases in the clonidine group had transient bradycardia ( $n = 5$ ) and hypotension ( $n = 3$ ) which were not statistically significant.

Only one patient had bradycardia and one patient had hypotension in both control and magnesium groups. Bradycardia and hypotension were treated with injection atropine 0.6 mg and IV crystalloid boluses, respectively.

Twelve patients of clonidine group had sedation in the perioperative period; they were awake but drowsy, calm, and easily arousable. None of the patients in all the three groups had any other side effects such as respiratory depression and dryness of mouth.

The results of our study suggest that epidural ropivacaine with clonidine produced significantly prolonged duration of post-operative analgesia with arousable sedation and minimal side effects when compared to epidural ropivacaine with magnesium sulfate and control groups, while magnesium sulfate produced shorter onset of sensory and motor blockade with significantly prolonged post-operative analgesia without sedation and side effects. Hemodynamics were comparable in all the groups. Hence, it can be concluded that magnesium sulfate may be a useful alternative as an adjuvant to epidural ropivacaine with safety and efficacy in the doses used.

The main limitation of this study is that the sample size is small. Most of studies were done with epidural bupivacaine.<sup>[20]</sup> There is a need for further clinical trials and research to be done with epidural ropivacaine and magnesium sulfate to establish the optimal and safe doses that can produce effective and prolonged duration of post-operative analgesia.

## CONCLUSION

Our study concluded that addition of magnesium sulfate to epidural ropivacaine produced earlier onset of sensory and motor blockade while significantly prolonging the post-operative analgesia when compared to control group but less duration of anesthesia when compared to clonidine group, without any significant side effects. Hence, magnesium sulfate has been proved to be a promising alternative as an adjuvant to regional analgesia in the perioperative period.

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# Buprenorphine with Local Anaesthetic Combination in Supraclavicular Brachial Plexus Block Produced Prolonged Post-operative Analgesia Compared to Butorphanol with Local Anaesthetic: A Prospective, Randomized, Comparative Study

Gadi Grace Priyanka<sup>1</sup>, S K Farooq Basha<sup>2</sup>

<sup>1</sup>Assistant Professor, Department of Anaesthesiology, ACSR Government Medical College, Nellore, Andhra Pradesh, India, <sup>2</sup>Assistant Professor, Department of Anaesthesiology, ACSR government Medical College, Nellore, Andhra Pradesh, India

## Abstract

**Background:** Supraclavicular approach for brachial plexus block offers an alternative anesthesia for upper extremity surgery. Addition of opioid agents in local anesthetic solutions for prolongation of analgesia through brachial plexus block has been very effective in controlling post-operative pain. The time to request for the 1<sup>st</sup> dose of rescue analgesia can be prolonged by adding buprenorphine or butorphanol in local anesthetic solutions.

**Methodology:** After institutional ethical committee approval, 60 American Society of Anesthesiologists I/II patients were randomized for this study. They belong to either gender, aged between 18 and 55 years of age. Patients who required brachial plexus block through supraclavicular approach were included and the study drugs were administered according to group allocation into Group I and Group II. Sensory and motor block characteristics were monitored and recorded in all patients, complications as well. Hemodynamic monitoring was done every 5 min interval in the intraoperative period and every 15 min intervals in the post-operative period. Patients were administered rescue analgesia postoperatively when visual analog scale (VAS) scores were  $\geq 4$ . Data were analyzed statistically.

**Results:** Onset time to sensory block was 3.1 (1.1) min in Group I and 4.9 (1) min in Group II, and there was statistically significant difference between groups ( $P < 0.0001$ ). Onset time to motor block was 5.4 (1.3) min in Group I and 9.3 (1.5) min in Group II, and the difference between groups was found to be significant statistically ( $P < 0.0001$ ). The time to 1<sup>st</sup> request of analgesia was found to be statistically significantly between I and II groups (354.8 [55.6] vs. 448.3 [34.4] min,  $P < 0.0001$ ), respectively.

**Conclusion:** Both buprenorphine and butorphanol produced effective analgesia in combination with local anesthetics without significant side effects, but buprenorphine produced prolonged analgesia when compared to butorphanol.

**Key words:** Bupivacaine, Buprenorphine, Butorphanol, Lignocaine, Supraclavicular brachial plexus block

## INTRODUCTION

Post-operative pain management is a challenge to the attending physician as it is the most crucial period of

stress to the surgical patient. Improper or inadequate analgesia leads to stress-related complications, especially hemodynamic and cardiac complications. Hence, it is the duty of the anesthesiologist to provide optimum post-operative analgesia to the surgical patient in the immediate period, especially the first 24 h after surgery. Brachial plexus block provides adequate anesthesia and post-operative analgesia for all the upper limb procedure. Supraclavicular brachial plexus block was first introduced in 1911 by Kulenkampff as a landmark-based approach.<sup>[1,2]</sup> With the advent of many adjuvants, preferably opioid agents are

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**Corresponding Author:** Dr. S K Farooq Basha, Flat No: 403, Teaching Staff Quarters, ACSR Government Medical College Campus, Nellore - 524 004, Andhra Pradesh, India.

used for prolongation of post-operative analgesia through brachial plexus block due to their potency and reliability though not with complications.<sup>[3]</sup> Many randomized clinical trials proved that opioids such as fentanyl, tramadol, butorphanol, nalbuphine, and buprenorphine were used with varying efficacies along with local anesthetics in brachial plexus blockade to prolong post-operative analgesia.<sup>[4,5]</sup> Recently, there has been interest in the adjuvant buprenorphine as it is partial agonist with high potency and easily available. The aim of this study is to compare the efficacy of buprenorphine versus butorphanol when administered in combination with local anesthetics in supraclavicular approach of brachial plexus blockade.

## METHODOLOGY

After institutional ethical committee approval and written, informed consent from patient attendants, patients of the American Society of Anesthesiologists (ASA) I/II posted for forearm and elbow procedures, of both genders and age group between 18 and 55 years were randomly allocated into two groups of 30 each.

### Exclusion Criteria

The following criteria were excluded from the study:

- ASA III/IV
- Bleeding disorders
- Cardiovascular, respiratory, renal, and liver diseases
- Hemodynamic instability
- Patient with known hypersensitivity to local anesthetics
- Addiction to opioids.

Group I (butorphanol) was allocated to receive inj. 2% lignocaine hydrochloride – 10 ml, inj. 0.5% bupivacaine hydrochloride – 19 ml, and inj. butorphanol – 1 mg (1 ml), total volume made to 30 ml.

Group II (buprenorphine) was allocated to receive inj. 2% lignocaine hydrochloride – 10 ml, inj. 0.5% bupivacaine hydrochloride – 19 ml, and inj. butorphanol – 100 µg (1 ml), total volume made to 30 ml.

In the pre-operative room, baseline hemodynamic parameters such as heart rate, blood pressure, respiratory rate, and SpO<sub>2</sub> were recorded. Patients were not premedicated with any sedatives. Procedure of supraclavicular brachial plexus block was explained in detail before shifting the patient to the operating room. 18 G intravenous (IV) cannula was secured. Maintenance IV fluids were started with balanced salt solution. Pulse oximetry and cardiac monitors were attached. Patients were instituted supraclavicular brachial plexus block using nerve stimulator-guided technique and study drugs

were given as per the group allocation. The study drugs were supplied to the operating room just before administering them by the principal investigator who was aware of group allocation. The anesthesiologist who performed brachial plexus block and the observer anesthesiologist who recorded the data were blinded to the group allocation to ensure blinding. After instituting supraclavicular block, patients were monitored for hemodynamic parameters such as heart rate and blood pressure every 5 min throughout the intraoperative period. Patients were also assessed for time of onset to sensory and motor block and duration of post-operative analgesia (time to 1<sup>st</sup> request analgesia). Postoperatively, visual analog scale (VAS) scores were assessed and patients were given rescue analgesia when VAS ≥4.

VAS was explained to the patients in native language. The patients were shown a 10 cm long scale marked 0–10 on a blank paper and told that the number 0 indicates no pain and number 10 indicates worst possible pain. Patients were observed in the post-anesthesia care unit for 2 h and then shifted to the ward for further monitoring. All the recorded data were compiled, tabulated, and analyzed statistically.

## RESULTS

All the 60 patients completed the study. None of the patients had failed block. Patients of three groups were comparable with respect to demographic data such as age, weight, ASA grading, gender ratio, and duration of surgery,  $P > 0.05$ , statistically insignificant. This is represented in Table 1. Types of surgical procedures performed were mentioned in Table 2.

On analyzing the baseline and perioperative hemodynamic parameters, there was no significant difference in heart rate and systolic blood pressure preoperatively, at 0, 15, 30, 45, 60, 75, 90, and 120 min and postoperatively between groups as shown in Figures 1 and 2, respectively.

The time to onset of sensory block was 3.1 (1.1) min in Group I (butorphanol) and 4.9 (1) min in Group II

**Table 1: Demographic data**

Demographic variable	Group I (butorphanol) n=30	Group II (buprenorphine) n=30	P-value
Age in years	43.5±8.58	47.7±9.08	0.76
Weight in kg	55.87±8.90	59.65±6.98	0.87
American Society of Anesthesiologists grading, I/II	17:13	20:10	0.34
Male: female ratio	18:12	16:14	0.45
Duration of surgery	115±16	122±12	0.56

$P > 0.05$  considered statistically insignificant. Data represented as mean/standard deviation. Fisher's exact test

(buprenorphine), and there was statistically significant difference between groups ( $P < 0.0001$ ). The time of onset of motor block was 5.4 (1.3) min in Group I and 9.3 (1.5) min in Group II, and there was statistically significant difference between groups ( $P < 0.0001$ ) which was represented in Table 3 and Figure 3. Butorphanol group had earlier onset of sensory and motor block when compared to buprenorphine group which is statistically significant.

The duration of post-operative analgesia was found to be statistically significantly varied between I and II groups (354.8 [55.6] vs. 448.3 [34.4] min,  $P < 0.0001$ ), respectively as represented in Table 3 and Figure 4. Buprenorphine group produced significantly prolonged analgesia when compared to butorphanol group. Complications are observed in three patients in Group I and four patients in Group II had vomiting, and one patient in Group I had pruritis. There was no significant difference between Groups I and II in occurrence of adverse effects ( $P = 1.0$ ) as represented in

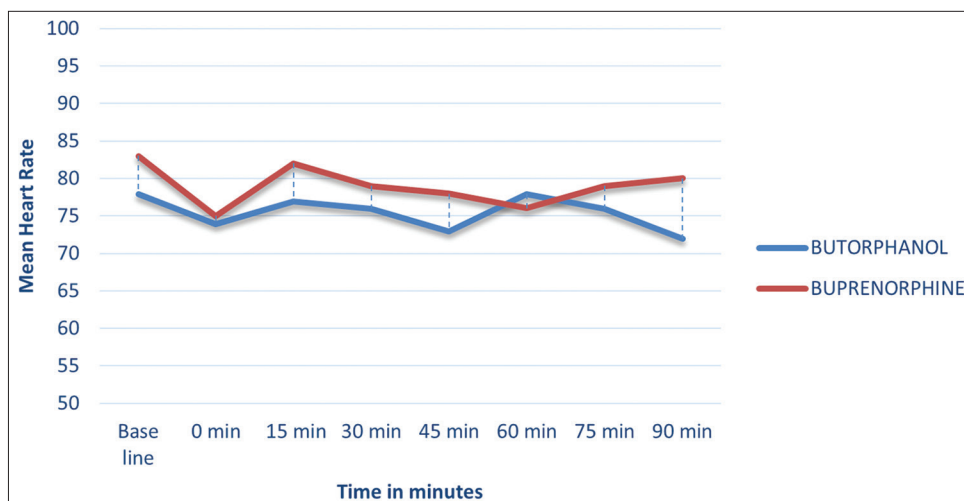
**Table 2: Types of surgeries**

Surgical procedure	Group I (butorphanol) n=30	Group II (buprenorphine) n=30
Fracture both bones fore arm	16	14
Fracture lower third humerus	4	6
Fracture distal third radius	7	4
Fracture distal third ulna	3	6

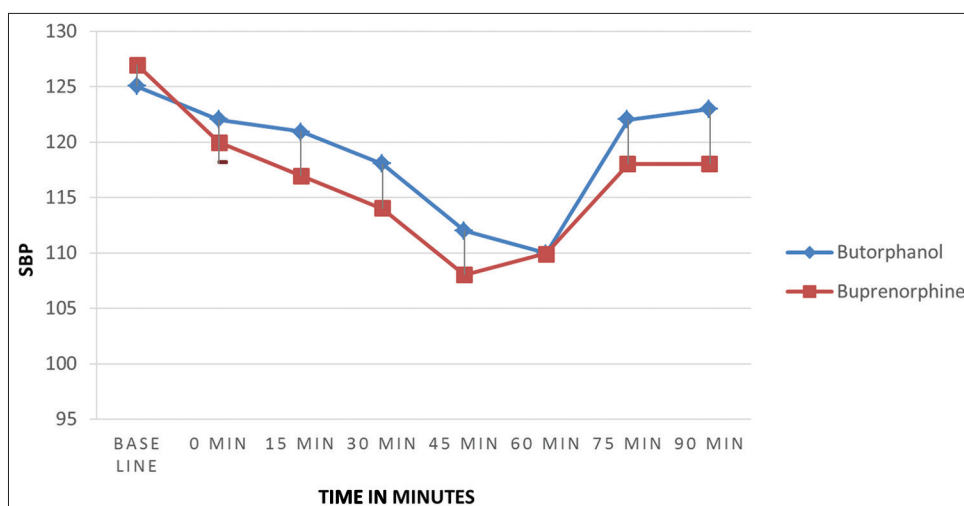
**Table 3: Sensory and motor block characteristics**

Time in minutes	Group I (butorphanol) n=30	Group II (buprenorphine) n=30	P-value
Onset time to sensory block	3.1 (1.1)	4.9 (1.0)	0.001
Onset time to motor block	5.4 (1.3)	9.3 (1.5)	0.001
Time to 1 <sup>st</sup> request analgesia	354.8 (55.6)	448.3 (34.4)	0.001

$P < 0.05$  considered statistically significant. Data represented as mean/standard deviation. Student's t-test



**Figure 1: Mean heart rate**



**Figure 2: Mean systolic blood pressure**



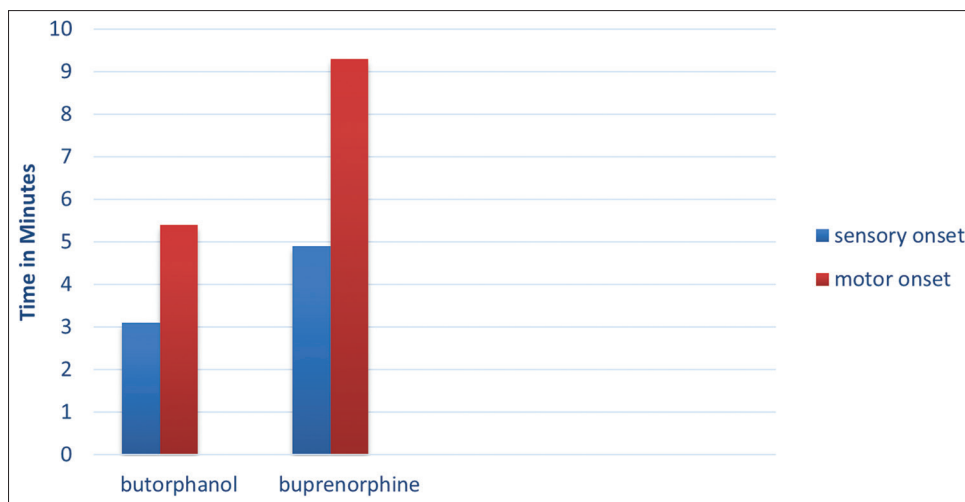


Figure 3: Onset time of sensory and motor block

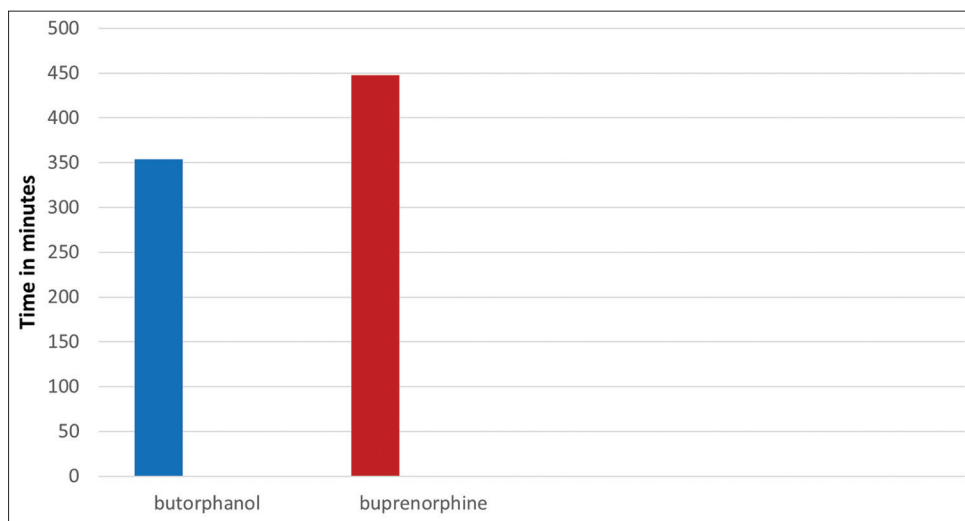


Figure 4: Duration of post-operative analgesia

Table 4: Side effects

Parameter	Group I (butorphanol) n=30 (%)	Group II (buprenorphine) n=30 (%)	P-value
Vomiting	3 (10)	4 (13.3)	1.0
Pruritus	2 (6.6)	0	1.0
Pneumothorax	0	0	-
Nerve palsy	0	0	-

*P* > 0.05 considered statistically insignificant. Data represented as absolute numbers and percentage. Chi-square test

Table 4. None of the patients in both groups developed complications related to supraclavicular brachial plexus block technique such as pneumothorax or nerve palsy.

## DISCUSSION

Supraclavicular brachial plexus block is commonly performed upper limb brachial plexus block for orthopedic

procedures. It provides effective and profound sensory and motor blockade and is also easy to perform. With the aid of nerve stimulator guided technique, supraclavicular blocks are being performed with high success rate.<sup>[6]</sup> Single-shot supraclavicular techniques may not provide post-operative analgesia for prolonged periods. With the availability of various adjuvants, it has been traditional method to combine adjuvants to local anesthetics to prolong the post-operative analgesia as well as enhance the quality of blockade.<sup>[7,8]</sup> Butorphanol is a partial agonist-antagonist and potent opioid, documented in various studies to prolong analgesia when administered with brachial plexus blocks.<sup>[9]</sup>

In this randomized, double-blinded trial, we compared butorphanol and buprenorphine as an adjuvant to local anesthesia mixture in supraclavicular brachial plexus block and found that buprenorphine group had delayed onset of sensory, motor blockade, and longer duration of post-operative analgesia than butorphanol group.

Wajima *et al.* have studied butorphanol in local anesthetic through continuous brachial plexus block and have demonstrated that butorphanol produces prolonged pain relief in post-operative period.<sup>[10]</sup>

Viel and Eledjan have shown that buprenorphine 3 µg/kg in supraclavicular brachial plexus block produces significantly longer pain relief than morphine after upper limb surgery.<sup>[11]</sup> So here, in this study, we have used butorphanol 100 mg versus buprenorphine 100 µg in addition to local anesthetic drugs through supraclavicular brachial plexus block. In our study, postoperatively, comparison of the duration of postoperatively analgesia was done by VAS score and showed statistically significant prolonged duration of analgesia in Group-II buprenorphine compared to Group I butorphanol ( $P < 0.0001$ ).

Salins *et al.* conducted the study on extension of brachial plexus block with 1.5% lignocaine adrenaline and buprenorphine a comparison with 1.5% lignocaine and adrenaline.<sup>[12]</sup> Although the addition of buprenorphine had no significant effect on the quality of analgesia, the duration of analgesia was significantly prolonged more than 3 times than other groups.

Our study is comparable with the study of Viel and Eledjan. They have studied comparison of buprenorphine and morphine in supraclavicular brachial plexus block and evaluated that buprenorphine significantly produces prolonged post-operative pain relief.

Our study is also comparable with the study of Trivedi and Shah. They have studied comparison of buprenorphine 100 µg and butorphanol 1 mg in supraclavicular brachial plexus block and evaluated that buprenorphine significantly produces prolonged post-operative pain relief.<sup>[13]</sup>

## CONCLUSION

We concluded that both opioids are potent and safe postoperative analgesics in brachial plexus block without significant side effects and hemodynamic changes. Buprenorphine is more potent and produces longer duration of postoperative analgesia compared to butorphanol.

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# A Study of 25 Diagnosed Cases of Abdominal Tuberculosis – A Review Article

Nilesh Punjabhai Sondarva<sup>1</sup>, Kishan D Shah<sup>2</sup>, Sudhir G Mehta<sup>3</sup>

<sup>1</sup>Resident, Department of General Surgery, MP Shah Medical College, Jamnagar, Gujarat, India, <sup>2</sup>Associate Professor, Department of General Surgery, MP Shah Medical College, Jamnagar, Gujarat, India, <sup>3</sup>Professor and Head, Department of General Surgery, MP Shah Medical College, Jamnagar, Gujarat, India

## Abstract

**Background:** The objective of this study is to evaluate diagnosed cases of abdominal tuberculosis (TB) in terms of incidence, manifestation in different age groups, clinical presentations, treatment received (conservative or surgical), lesions found intraoperatively, and its outcome on follow-ups.

**Methods:** It is a retrospective study with 25 cases of abdominal TB treated at Guru Gobind Singh Hospital, Jamnagar, during the period of 2005–2007. Detailed history, physical examination, necessary investigations such as complete blood counts, ESR, urine examination, sputum examination, and radiological investigations were prescribed in all cases. Barium study, Mantoux test, ascitic fluid examination, and computed tomography scan abdomen were carried out when indicated. Tissue or biopsy materials were histologically examined. Results were analyzed with patient's health status.

**Results:** In 25 case series of abdominal TB, the average age of presentation was between 10 and 40 years with definite male predominance (male:female = 3:2). Most of the patients belonged to low socioeconomic class which, in turn, reflects overcrowding, undernourishment, bad sanitation, and poor hygiene in living conditions. In our study, ESR was raised in more than 90% of patients. Abdominal pain was the most common presenting symptom followed by anorexia, fever, and vomiting. About 25% of patients were having TB foci in lung either active or healed lesion. Uncorrected anemia, malnutrition, and pulmonary TB were all contributory to poor prognosis and prolonged morbidity. Anti-TB drugs gave most satisfactory results in our patients.

**Conclusions:** Koch's abdomen is a clinical entity with varied clinical presentation. It is very common in tropics and may present with complications. Most of the patients are cured with conservative treatment and anti-TB drugs. Surgery is required in case of complications only. No drug-resistant cases have been found in this study. Investigations have played major role in confirmation of disease.

**Key words:** Abdominal tuberculosis, Intestinal resections, Koch's abdomen, Stricture plasty

## INTRODUCTION

Tuberculosis (TB) has become a big health issue, especially in developing countries like India, where illiteracy, poverty, overcrowding, lack of basic living facilities, large families, poor sanitation, and malnutrition are prevalent.<sup>[1]</sup> Approximately one-third of the world population is infected with TB and about 3 million die each year from this

disease.<sup>[2]</sup> Therefore, the World Health Organization has raised a global concern and declared as the most important communicable disease worldwide.<sup>[3]</sup> It is a chronic granulomatous disease caused by *Mycobacterium tuberculosis* and the reservoir of infection in humans with active TB. Pulmonary TB is the most common form and it primarily involves the lung, but any part of the body can be involved by the disease.<sup>[4,5]</sup> Abdominal TB constitutes a major public health problem in developing countries and associated with significant morbidity and mortality.<sup>[6]</sup> It is the sixth most frequent site for the extrapulmonary involvement and it can involve any part of the gastrointestinal tract, peritoneum, and hepatobiliary system. Approximately 1–3% of total TB cases are extrapulmonary,<sup>[7,8]</sup> while abdominal TB accounts for 11%–16%.<sup>[9]</sup> However, in HIV-positive patients, the

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**Corresponding Author:** Dr. Nilesh Punjabhai Sondarva, F/303, Nilkanth Greens, Behind Delhi Public School, Kalali Road, Vadodara - 390 012, Gujarat, India.

incidence of extrapulmonary TB is up to 50%. The modes of infection of abdominal TB include hematogenous spread from a primary lung focus that reactivates later or miliary TB, spread through lymphatics from infected nodes, ingestion of bacilli either from the sputum or from infected sources such as milk products, or by direct spread from adjacent organs.<sup>[10]</sup> The most common site of predilection is the ileocecal region, attributed to the minimal digestive activity, relatively increased physiological stasis, higher rate of fluid and electrolyte absorption, and more lymphoid tissue at this site.<sup>[11,12]</sup> Peritoneal involvement may occur due to spread of the bacilli from mesenteric lymph node. However, one-third of cases show abdominal lymph node and peritoneal TB without any evidence of gastrointestinal involvement.<sup>[13]</sup> Abdominal TB is characterized by different modes of presentations, namely, chronic, acute, and acute on chronic, or it may be an incidental finding at laparotomy for other diseases;<sup>[14]</sup> the clinical presentation depends on the site and type of involvement. It usually runs an indolent course and presents late with complications, especially acute or subacute intestinal obstruction due to mass (tuberculoma) or stricture formation in small gut and ileocecal region or gut perforation, leading to peritonitis.<sup>[15]</sup> Whereas intestinal (enteric) TB exists in one of the three main forms, i.e. ulcerative, hypertrophic or ulcerohypertrophic causing fibrous strictures, while peritoneal involvement (TB peritonitis) exists in four main forms, namely, ascitic, loculated (encysted), plastic (fibrous), and purulent forms.<sup>[16,17]</sup> The lymph nodes in the small bowel mesentery and the retroperitoneum are commonly involved, and these may caseate and calcify. Disseminated abdominal TB involving the gastrointestinal tract, peritoneum, lymph nodes, and solid viscera has also been described.<sup>[17]</sup> The diagnosis of abdominal TB in initial stages is difficult as the clinical features are vague, diverse and there is no specific diagnostic test. It remains a considerable diagnostic challenge, especially in the absence of pulmonary infection, as the disease can mimic various gastrointestinal disorders, particularly the inflammatory bowel disease, colonic malignancy, or other gastrointestinal infections. The most common complication of intestinal TB is intestinal obstruction attributed to strictures or by adhesions. In India, approximately 3–20% of all cases of bowel obstruction are due to the TB.<sup>[18,19]</sup> One of the serious complications of abdominal TB is perforation, causing high morbidity and mortality and it accounts for 5–9% of small intestinal perforations.<sup>[20]</sup> Surgical intervention is reserved only for complications such as obstruction, perforation, fistula, or a mass which does not resolve with medical therapy. In most cases, a trial of medical therapy should be undertaken before surgical intervention.<sup>[21]</sup> Mortality rate has come down to 3% from 20% to 50% after introduction of antitubercular chemotherapy and multidrug treatment. Surgical management of abdominal

TB (intestinal TB) has changed considerably from bypass operations, hemicolectomies to conservative resections, and stricturoplasties.<sup>[22]</sup> This study aims at a fresh look in to abdominal TB and at a better understanding of its clinical manifestations, diagnostic modalities, management, and its complications.

## METHODS

The study was conducted at Guru Gobind Singh Hospital, M. P. Shah Medical College, Jamnagar, Gujarat, India, during May 2005–May 2007. This study had included 25 confirmed cases of abdominal TB.

Detailed history, physical examination, and most of the investigations such as complete blood counts, erythrocyte sedimentation rate (ESR), sputum examination, and radiological investigations (X-ray chest, X-ray abdomen, and ultrasound of abdomen) were done in all cases.

Barium meal, barium enema, Mantoux test, and ascitic fluid examination were carried out when indicated.

In all cases, histopathological examination of biopsy material was done when biopsy was performed. Culture and guinea-pig inoculation could not be done due to inadequate facility.

In follow-up, all relevant medical data were inquired and recorded. Results of treatment given were analyzed and necessary corrections were made.

## RESULTS

In this study, of 25 patients, 96% were Hindus and 4% were Muslims which indicate majority of Hindu people living in this region [Table 1]. In addition, majority of people (72%) belonged to low-income group (annual income <10,000 INR/year) while 28% of people were from middle-income group (annual income between 10,000 and 20,000 in a year) [Table 2]. No age is bar to abdominal TB but, in our study, minimum and maximum age of patients were 9 years and 60 years, respectively.

The most common age groups affected with abdominal TB were 10–39 years which account for 64%. In total, 68% of males (17 of 25) and 32% of females (8 of 25) were affected with disease [Table 3] which bring the male-to-female ratio around 3:2.

In our study, 68% of patients presented with chronic complaints while 32% presented with acute complaints (duration of symptoms within 15 days) [Table 4]. The most

common acute presentation was intestinal obstruction in our study.

In all patients, abdominal pain (100%) was the main presenting complaints followed by anorexia (96%), fever (60%), vomiting (52%), constipation (40%), loss of weight (40%), abdominal distension (24%), and diarrhea (16%) in descending orders. The least common complaints were lump in abdomen accounts for 8% only in this study [Table 5].

The most common intraoperative procedure was release of adhesions/bands among small intestines (36%) followed by stricturoplasty (22%) and intestinal resection and anastomosis (18%). Meanwhile, the least common procedures were perforation closure and right hemicolectomy both had 4% of recurrence in this study [Figure 1].

**Table 1: Race and religion distribution**

Religions	Numbers	Percentage
Hindus	24	96
Muslims	1	4
Total	25	100

**Table 2: Income group-wise distribution**

Income groups	Numbers	Percentage
Low income	18	72
Middle income	7	28
High income	0	0
Total	25	100

**Table 3: Age group-wise distribution**

Age groups in years	Males	Females	Total	Percentage
0–9	1	0	1	4
10–19	3	3	6	24
20–29	3	3	6	24
30–39	4	0	4	16
40–49	4	1	5	20
50–59	1	1	2	8
60–69	1	0	1	4
Total	17	8	25	100

**Table 4: Acute versus chronic presentation**

Presentation	Numbers	Percentage
Chronic	17	68
Acute	8	32
Obstruction	4	16
Perforation	1	4
Peritonitis	1	4
RIF lump	2	8

RIF: Right iliac fossa

The prominent histopathological findings in descending order of frequency were hyperplastic lesions in small bowels (32%), mesenteric lymph nodal disease (24%) (caseation necrosis and giant cells presence), stricturous lesions in small bowels (20%), and peritoneal surface miliary lesions (16%). The least frequent findings were ulcerative bowel lesions and dense serosal adhesions with same recurrence of 4% [Figure 2].

In this study, tuberculous infections to intraabdominal organs with the highest degree of involvement is seen with small intestines (32%), followed by mesenteric lymph nodes (24%), appendix with ileocecal junction (20%), peritoneal surface (16%) and large intestines (8%) in decreasing order of frequency. We have not encountered any cases with involvement of stomach, duodenum, rectum, and anal canal [Table 6].

## DISCUSSION

In our series, in all cases, tissues were sent for histopathological examination and positive histology was obtained in all cases whether in the form of presence of tubercle bacilli in 60% of cases while caseation necrosis/giant cell in remaining 40% of cases.

In our series, no post-operative death has occurred. Two patients had post-operative wound infections. One patient developed diarrhea after conservative ileocecal resection. Post-operative fecal fistula was not found in a case.

**Table 5: Signs and symptoms of distribution**

Signs and symptoms	Presence of symptoms (of 25 cases)	Percentage
Abdominal pain	25	100
Anorexia	24	96
Fever	15	60
Vomiting	13	52
Constipation	10	40
Loss of weight	10	40
Abdominal distension	6	24
Diarrhea	4	16
Lump in abdomen	2	8

**Table 6: Site of lesions**

Anatomical site	Number of cases	Percentage
Stomach and duodenum	0	0
Small intestines	8	32
Appendix and ileocecal junction	5	20
Large intestines	2	8
Peritoneal tubercles	4	16
Mesenteric lymph nodes	6	24
Rectum and anal canal	0	0



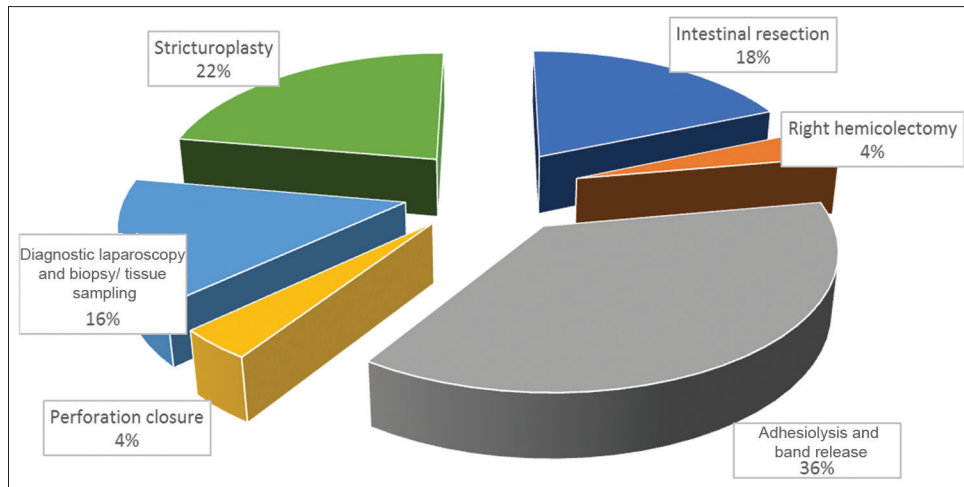


Figure 1: Types of operative procedures

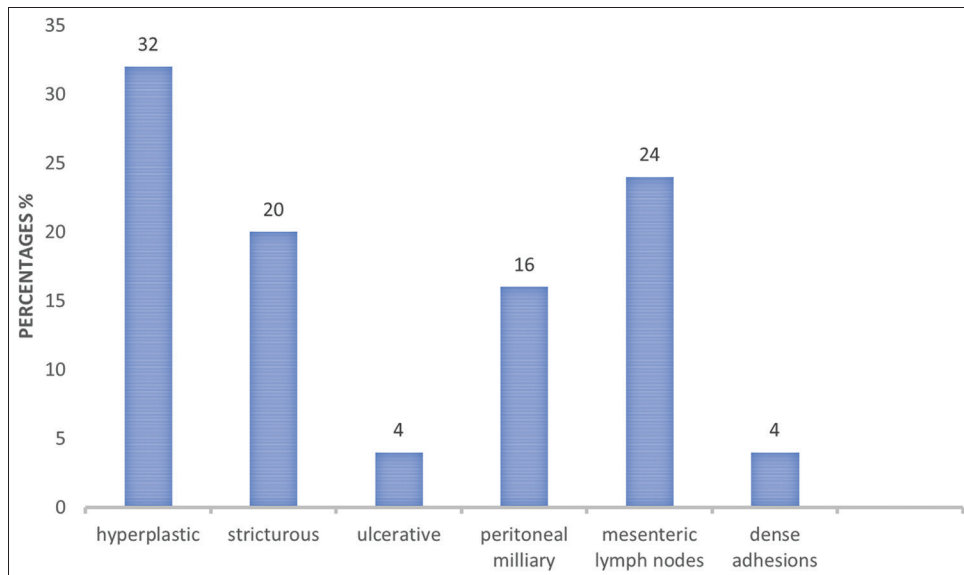


Figure 2: Types of lesions

Follow-up was done in all cases. Follow-up schedule was like, every 15 days visit for initial 3 months, then every month for a year. In follow-up visit, patients were inquired about symptoms, any post-operative complaints, duration, and regularity of AKT. Any change in weight, appetite, and general condition were noted along with hemoglobin and ESR values.

Patient conditions were classified under the following headings:

- Well = No complaints
- Improved = Overall improvement in symptoms, weight gain, good appetite, good and general conditions but some vague, inconstant abdominal symptoms revealed only when interrogated carefully
- Not improved = Little benefit from operation.

In our series, 20 patients became well accounts for 80% while 5 patients (20%) were improved with treatment. In our series, there was not any patient with no improvement.

## CONCLUSIONS

Koch's abdomen is a clinical entity with varied clinical presentations. It is widely prevalent in developing country like India and most often present with complications. It's quite crucial for clinicians to rule out Koch's abdomen from other conditions who can mimic with it. Most of the patients are cured with conservative treatment with anti-TB drugs. Surgery is required in case of complications occurred. No drug resistance has been found in this study.

Investigations play a major role in establishing the diagnosis and treating the patients.

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# A Prospective Study on Outcome of Transnasal Endoscopic Repair of Cerebrospinal Fluid Rhinorrhea

A Shahul Hameed<sup>1</sup>, R T Abdul Salam<sup>2</sup>, K Shilpa Nair<sup>3</sup>

<sup>1</sup>Additional Professor, Department of ENT, Government Medical College, Calicut, Kerala, India, <sup>2</sup>Associate Professor, Department of ENT, Government Medical College, Calicut, Kerala, India, <sup>3</sup>Senior Resident, Department of ENT, Government Medical College, Calicut, Kerala, India

## Abstract

**Background:** Cerebrospinal fluid (CSF) rhinorrhea is the result of an osseous defect in the skull base coupled with a disruption of dura mater and arachnoid mater with a resultant pressure gradient, leading to CSF leak. CSF leak can be categorized into spontaneous (idiopathic), traumatic, and non-traumatic. Endoscopic transnasal approach is an extracranial approach which has the advantage of being less invasive, no external scar, excellent site localization with preservation of the surrounding anatomy, and shorter hospital stay.

**Aim of the Study:** The aim of the study was to assess the outcome of repair, cause, site of leak, and efficacy of materials used for the repair, elucidate the advantages of endoscopic approach.

**Materials and Methods:** A total of 25 patients with CSF rhinorrhea arising from anterior and middle cranial fossa not subsiding with medical management were included in this prospective study. Patients of all ages and gender were included in the study. Patients with recent history of meningitis were excluded from the study. All the patients were evaluated for CSF rhinorrhea using battery of tests including clinical examination for reservoir sign, biochemical and microbiological analysis of fluid, radiological investigations, and diagnostic nasal endoscopy to assess the site of leak. The demographic data, CSF leak site and size, etiology, complications, surgical closure techniques, complications of surgery, and recurrences and its management were observed and recorded. All the data were analyzed using standard statistical methods.

**Observation and Results:** Among the 25 patients, 14/25 (56%) patients were aged below 30 years followed by 11/25 (44%) patients who were aged between 30 and 60 years. The mean age was  $34.20 \pm 2.35$  years. 16/25 (64%) patients were female and 9/25 (36%) patients were male. 22/25 patients (88%) had spontaneous leaks and 3 patients (12%) had traumatic leaks. In 18/25 (72%) of the patients, the site of leak was in the cribriform plate, 4/25 (16%) from fovea ethmoidalis, 2/25 (8%) from the sphenoid, and 1/25 (4%) from the frontal sinus. Immediate post-operative results were observed in 23/25 (92%) of the patients and there was no CSF leak. 2/25 (8%) patients had CSF leak for 10 days which later subsided.

**Conclusions:** The most common etiology of CSF rhinorrhea was spontaneous, most common site being the cribriform plate. Autologous fat graft was used as the first layer of underlay technique in most of the cases which act as a good sealant. The efficacy of transnasal endoscopic CSF leak repair in our study was found to be 100%, and it is a highly successful and safe procedure.

**Key words:** Cerebrospinal fluid, Cerebrospinal fluid rhinorrhea, Cisternogram, Spontaneous leak, Transnasal endoscopic repair

## INTRODUCTION

Cerebrospinal fluid (CSF) is a clear, colorless fluid present in ventricles, cisterns, and subarachnoid space around the brain

and spinal cord. An average of 500 ml/day is produced mainly by choroid plexus and absorbed back through arachnoid villi.<sup>[1]</sup> Any mismatch paranasal sinus leading between production and absorption leads to increased intracranial pressure and CSF pressure. CSF rhinorrhea occurs when an osseous defect in the skull base with a disruption of dura mater and arachnoid resulting a communication of subarachnoid space to nose and paranasal sinus, leading to CSF leak.<sup>[2]</sup> CSF leak can be categorized into spontaneous (idiopathic), traumatic, and non-traumatic. Traumatic may be accidental or iatrogenic. Non-traumatic can be due to hydrocephalus, tumors, congenital

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**Corresponding Author:** Dr. R T Abdul Salam, Department of ENT, Government Medical College, Calicut - 673 008, Kerala, India.

defects, etc. About 70–80% of CSF rhinorrhea is caused by accidental trauma.<sup>[3]</sup> Due to adherence of dura mater to bone in the region of anterior skull base, fracture often results in dural tear and CSF leak, mostly in fovea ethmoidalis, and posterior wall of frontal sinus. Common sites of leak after sinus surgeries are cribriform plate and fovea ethmoidalis.<sup>[4]</sup> The postulations regarding spontaneous leak are focal atrophy,<sup>[1]</sup> persistence of embryonic lumen in the cribriform area, and intracranial hypertension. Hyperpneumatization of paranasal sinuses has a risk of spontaneous leak, particularly in lateral recess of sphenoid sinus.<sup>[5]</sup> Spontaneous healing of dura mater is interfered by herniation of meninges (meningocele) or with brain (meningoencephalocele). Most traumatic leaks heal within 7–10 days with conservative measures such as bed rest, head end elevation, avoidance of straining, nose-blowing, and use of laxative.<sup>[6]</sup> Antibiotics were also given to prevent meningitis and facilitate healing. CSF rhinorrhea developing few days or weeks after a trauma and spontaneous leaks is less likely to heal, so surgical closure is mandatory. Surgical management of CSF rhinorrhea can be intracranial or extracranial approaches. Endoscopic transnasal approach is an extracranial approach which has the advantage of being less invasive, no external scar, excellent site localization with preservation of the surrounding anatomy, and shorter hospital stay. Excessive mobilization and injury of brain and dura mater are avoided and offer wide and site-specific view through a smaller exposure than that achieved through a microscope. The aim of the present study was to assess the outcome of repair, cause, site of leak, and efficacy of materials used for the repair, elucidate the advantages of endoscopic approach.

## MATERIALS AND METHODS

The present study included 25 patients with CSF rhinorrhea arising from anterior and middle cranial fossa not subsiding with medical management. This prospective study was done from January 2016 to June 2017 in the ENT Department of Government Medical College, Calicut.

### Inclusion Criteria

1. Patients of all ages and gender were included
2. Patients with CSF rhinorrhea not responding to medical treatment were included
3. Patients with spontaneous CSF rhinorrhea were included.

### Exclusion Criteria

1. Patients with recent history of meningitis were excluded
2. Patients with acute renal, cardiovascular, or hepatic dysfunctions were excluded. All the patients were evaluated for CSF rhinorrhea using battery of tests including clinical examination for reservoir sign, biochemical and microbiological analysis of

fluid, radiological investigations, and diagnostic nasal endoscopy (DNE) to assess the site of leak. Spontaneous cases were evaluated by neurologist and ophthalmologist to rule out intracranial causes and benign intracranial hypertension. Patients who did not respond with medical management for a period of 6 weeks and those with smaller defects were taken for surgery. The demographic data, CSF leak site and size, etiology, complications, surgical closure techniques, complications of surgery, and recurrences and its management were observed and recorded. All the data were analyzed using standard statistical methods.

## OBSERVATION AND RESULTS

A total of 25 patients undergoing CSF rhinorrhea repair using transnasal approach for repair of the leak were included in this study. 14/25 (56%) patients were aged below 30 years followed by 11/25 (44%) patients who were aged between 30 and 60 years. The youngest patient was aged 3 years and the eldest patient was aged 84 years. The mean age was  $34.20 \pm 2.35$  years.

16/25 (64%) patients were (64%) female and 9/25 (36%) patients were male [Table 1]. 15/25 (60%) patients CSF leak from the right side of the nasal cavity. 10/25 (40%) of the patients had a left-sided CSF leak.

All the patients were presented within a period of 6 months since the onset the leak. All patients had intermittent leaks and 20/25 (80%) patients had active leak during examination. 4/25 (16%) patients had hypothyroidism. 2/25 (8%) patients had dyslipidemia. 22/25 patients (88%) had spontaneous leaks and 3 patients (12%) had traumatic leak and one of these was iatrogenic in nature and not detected intraoperatively [Table 2].

**Table 1: The age and gender incidence among the study sample (n=25)**

Age group (%)	Male-9(%)	Female-16(%)	Mean age in years
Below 30 years (14-56)	5 (20)	9 (36)	24.70±1.40
Above 30 years (11-44)	4 (16)	7 (28)	

**Table 2: The type of CSF leaks observed in the study (n=25)**

Observations	Male	Female
Spontaneous leak-22	7	15
Traumatic leak-3	2	1
Intermittent leak-20	8	12
Active leak-5	1	4
Iatrogenic leak-1	1	0



21/25 (84%) patients were evaluated with high-resolution computed tomography (HRCT) and magnetic resonance imaging (MRI). 4/25 patients (16%) were evaluated with computed tomography (CT) cisternogram. In 18/25 (72%) of the patients, the site of leak was in the cribriform plate, 4/25 (16%) from fovea ethmoidalis, 2/25 (8%) from the sphenoid, and 1/25 (4%) from the frontal sinus [Table 3].

In 16/25 (64%) patients, the defect size was 2–5 mm, 7/25 (28%) of the patients had defect measuring <2 mm, and in 2/25 (8%) patients, the defect was measuring 5–8 mm [Table 4].

The graft materials used were as follows: Fat + fascia lata in 4/25 (16%) patient; fat + fascia + Hadad flap was used in 6/25 (24%) patients, underlay fascia + fat + overlay fascia in 2/25 (8%), fascia + Hadad flap was used in 2/25 (8%) of the patients, and fat + Hadad flap was used in 11/25 (44%) patients. Tissue sealant was used in all the patients to close the rent and to stabilize the graft [Table 5].

Immediate post-operative results were observed in 23/25 (92%) of the patients and there was no CSF leak. 2/25 (8%) patients had CSF leak for 10 days which later subsided. All the patients received post-operative IV antibiotics for 10 days. 2/25 (4%) of the patients received antibiotics for 15 days. Outcome of repair after 6 months follow-up by DNE showed no leak (0%), i.e., 100% success rate. No statistical significance among age group and etiology was noted. 14/25 (56%) of the patients with CSF leak were spontaneous type in females. 14/25 (56%) of the patients were of normal weight and body mass

**Table 3: The site of cerebrospinal fluid leaks (n=25)**

Gender	Cribriform plate-18	Fovea ethmoidalis-4	Sphenoid-2	Frontal sinus-1
Male-16	15	1	0	0
Female-9	3	3	2	1

**Table 4: The size of defects in the bone in cerebrospinal fluid rhinorrhea patients (n=25)**

Gender	<2 mm-16	2-5 mm-7	6-8 mm-2
Male-9	3	4	2
Female-16	13	3	0

**Table 5: The types of flaps used in the study (n=25)**

Types of flaps used	Male-9	Female-16
Fat+fascia lata-4	1	3
Fat+fascia+Hadad flap-6	1	5
Underlay fascia+fat+overlay fascia-2	2	0
Fascia+Hadad flap-2	1	1
Fat+Hadad flap-11	4	7

index (BMI), and 7/25 (28%) of them were overweight and BMI above 37 and all of them were found to have spontaneous leaks. The most common site of spontaneous leak was in cribriform plate which was correlating with the radiological findings.

## DISCUSSION

In this study, 25 patients with CSF rhinorrhea were treated by endoscopic surgical approach after failed medical management. The sociodemographic and clinical data were studied and analyzed to determine the common sites of CSF leak presented with various etiologies. The study also analyzed various materials used for the defect closure, elucidating our experience of CSF leak closure intraoperatively and postoperatively and the efficacy of endoscopic closure of skull base defects. Banks *et al.*,<sup>[7]</sup> McMain *et al.*,<sup>[8]</sup> Jain *et al.*,<sup>[9]</sup> Lanza *et al.*,<sup>[10]</sup> all similarly analyzed the etiology, site of leak, and graft material used. Majority were in age between 20 and 30 years. Twenty-two were spontaneous cases (similar to Singh *et al.*<sup>[11]</sup> and Sanna Reddy)<sup>[12]</sup> and three had a history of trauma, in which one was iatrogenic. In the present study, trauma was not common as the cause of CSF leak, they were conservatively for 6 weeks and only failed cases were selected for surgery. Among the spontaneous CSF leak patients, there were 14 females and 8 males. Virk *et al.*,<sup>[2]</sup> in his study, also observed more females (75%) than males with spontaneous leaks. Regarding comorbidities, two patients with dyslipidemia and four with hypothyroidism and all are among spontaneous leaks. HRCT and MRI were the mainstay of radiological evaluation in this study in our institution as a protocol in 84% of patients. 4/25 (8%) patients were evaluated by HRCT and CT cisternogram as they were referred from other centers for management. The study by Ismail *et al.*<sup>[3]</sup> and Lloyd *et al.*<sup>[13]</sup> describes the use of combined CT and MRI quotes the sensitivity of detecting the CSF leak 97% using this modality. The use of CT cisternogram was reserved for cases with low flow leaks where the previous imaging has failed to localize site of leak as according to Psaltis *et al.*<sup>[14]</sup> In two patients, it was observed on MRI that there were empty sellae in females presented with spontaneous leak. It was also observed that in all cases of trauma, the CSF leak was associated with meningocele through the defect which probably delayed and prevented spontaneous closure. Cribriform plate was the common site of leak (72%) seen closely associated with spontaneous etiology followed by fovea (16%). This observation was similar to data published by Virk *et al.*<sup>[2]</sup> and Singh *et al.*<sup>[11]</sup> In five cases, difficulty in locating the defect was encountered, where intrathecal fluorescein was injected to identify the site of leak, similar to Lanza *et al.*<sup>[10]</sup> 16/25 (64%) of the patients had bony defect of the



size between 2 mm and 5 mm (mean value 3.2 mm) and the largest defect was 8 mm in posterior table of frontal sinus. A correlation was obtained intraoperatively with radiological findings of HRCT and MRI in 21/25 (84%) patients. All the 4/25 (8%) patients who underwent CT scan and cisternogram were also correlating with the operative findings. Fat was the most common material, placed in dumbbell fashion, and used in 16 (64%) cases reinforced by Hadad flap, tissue sealant, and surgical. Fascia lata was used as overlay in 14 cases. Gendeh *et al.*,<sup>[14]</sup> Kirtane *et al.*,<sup>[15]</sup> and Sannareddy *et al.*,<sup>[12]</sup> all used mainly fat and fascia lata in their series. Fibrin sealant was also used in this study to seal the defect in the bone in addition to soft tissue, similar to the author Sannareddy *et al.*<sup>[12]</sup> The largest defect in the posterior wall of frontal sinus was approached by a combined approach externally and transnasally with endoscope. It was closed by a sandwich technique of placing fascia lata as underlay, fat in between, and another fascia lata as overlay. None of the patients in this study had lumbar drain during the procedures. All patients were advised strict bed rest, propped position, and advised to avoid any form of strain. Intravenous antibiotics, anti-edema measures, and antiepileptic drugs were given for minimum of 7 days. Two patients had CSF leak on the 3<sup>rd</sup> post-operative day after removal nasal pack, it is assumed to be the collected fluid in nasal cavity or due to slight rise in intracranial pressure while the wound was still healing, and no leak was noticed after the 5<sup>th</sup> day. There were no complications during our follow-up period and none had any evidence of leaks in follow-up DNE after 6 months. Similar observations were reported by Hegazy *et al.*,<sup>[6]</sup> who published a meta-analysis revealing that graft material type does not affect success rates when good surgical technique is employed. From literature, the results from endonasal endoscopic repair of CSF fistulas are exceptional, with published success rates ranging from 92% to 98% in large retrospective reviews.<sup>[8,7,10,12,15]</sup> The success rate was 100% in the present study, but it might be due to the small number of subjects observed.

## CONCLUSIONS

The most common etiology of CSF rhinorrhea was spontaneous, most common site being the cribriform plate. Autologous fat graft was used as the first layer of

underlay technique in most of the cases which act as a good sealant. The use of autologous fascia lata graft was also found equally effective. Both of the above materials were reinforced with a nasoseptal flap and tissue seal and supported by fascia. The method of closure may vary, but identification of the site of leak and plane between dura mater and bone around the defect is an important determinant of the success of procedure than the choice of materials. The efficacy of transnasal endoscopic CSF leak repair in our study was found to be 100%, and it is a highly successful and safe procedure.

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# A Prospective Observational Study on Retinopathy of Prematurity in Low Birth Weight Babies at a Tertiary Care Centre of West Bengal

Pampa Halder<sup>1</sup>, Sabyasachi Sinha<sup>2</sup>, Manas Bandyopadhyay<sup>3</sup>

<sup>1</sup>Assistant Professor, Department of Ophthalmology, R.G Kar Medical College, Kolkata, West Bengal, India, <sup>2</sup>Resident, Department of Ophthalmology, R.G Kar Medical College, Kolkata, West Bengal, India, <sup>3</sup>Professor, Department of Ophthalmology, R. G. Kar Medical College, Kolkata, West Bengal, India

## Abstract

**Aims:** The aim of the study was to know the prevalence, severity, and progression of retinopathy of prematurity (ROP) among the screened low birth weight (LBW) and preterm babies and to determine how many of these babies require treatment.

**Methods:** Prospective, observational study was done between August 2018 and March 2019. Screening for the presence of ROP and its severity in 588 eyes of 294 infants below 2000 g birth weight and/or period of gestation <34 weeks in Special Newborn Care Units. The retinal findings were documented and staging of ROP was determined, based on the International Classification of ROP guidelines. Further follow-up and treatment were done accordingly.

**Results:** In our study, 14.28% of the total numbers of babies screened were found to have different stages of ROP and 6.5% of the total number needed treatment. Among babies with birth weight above 1250 g, screening of 418 eyes of 209 babies was done, of which 28 eyes of 14 babies were diagnosed as ROP (6.7%). Of which 12 babies received oxygen and 4 babies (8 eyes) required treatment. Among babies with  $\leq 1250$  g body weight, screening of 170 eyes of 85 babies was done, of which 56 eyes of 29 babies developed ROP (33%), of which 25 babies received oxygen and 15 babies (30 eyes) required treatment such as laser photocoagulation and intravitreal ranibizumab.

**Conclusion:** ROP is emerging as one of the leading causes of irreversible childhood blindness, if not diagnosed and treated early. As very LBW babies are increasingly surviving because of the ever-improving perinatal care, the prevalence of ROP is also increasing. That's why regular ocular screening and timely intervention of those babies are to be done to prevent permanent blindness. Moreover, the magnitude of the problem in this part of our country will enable us to prepare our infrastructure to tackle it.

**Key words:** Childhood blindness, low birth weight, retinopathy of prematurity

## INTRODUCTION

Retinopathy of prematurity (ROP) is emerging as one of the leading causes of preventable childhood blindness in India. Incidence of ROP varies between 38 and 51.9% in low birth weight (LBW) infants.<sup>[1,2]</sup> It is an ischemic retinopathy of premature and LBW infants. Normal retinal vascularization proceeds from the optic disc to the periphery and is complete in the nasal quadrants at approximately 36 weeks of gestation

and on the temporal side at 40 weeks. Although an important contributing factor, oxygen is no longer considered the sole factor in the pathogenesis of ROP. Other factors, such as genetic predisposition, LBW, and a short gestational period, also increase the risk of developing the disease. Clinically, vascularized retina in the premature infant without ROP normally blends almost imperceptibly into the anterior, grey, non-vascularized retina. With ROP, however, the juncture between the two becomes more distinct due to variable glial hyperplasia, shunts, and neovascularization leading to vitreous hemorrhage, tractional retinal detachment, and loss of vision.

Prematurity is the single most important risk factor responsible for ROP. ROP begins to develop between 32 and 34 weeks after conception, regardless of gestational

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**Corresponding Author:** Dr. Pampa Halder, Department of Ophthalmology, R. G Kar Medical College, Kolkata, West Bengal, India.

age at delivery.<sup>[3]</sup> Incidence of ROP in India varies between 38% and 51.9% in LBW infants, but more recent studies showed lower incidence ranging from 20% to 30%.<sup>[4]</sup>

## Aims and Objectives

### General objective

To screen all LBW and preterm infants admitted at Special Newborn Care Units (SNCU) and NICU and who were referred for ROP screening within August 2018–March 2019 (approximately 6 months) at R. G. Kar Medical College of Kolkata.

### Specific objective

The specific objective of the study was:

1. To know the prevalence of ROP among the LBW babies in a tertiary care center of Kolkata, who are screened for it (criteria suggested by National Programme for Control of Blindness,<sup>[5]</sup> National Neonatology Forum and Neonatal Intensive Care Unit (NICU), and AIIMS, New Delhi)<sup>[6]</sup>
2. To determine the severity and progression of ROP among these babies
3. To know the distribution of the disease varying with the birth weight of these babies
4. To know the prevalence of the disease among those babies who received oxygen supplementation by any means
5. To determine how many of these babies require treatment (laser, intravitreal injection of anti-vascular endothelial growth factor (VEGF), or vitreoretinal surgery).

## METHODOLOGY

### Study Design/Experimental Design

This was a prospective observational study.

### Place of Study

This study was conducted at SNCU and NICU of R. G. Kar Medical College of Kolkata.

### Period of Study

The study was from August 2018 to March 2019 (8 months).

### Study Population

Infants below 2000 g birth weight and/or period of gestation (POG) <34 weeks and infants with unstable postnatal clinical course, attended for ROP screening in SNCU of a tertiary care center of Kolkata.

### Sample Size

A total of 588 eyes of 294 babies, who attended for ROP screening in SNCU, of a tertiary care center of Kolkata, from September 2018 to February 2019.

## Inclusion and Exclusion Criteria

### Inclusion criteria

The following criteria were included in the study:

1. Birth weight <2000 g
2. Gestational age <34 weeks
3. Gestational age between 34 and 36 weeks but with risk factors such as cardiorespiratory support, prolonged oxygen therapy, respiratory distress syndrome, chronic lung disease, fetal hemorrhage, blood transfusion, neonatal sepsis, exchange transfusion, intraventricular hemorrhage, apnea, and poor postnatal weight gain
4. Infants with an unstable clinical course who are at high risk (as determined by the neonatologist).

### Exclusion criteria

Fulfilling inclusion criteria but babies severely sick to examine were excluded from the study.

### Study Variables

Babies with ROP, without ROP, stages of ROP, gender, birth weight, POG, postnatal exposure to oxygen supplementation, and requirement of treatment for ROP.

### Procedure

#### Ocular examination and investigation

1. Consent form and case record form
2. Indirect ophthalmoscope with +20 D lens
3. Alfonso eye speculum for newborn and wire vectis
4. 50% dilution of a combination of 5% phenylephrine and 0.8% tropicamide eye drop
5. Proparacaine eye drops 0.5%, normal saline eye drops, and moxifloxacin eye drops
6. Gauge soaked with 25% dextrose as pacifier.

### Outcome Definition and Parameters

The retinal findings should be documented and stage of the ROP to be determined based on the International Classification of ROP guidelines.<sup>[7]</sup>

Follow-up based on retinal findings, according to AIIMS-NICU protocols (2010).

Findings that suggest further examinations are not needed include:

- Zone III retinal vascularization attained without previous Zone I or II ROP
- Full retinal vascularization Postmenstrual age of 45 weeks and no pre-threshold disease (defined as Stage 3 ROP in
- Zone II, any ROP in Zone I) or worse ROP is present
- Regression of ROP.

### Treatment

1. All eyes with plus disease
2. Eyes without plus disease having new extraretinal

vessels (Stage 3), especially if the condition has worsened since the previous visit

3. Aggressive posterior ROP (APROP) eyes urgently and aggressively (involves Zone I and posterior Zone II).

#### No treatment

All eyes with ROP in Zone III; Eyes with Zone II with no new vessels and no plus. They should be followed closely, every 7–10 days, to watch for regression or progression of disease and if any treatment is needed.<sup>[8]</sup>

Treatment options including intravitreal anti-VEGF, laser photocoagulation.<sup>[9]</sup>

#### Data Collection and Interpretation

After taking clearance from the Ethical Committee the study was performed. The consent form was signed by one or both of the parents of the infant. Case record sheet was filled up after examination. A thorough ophthalmological evaluation was done under neonatal monitoring. The data collected were studied, analyzed and compared by suitable statistical method.

#### Statistical Analysis

The data were tabulated in Microsoft Excel sheet and presented as tables and bar charts and interpreted by SPSS Version 20 and excel (by student *t*-test, Chi-square tests, and Mann-Whitney U test).

## RESULTS

Babies fulfilling criteria for screening of ROP were examined, followed up, and treated as per schedule under proper aseptic condition and neonatal care.

#### Prevalence of ROP among Different POG Group

We divided our study population in three group based on POG, i.e.: <32 weeks, 32–<34 weeks, and 34–<40 weeks, and there were 109 babies in the first group, 120 in second, and 65 in last one. Prevalence of ROP was 27% in <32 weeks of POG, 7.9% in 32–<34 weeks of POG, and 4.6% in 34–<40 weeks of POG. Table 1 shows most of the ROP are found in less than 32 weeks of POG.

#### Prevalence of ROP among Different Birth Weight Group

According to birth weight, we divide our study population into four group:

There were 30 babies in the first group, 55 in Group 2, 149 in Group 3, and 60 babies in last group. The prevalence of ROP was 53% in first group, 22.2% in second, 6.7% in third, and 6.5% in last group. Table 2 shows most of the ROP occurred in less than 1kg weight babies.

Of total 294 babies, 149 babies were female and 145 were male.

Moreover, findings of 4 babies were APROP.

Of total 294 babies, 160 babies received oxygen by any means (face mask, continuous positive airway pressure, ventilation, etc.) and 134 babies not received oxygen irrespective of birth weight and POG. Table 3 confirms that exposure to oxygen is a risk factor for ROP.

Hence, the risk ratio is 5.1646 for developing ROP in babies with history of postnatal oxygen therapy.

A number of babies defaulted during the study period:

- A total of 48 babies were lost to follow-up of 294 babies within the study period (16.3%), of which, findings of 4 babies with Stage 2 Zone II or III and 6 babies with large temporal avascular retina and rest were no ROP.
- A total of 20 babies died of different postnatal complications.
- In this study, 38 eyes of 19 babies of 588 eyes of 294 babies required treatment for ROP.

**Table 1: Distribution of ROP in different POG group**

POG (in week)	Eyes examined	Eyes with ROP	Frequency (%)
<32	218	59	27
32–<34	240	19	7.9
34–<40	130	6	4.6
Total	588	84	14.28

ROP: Retinopathy of prematurity, POG: Period of gestation

**Table 2: Distribution of ROP in different birth weight group**

Birth weight	Eyes examined	Eyes with ROP	Frequency (%)
≤1000	60	32	53
1001–≤1250	110	24	22.2
1250–≤1500	298	20	6.7
>1500	120	8	6.5
Total	588	84	14.28

ROP: Retinopathy of prematurity

**Table 3: Comparison between development of ROP with postnatal oxygen therapy**

Exposure to oxygen	ROP	No ROP
Yes	37	123
No	6	128

ROP: Retinopathy of prematurity

**Table 4: Number of babies required treatment**

Birth weight	No of babies required treatment
≤1250 g	15 (30 eyes)
>1250 g	4 (8 eyes)



Table 4 shows most of the eyes requiring treatment are below 1250 gm in birth weight. Hence, 44.2% babies with ROP needed treatment irrespective of birth weight and POG.

## DISCUSSION

Within the 8 months of the study period, over 294 babies were screened for ROP. A total of 48 babies were lost for follow-up and 20 were died after first examination. Hence, all babies were included in the study population and statistical calculation.

Of all LBW babies, 204 babies were very LBW (1001 to  $\leq 1500$  g), and 30 were extremely LBW baby ( $\leq 1000$  g).

According to POG, 13 babies were extremely preterm ( $<28$  weeks), 96 babies were very preterm ( $<32$  weeks), 120 babies were late preterm ( $<34$  weeks), and remaining 65 babies were term.

The prevalence of ROP among our study population was 14.28% (84 eyes of 588 eyes). Whereas a study was done on “incidence and severity of ROP in China”<sup>[10]</sup> by Xu *et al.* in 2010–2012, they found incidence of ROP in China was 17.8%.<sup>[11]</sup> It is also noted that the prevalence of ROP in Saudi Arabia was 33.7% in 2016 (mean POG - 26.7 and mean birth weight 843 g).<sup>[12]</sup> In Egypt, 36.5% in 2016 (mean POG - 31.3 week and mean birth weight - 1234.6 g).<sup>[13]</sup> In Pakistan, 11.5% in 2014 in infants meeting the current screening criteria of Pakistan.<sup>[14]</sup> In India recent studies reported that the prevalence of ROP ranging from 20% to 30%.<sup>[4,10]</sup>

Incidence of ROP in this study, among extremely LBW babies were 53.3% (32 eyes of 60 eyes) and very LBW babies 10.8% (44 eyes of 408 eyes). In a study on “prevalence of ROP” done by Ali *et al.*, they found much higher prevalence of ROP in extremely LBW babies (86.7%) than very LBW babies (27.8%).<sup>[15]</sup>

It was also noted that the prevalence of ROP in Hong Kong – 16.9% (mean birth weight – 1285 g) and 70.6% (in babies whose birth weight were  $<1000$  g).<sup>[16]</sup>

Incidence of ROP in our study was 32.9%, among those birth weight  $\leq 1250$  g (56 eyes of 170 eyes) and 6.7% among those birth weight  $>1250$  g (28 eyes of 418 eyes).

In the Indian scenario, more than 50% of preterm infants weighing  $<1250$  g at birth show evidence of ROP.<sup>[17]</sup>

Oxygen therapy, by any means, is a risk factor for the development of ROP, (ROP is 5.16 times more associated with oxygen therapy).

Chaudhari *et al.* done a study on ROP in 2009 where the incidence of ROP was 22.3% among babies gestational age  $\leq 32$  weeks or birth weight  $<1500$  g or babies with significant perinatal illness and they also found that postnatal oxygen therapy is a significant risk factor for development of ROP.<sup>[4]</sup>

In our study, 44.2% babies with ROP needed treatment whereas, 39.3% babies with ROP needed treatment in a study done by P. Sharma in 2009 among infants with birth weight  $\leq 1500$  g or gestational age  $\leq 32$  week.

As a significant portion of study population defaulted (16.3%), we have to improve our peripheral infrastructure and awareness of the people by IEC (Information, Education, Communication) activities so that we can screen all the babies where it is needed.

## CONCLUSION

In our study, though in a small study population, 14.28% of the total numbers of babies screened were found to have different stages of ROP and 6.5% of the total number needed treatment. Timely screening of those babies averted permanent blindness in them. That's why regular ocular screening and timely intervention is required, especially for severely LBW babies to prevent permanent blindness. The infrastructure in the peripheral regions of our country is needed to be improved to tackle this significant and emerging cause of childhood blindness. Moreover, we should be concerned among the significant number of the defaulter group (16.3%) and should try to increase the awareness of the disease and importance of regular screening among the mothers and other family members.

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# Refractory Allergic Fungal Sinusitis and its Medical Management in a Tertiary Hospital

M Ravikumar<sup>1</sup>, Benhur Benraj Kommu<sup>2</sup>, P Lavanya<sup>2</sup>

<sup>1</sup>Associate Professor, Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, India, <sup>2</sup>Junior Resident, Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, India

## Abstract

**Background:** Allergic fungal sinusitis (AFS) is the most common form of fungal sinus disease with a high rate of recurrence rate despite the advent of advanced endoscopic sinus surgery and usage of steroids. Refractory AFS is defined as a condition of allergy due to fungal antigenic elements not amenable to surgical removal or prolonged medical management. Oral itraconazole is an antifungal agent that seems to be benefit to the patients with refractory AFS. Hence, this study was conducted to compare the outcome of AFS after addition of oral itraconazole to the treatment protocol.

**Aim of the Study:** The aim of the study was to evaluate the acceptance and usefulness of itraconazole, an oral antifungal drug, in the treatment of refractory AFS.

**Materials and Methods:** A total of 84 patients with refractory AFS were included in this study. The medical records of these patients were retrieved from the medical records section and analyzed. A detail history of the AFS was elicited and demographic data were tabulated. Nasal endoscopy was done before and 3 months after the itraconazole therapy and the findings were classified according to Lund-Kennedy endoscopic grading system, Scoring from 7 to 10 was graded as severe; scoring from 4 to 6 was graded as moderate and 1 to 3 as mild grade. Itraconazole was administered in the form of capsule 100 mg 2 times daily for 3 months. Prior hepatic function and renal function tests were undertaken for all the patients. All the data were analyzed using standard statistical methods.

**Observations and Results:** Among the 84 patients, there were 52 (61.90%) males and 32 (38.09%) females with a male to female ratio of 1.6:1. The patients were aged between 18 years and 78 years with a mean age of  $33.45 \pm 4.15$  years. Conversion of severe grade patients to mild grade following itraconazole therapy was noted; post-treatment findings were severe in 5 patients, moderate in 1, and mild in 78 patients.

**Conclusions:** Itraconazole may be useful as an adjunct in the management of AFS. However, more studies, including a prospective randomized clinical trial, are required to determine if itraconazole is effective in the management of AFS.

**Key words:** Allergic fungal sinusitis, Functional endoscopic sinus surgery and allergy, Refractory Allergic fungal sinusitis, Rhinosinusitis

## INTRODUCTION

The allergic fungal sinusitis (AFS) is defined as an allergic disease of the nasal cavity and paranasal sinuses triggered by fungal antigen and clinically characterized by polyposis; stringy allergic mucin and rhinorrhea. Its pathogenesis is due to atopy, continuous antigenic exposure, and inflammation all playing their roles in the perpetuation

of the disease. AFS is prevalent worldwide for the past two decades. The fungal species commonly believed to be involved are aerosolized environmental fungi of the dematiaceous species in an immunocompetent host.<sup>[1,2]</sup> The patients with AFS have previous history of allergic rhinosinusitis. Nearly 7–12% of patients affected by chronic rhinosinusitis actually carry a diagnosis of (AFS). The prevalence of AFS is also impacted by geographic factors; literature shows the majority of sites reporting cases of AFS to be located in temperate regions with relatively high humidity.<sup>[3]</sup> In view of the complicated pathophysiology of AFS a wide variety of management plans are being used such as certain major and minor criteria are used to define and diagnose AFS, endoscopic surgical removal of the disease from the sinuses by

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**Corresponding Author:** Dr. M Ravikumar, Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, India.

exploration and supportive medical treatment using steroids, immunotherapy, and antifungal chemotherapeutic agents.<sup>[4,5]</sup> Any attempt to control this disease by not or partially treating the underlying causes is likely that the patients would have a high rate of residual disease resulting in refractory AFS.<sup>[6,7]</sup> Hence, successful treatment of AFS consists of a treatment plan to account for each of the factors responsible for the establishment of the disease which would result in the best chance of long-term disease control. This multipronged approach to eradicate the AFS consists of complete removal of all fungal mucin (usually requiring surgery) and long-term prevention of recurrence through either immuno-modulation (immunotherapy and/or corticosteroids) or fungistatic antimicrobials. In addition, one has to consider various related issues in such an approach such as (1) as there are different forms of fungal sinusitis, and each requires a specific therapeutic regimen, targeted at the pathogen, (2) antifungal agents induced hepato- and neurotoxicity should be addressed, and (3) The cost factor should be kept in mind while prolonged usage is required; many newer antifungal drugs are extremely expensive. (4) There are a very few randomized controlled trials which able to validate various studies.<sup>[8,9,10]</sup> Itraconazole inhibits the cytochrome P-450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes. Bent and Kuhn<sup>[11]</sup> showed that many of the fungi in AFRS have *in vitro* susceptibility to itraconazole. They include *Aspergillus*, *Bipolaris*, *Alternaria*, and *Curvularia*. In this context, the present study was conducted to evaluate the acceptance and usefulness of itraconazole, as an oral antifungal drug in addition to steroid therapy, in the treatment of refractory AFRS.

## MATERIALS AND METHODS

A total of 84 patients attending the outpatient department of Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, were included in this study. The medical records of these patients were retrieved from the medical records section and analyzed. An Institutional Ethical Clearance was obtained before commencement of the study.

### Inclusion Criteria

1. Patients diagnosed with refractory AFS were included in the study
2. Patients of all age groups were included in the study
3. Patients of both genders were included in the study.

### Exclusion Criteria

1. Patients who are immuno-compromised are not excluded from the study
2. Patients with acute hepatotoxicity or renal toxicity were excluded from the study

3. Patients with recent history of functional endoscopic surgery were excluded from the study.

All the patients diagnosed as refractory AFS alone were included, and detail history taking and demographic data were tabulated. Before starting the itraconazole diagnostic nasal endoscopy was done to grade the mucosal disease of the nasal cavity and paranasal sinuses. They were graded based on Lund-Kennedy endoscopic grading system<sup>[12]</sup> [Table 1]. Scoring from 7 to 10 was graded as severe; scoring from 4 to 6 was graded as moderate and 1 to 3 as mild grade. Similarly, at the end of 3 months trial with itraconazole nasal endoscopy was done to observe the effectiveness of treatment. Itraconazole was administered in the form of capsule 100 mg 2 times daily for 3 months. Prior hepatic function and renal function tests were undertaken for all the patients. All the data were analyzed using standard statistical methods.

## OBSERVATIONS AND RESULTS

Among the 84 patients, there were 52 (61.90%) males and 32 (38.09%) females with a male to female ratio of 1.6:1. The patients were aged between 18 years and 78 years with a mean age of  $33.45 \pm 4.15$  years. The youngest patient was age 19 years, and the eldest patient was aged 64 years. The demographic data were analyzed and tabulated in Table 2. There was no statistical significance in the correlation of the observations with incidence of refractory AFS data studied.

Using Lund-Kennedy endoscopic grading system,<sup>[12]</sup> the pre-treatment endoscopic findings and post-treatment (with itraconazole) endoscopic findings were correlated and tabulated in Table 3. Before treatment, there were 71 patients with severe endoscopic findings classified with Lund-Kennedy endoscopic grading, moderate grade was seen in 4 and mild in 9 patients. Post-treatment findings were severe in 5 patients, moderate in 1, and mild in 78 patients [Table 3].

## DISCUSSION

AFS is being managed by a variety of methods which include pre-operative local steroid spray, systemic steroids,

**Table 1: The Lund-Kennedy endoscopic grading system<sup>[12]</sup>**

Characteristics	Score definition
Nasal polyps	0=none; 1=confined to middle meatus; 2=beyond middle meatus
Discharge	0=none; 1=clear and thin; 2=thick and purulent
Edema	0=absent; 1=mild; 2=severe
Scarring	0=absent; 1=mild; 2=severe
Crusting	0=absent; 1=mild; 2=severe

**Table 2: The age, gender, and demographic data of the study group (n=84)**

Observation	Male-52 (61.90%)	Female-32 (38.09%)	P-value
Age			
18–38 years	17 (20.23)	11 (34.37)	0.214
39–58 years	21 (25)	12 (37.50)	
59–78 years	14 (16.66)	9 (28.12)	
Allergy			
Dust	25 (29.76)	13 (40.62)	0.310
Diet	14 (16.66)	7 (21.87)	
Dandruff	13 (15.47)	12 (37.50)	
Smoking	28 (33.33)	4 (12.50)	0.135
Alcohol	21 (25)	1 (3.12)	0.132
Profession			
Agriculture	15 (17.85)	9 (28.12)	0.101
Student	4 (4.76)	2 (6.25)	
House wife	8 (9.52)	5 (15.62)	
Transport	16 (19.04)	14 (43.75)	
Office goes	9 (10.71)	2 (6.25)	
Socio-economic group			
Low	22 (26.19)	10 (31.25)	0.182
Middle	17 (20.23)	13 (40.62)	
High	13 (15.47)	9 (28.12)	
Previous history FESS	28 (33.33)	19 (59.37)	0.113

FESS: Functional endoscopic sinus surgery

**Table 3: The before and after treatment grading of the endoscopic findings in the study group (n=84)**

Lund-Kennedy endoscopic grading	Pre-treatment -84 (%)	Post-treatment -84 (%)	P-value
Mild	9 (28.12)	78 (92.8)	0.015
Moderate	4 (4.76)	1 (1.19)	0.152
Severe	71 (84.52)	5 (5.955)	0.001

antihistamines, antibiotics, and local antihistamines for 6 weeks and followed by functional endoscopic sinus surgery. Itraconazole is being used by few authors as adjunct therapy of AFRS. However, very few studies are available in the form of prospective randomized clinical trials to determine if itraconazole is an effective method or not. To give a successful treatment for AFS, there is a need to arrange the treatment plan addressing each factor that is responsible for the propagation of this disease. The potent anti-inflammatory and immuno-modulatory effects of corticosteroids are suitable to control the recurrence. However, the optimal dose and length of steroid therapy are not clearly discussed in the literature.<sup>[4,13]</sup> Long-term follow-up of AFS patients shows high recurrence despite prolonged usage of corticosteroids in these patients.<sup>[10]</sup> Hence, another method of AFS therapy was systemic antifungal therapy that was suggested by authors using exclusively medical treatment.<sup>[13,11]</sup> Hence, antifungal therapy often was used in an attempt to provide some degree of control over recurrence of AFS. Denning *et al.* studied initially the effect of systemic itraconazole in patients with allergic bronchopulmonary aspergillosis and

demonstrated a decrease in total immunoglobulin E.<sup>[13]</sup> In his study itraconazole was used in six patients and found that they were able to decrease the amount of prednisone required to prevent disease relapse and progression. Later on Rains and Mineck<sup>[12]</sup> using up to 400 mg of itraconazole/day and then tapering down to 200 mg/day over 3 months, showed no major side effects. The rise in liver enzymes was only in 4% of their patients. Itraconazole appears to have a modest benefit as an adjunct in the management of refractory AFS.<sup>[12]</sup> However, Ferguson<sup>[14]</sup> opines that the cost of treatment with itraconazole, limited available data in the literature, and potential drug-related morbidity due to hepatotoxicity of systemic antifungal therapy may limit the usefulness of this form of treatment for non-invasive fungal disease. The other side effects of itraconazole and fluconazole are cardiac dysrhythmias, hepatic dysfunction, urticaria, and anaphylaxis. In the present study, the numbers of patients before treatment were 71 patients with severe endoscopic findings classified with Lund-Kennedy endoscopic grading; moderate grade was seen in 4 and mild grade in 9 patients. There was dramatic conversion of severe grade patients to mild grade following itraconazole therapy; post-treatment findings were severe in 5 patients, moderate in 1, and mild in 78 patients [Table 3]. In a similar study by Hashemi *et al.*,<sup>[15]</sup> the authors observed upgrading of clinical findings and quality of life, also imaging studies, and after 3 months of treatment Lund-Mackay score of computed tomography scan were found to be lowered.

## CONCLUSIONS

Itraconazole may be useful as an adjunct in the management of AFRS. However, more studies, including a prospective randomized clinical trial, are required to determine if itraconazole is effective in the management of AFRS.

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# Changing Modalities in the Management of Lung Cancer after the Invention of Computed Tomography

Joseph Raj<sup>1</sup>, P Rani<sup>2</sup>

<sup>1</sup>Professor, Department of Cardiothoracic Surgery, Madurai Medical College, Madurai, Tamil Nadu, India, <sup>2</sup>Assistant Professor, Department of Cardiothoracic Surgery, Madurai Medical College, Madurai, Tamil Nadu, India

## Abstract

**Introduction:** Lung cancer is the leading cause of cancer-related mortality in both men and women. The prevalence of lung cancer is second only to that of prostate cancer in men and breast cancer in women. Lung cancer recently surpassed heart disease as the leading cause of smoking-related mortality. Most lung carcinomas are diagnosed at an advanced stage, conferring a poor prognosis. The need to diagnose lung cancer at an early and potentially curable stage is obvious. In addition, most patients who develop lung cancer smoke and have smoking-related damage to the heart and lungs, making aggressive surgical or multimodality therapies less viable options.

**Aim:** This study aims to assess the role of computerized tomography in the surgical management of carcinoma of the lung.

**Materials and Methods:** This is a prospective study from 2014 to 2019, a period of 5 years. A total of 22 cases entered in the study. In this study, we compare both pre-operative computed tomography (CT) image and intraoperative findings and level of operability.

**Results:** CT imaging will continue to play a major role in the evaluation of lung cancer. With the advent of non-invasive imaging modalities like multi-slice/spiral CT scan, the use of invasive screening and staging procedures including bronchography has been pushed to the periphery of staging workup; a total of 35 patients with carcinoma lung were studied. Seven patients were with carcinoma lung Stage II, one patient with carcinoma Stage III, and 27 were in Stage IV. Seven patients underwent primary surgical treatment. Other patients were treated appropriately with chemotherapy or radiotherapy or a combination of both.

**Conclusion:** CT is still the cornerstone of imaging studies in the pre-operative staging and post-therapeutic evaluation of lung cancer. Treatment of lung cancer depends on the cancers specific cell type, how far it has spread and the patient's performance status. CT is very useful for this purpose.

**Key words:** Carcinoma of the lung, ChemoRT, Computed tomography scan, Pneumonectomy

## INTRODUCTION

Carcinoma of the lung is the leading cause of cancer death. Lung cancer incidence in males has been decreasing since the early 1980s. Incidence and mortality rates for lung cancer tend to mirror one another because most persons who are diagnosed with lung cancer eventually succumb to it. In woman, lung cancer incidence rates have been stable since 1991.<sup>[1]</sup> Cancer of the lung and bronchus still accounts for 31% of cancer deaths in men and 25% of cancer deaths

in women. The overall 5-year survival rate for lung cancer remains a dismal 14%.<sup>[2]</sup> Cigarette smoking is associated with 70% increase in the age-specific death rates of men and a less increase in the death rates of women.<sup>[3]</sup> Cigarette smoking is found to be causally related to lung cancer in men. The magnitude of the effect of cigarette smoking far outweighed all other factors leading to lung cancer.<sup>[4]</sup> The risk of developing lung cancer increased with the duration of smoking and the number of cigarettes smoked per day. The report estimated that the average male smoker had an approximately 9- to 10-fold risk of developing lung cancer, whereas heavy smokers had at least a 20-fold risk.<sup>[5]</sup> The major cell types of cancer are small-cell lung cancer (SCLC) and non-SCLC (NSCLC), with the latter category comprising several histological subtypes, the major ones being squamous cell cancer, adenocarcinoma, and large cell cancer.<sup>[6]</sup> The cell types with the strongest association with cigarette smoking are SCLC and squamous cell lung

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**Corresponding Author:** Dr. P Rani, Department of Cardiothoracic Surgery, Madurai Medical College, Madurai, Tamil Nadu, India.

cancer, but there is growing evidence that adenocarcinoma is also strongly associated with smoking.<sup>[7]</sup> In 1979, squamous cell lung carcinoma was significantly more common than adenocarcinoma, at a ratio of approximately 17:1. In the past 30 years, there has been a greater increase in adenocarcinoma relative to squamous cell cancer such that the ratio of the two cell types has become 1.4:1.<sup>[8-10]</sup>

### Aim

This study aims to access the role of computerized tomography in the surgical management of carcinoma of the lung.

## MATERIALS AND METHODS

This is a prospective study from 2014 to 2019, a period of 5 years, in the Department of Cardiovascular Thoracic Surgery, Government Rajaji Hospital, Madurai. All patients with biopsy-proven lung cancer are taken up for the study. For all patients, chest X-ray and computed tomography (CT) chest were taken.

### Inclusion Criteria

All patients with biopsy-proven lung cancer are taken up for the study irrespective of their operability and their staging.

### Exclusion Criteria

Patients with inconclusive biopsy reports, tuberculosis proved patients, and patients with lung secondaries are excluded from the study.

Patients fulfilling the above criteria were enrolled in the study after taking informed consent. A detailed history with special emphasis on symptoms were collected. Chest X-ray, CT thorax, routine hematological, biochemical investigations, and serological test for human immunodeficiency virus/hepatitis B surface antigen were done in all cases. For all patients, CT-guided biopsy or lymph node biopsy or biopsy of the secondaries was done.

## RESULTS

The total number of patients was 35. Seven patients were with carcinoma lung Stage II, one patient with carcinoma Stage III, and 27 patients were in Stage IV. Seven patients underwent primary surgical treatment (Right pneumonectomy – 1, left pneumonectomy – 4, and right lower lobectomy – 2). Other patients were treated appropriately with chemotherapy or radiotherapy or a combination of both;<sup>[11-13]</sup> male-to-female ratio is 3:1. The age range affected by carcinoma of the lung was between 22 and 69 years, with the mean age of 59 years; about 77% of cases were male (27 patients) and 33% of cases (8 patients) were female [Table 1].

In my study, the right lung upper lobe was commonly involved in 43% of patients, followed by the left lower lobe 23%, right lower lobe 17%, left upper lobe 14%, and right middle lobe 3% [Table 2].

In my study, nearly 77% of the cancer was in Stage 4, Stage 2 in 20%, and Stage 3 in 3%. Of which seven patients undergo curative surgery, remaining 28 undergo chemo or radiotherapy or both [Table 3]. In this group, 29 patients had NSCLC, remaining 6 had SCLC [Table 4].

## DISCUSSION

The effectiveness of various lung cancer screening programs in high-risk patients has been assessed in multiple studies in the past decade. Some of these programs were based on chest radiography, while others on low-dose CT (LDCT).<sup>[11,12]</sup> Two large clinical trials have shaped the current view of lung cancer screening. The non-randomized International Early Lung Cancer Action Program (I-ELCAP) published in 2006 showed that it was possible to detect early Stage IA lung cancer using LDCT with a predicted 10-year survival rate of 88%.<sup>[13,14]</sup> The study enrolled over 31,000 smokers, including former and passive smokers, aged 40–90 years. Nodular changes were detected in 30% of the participants and lung cancer in 2–3%.

In this study, population had a male predominance, of which 96% of them were smokers. About 94% of the patients

**Table 1: Baseline characteristic**

Total number of patients	35
Male	27
Female	8

**Table 2: Site of involvement**

Site of involvement	Percentage
Right upper lobe	43
Left lower lobe	23
Right lower lobe	17
Left upper lobe	14
Right middle lobe	3

**Table 3: Stage of lung carcinoma**

Stage I	0
Stage II	20%
Stage III	3%
Stage IV	77%

**Table 4: Histological type**

Non-small-cell lung cancer	Small-cell lung cancer
29	6

belong to the low socioeconomic group. About 78% of the patients in my study were presented in Stage IV. In my study, the right lung upper lobe was commonly involved. Dyspnea and chest pain were the most common presenting symptoms. The predominant type of lung tumor was non-small-cell type followed by small-cell lung tumor. Stage IV patients were treated with chemotherapy followed by radiotherapy.

The detection rate of LDCT diagnosed lung cancer reached 2.4% over a period of 3 years, and the positive and negative predictive values of LDCT were, respectively, 1.2% and 100%.<sup>[15]</sup>

About 20% reduction in mortality rate demonstrated in NLSST became a major supporting argument in the debate on the effectiveness of LDCT screening and its implementation into everyday clinical practice.<sup>[16-20]</sup>

Chest LDCT is a safe non-contrast diagnostic procedure involving 10–30% lower radiation doses than the standard CT examination. The dose absorbed by the individual is 2 mSv.<sup>[21]</sup> The purpose of the scan is to detect non-calcified nodules suspicious for lung malignancy based on their morphology and size. The high sensitivity of this method is associated with the potential for the detection of small-sized nodules.<sup>[22,23]</sup>

## CONCLUSION

CT is still the cornerstone of imaging studies in the pre-operative staging and post-therapeutic evaluation of lung cancer. Treatment of lung cancer depends on the cancer's specific cell type, how far it has spread and the patient's performance status. CT is very useful for this purpose. Imaging will continue to play a major role in the evaluation of lung cancer. Mutual recognition of the need for a cohesive multidisciplinary team approach is crucial in the detection and treatment of lung cancer. With the advent of non-invasive imaging modalities like multi-slice/spiral CT scan, the use of invasive screening and staging procedures including bronchography has been pushed to the periphery of staging workup.

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# Efficacy of Saline Nasal Irrigation in Chronic Rhinosinusitis

R Rachana<sup>1</sup>, T Santhi<sup>2</sup>

<sup>1</sup>Postgraduate MS Student, Department of ENT, Government T D Medical College, Alappuzha, Kerala, India, <sup>2</sup>Associate Professor, Department of ENT, Government T D Medical College, Alappuzha, Kerala, India

## Abstract

**Aim of the Study:** To test whether daily saline nasal irrigation (SNI) improves sinus symptoms in adult subjects with chronic rhinosinusitis (CRS) and also to study the safety of saline irrigation, incidence of any complication and improvement in quality of life (QOL) in these patients.

**Materials and Methods:** This was a prospective observational study conducted between two groups of patients at Government T D Medical College, Alappuzha. Patients who satisfied the criteria for diagnosing CRS were included in the study. The first group was given SNI with oral drug therapy, while the second group was put on oral drugs alone. Each subject was given a pretested, structured questionnaire. Along with socio-demographic information, the questionnaire also contained queries of QOL measure, compliance of nasal irrigation and adverse effects following its use.

**Results:** The pre-treatment scores and post-treatment scores were analyzed and the results were statistically significant with  $P < 0.001$  in all. About 77% of the patients in the saline irrigation group were strictly using SNI which meant satisfactory compliance and the improvement in post-treatment scores were statistically highly significant with a  $P < 0.001$ . Furthermore, there was a statistically significant difference between the mean pre-test and post-test scores between the two groups with  $P < 0.001$  and  $t$ -values of 51.942 using the paired  $t$ -test.

**Conclusion:** Chronic rhinosinusitis has a major negative impact on the health care and economy of not only the patients but also of society. SNI is an effective yet easy method of therapy in alleviating the symptoms of CRS and improving the QOL of these chronic sufferers.

**Key words:** Chronic rhinosinusitis, Economic burden, Quality of life, Saline nasal irrigation

## INTRODUCTION

Sinusitis refers to a group of disorders characterized by the inflammation of the mucosa of the peripheral nervous system.<sup>[1,2]</sup> The inflammation almost always involves the nose along with the sinuses, and hence, the preferred term is “rhinosinusitis.” Rhinosinusitis task force (RSTF) has mentioned a group of symptoms for the clinical diagnosis of rhinosinusitis, the criteria being either 2 major symptoms/1 major symptom+ 2 minor symptoms.<sup>[2,3]</sup> The major and minor symptoms are classified in Table 1.<sup>[3]</sup>

Chronic rhinosinusitis (CRS) was defined by the original (RSTF) in 1997 by the inclusion of 2 or more major factors or 1 major and 2 minor factors for more than 12 weeks. In 2007 based on the guidelines issued by the American Academy of Otolaryngology the definition of rhinosinusitis was updated requiring either radiographic or endoscopic evidence of inflammation in addition to the presence of 2 or more RSTF major criteria of symptoms.<sup>[4,5]</sup>

CRS is characterized by mucosal inflammation of the nose and paranasal sinuses and may be divided into two broad clinical categories such as CRS with and without nasal polyposis.<sup>[6]</sup> In epidemiologic studies, the prevalence of CRS is 5–12%.<sup>[7]</sup> Gliklich and Metson<sup>[8]</sup> have shown that rhinosinusitis has a significant impact on the quality of life (QOL) even in comparison to chronic debilitating diseases such as diabetes and congestive heart failure.

The rhinosinusitis disability index (RSDI) is a validated instrument that measures the physical, functional,

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**Corresponding Author:** Dr. T Santhi, Department of ENT, Government T D Medical College, Vandanam, Alappuzha - 688 005, Kerala, India.



and emotional impact of rhinosinusitis on a person's QOL.<sup>[9]</sup>

It measures 30 parameters with scores ranging from 0 to 120 [Table 2].

There is inflammation of the nasal mucosa in CRS, and the associated serous, mucus, and mucopurulent secretions from the nasal mucosa become an ideal growth medium for the various pathogens such as virus, bacteria, and fungus. Therefore, the removal of these secretions would

lead to a significant relief on the natural course of CRS.<sup>[10]</sup> The ability of the paranasal sinuses to clear the mucous secretions depends on the patency of the sinus ostia, the mucociliary action, and the consistency of the mucous. Once the sinus mucosa gets irritated by the etiological factors in CRS, inflammatory edema, sinus outflow block, and mucociliary dysfunction with proliferation of the pathogens ensure relentlessly.<sup>[4]</sup>

Medical management of CRS includes short- and long-term antibiotic therapy, topical and systemic steroids, topical and oral decongestants, oral antihistamines, mast cell stabilizers, anti-leukotriene agents, mucolytics, topical antibiotics, topical and systemic antimycotics, proton pump inhibitors, bacterial lysates, immunotherapy, and phytotherapy targeted biotherapeutic agents such as anti-immunoglobulin E, and anti-cytokine antibodies, and avoidance of environmental factors.<sup>[11-13]</sup>

Saline nasal irrigation (SNI) can be used as an adjunctive measure in CRS.<sup>[10]</sup> Originally described in the Ayurvedic

**Table 1: Rhinosinusitis symptoms/signs**

Major symptoms	Minor symptoms
Facial pain/pressure/fullness	Fever (other than acute sinusitis)
Nasal obstruction/blockage	Halitosis
Nasal or postnasal discharge or purulence as by history or examination	Fatigue
Hyposmia/anosmia	Dental pain
Purulence on nasal examination	Cough
Fever (acute only)	Ear pain/pressure/fullness

**Table 2: Rhinosinusitis disability index**

Scoring: Never = 1, Almost Never = 2, sometimes = 3, almost Always = 4, always = 5		
Physical Domain (11 items)		
1	The pain/pressure in my face makes it difficult for me to concentrate	
2	The pain in my eyes makes it difficult for me to read	
3	The pain/pressure in my face makes it difficult for me to bend down to lift objects	
4	This problem makes it difficult for me to do hard/difficult farm work and house work	
5	Straining (like when I use the toilet) increases or worsens the problem	
6	The continuous (or persistent) runny nose disturbs me	
7	Food does not taste good to me because of the change in my sense of smell	
8	Sniffing all the time disturbs those around me	
9	This problem disturbs my sleep	
10	My nasal blockage makes me feel weak / tired	
11	This problem affects my sexual activity	
Functional Domain (9 items)		
1	Because of this problem every activity is difficult and inconvenient for me	
2	This problem has resulted in reduction of my routine daily activity	
3	This illness has caused me to reduce my recreational activities	
4	Because of this problem, I feel frustrated	
5	This problem makes me feel generally weak	
6	Because of this problem I avoid travelling	
7	Because of this problem I miss work or social activities	
8	The way I see life has changed because of this problem	
9	This illness makes it difficult for me to stop thinking about the problems I am going through	
Emotional Domain (10 items)		
1	This problem is negatively affecting my relationships with friends and family	
2	This problem makes me feel confused	
3	This problem does not allow me to concentrate	
4	Because of this problem, I avoid being around people	
5	I get annoyed a lot because of this problem	
6	Because of this problem I do not like to attend social gatherings	
7	Because of this problem I usually feel tense or on edge	
8	Because of this problem I am frequently easily irritated	
9	Because of this problem I feel sad	
10	This problem causes tension (strain) in my relationship with my family and friends	



medical treatment which was known as “Jala Neti” this method was later taken up by the Western medicine in the late 19<sup>th</sup> century. The Lancet published in 1902 the indications and usage of SNI. Wingrave described nasal douching methods in 1902.<sup>[14]</sup> Proetz described isotonic saline irrigation of the nose and sinuses in his book “ the displacement method of sinus diagnosis and treatment.”<sup>[15]</sup>

Clinical trials have supported its use not only in CRS but also as adjunctive therapy for the upper respiratory infections and allergic rhinitis.<sup>[16]</sup> Although it is prescribed in everyday clinical practice, saline nasal irrigation is mentioned very briefly in the guidelines for the treatment of upper tract infections.<sup>[12]</sup> The first study to assess the use of SNI as adjunctive therapy for the upper respiratory infections by the family physicians in Wisconsin was conducted among the 286 physicians, and 90% recommended SNI in CRS.<sup>[16]</sup>

SNI reduces nasal dryness and facilitates clearing of thick mucus and crusts from the nasal cavity. However, there is an increasing perception that saline has a contributory role in the resolution of inflammation as well. Many theories exist for the potential beneficial physiological effects of topical saline. Improvement in mucus clearance, enhanced ciliary beat activity, removal of antigen, biofilm or inflammatory mediators, and a protective role on sino-nasal mucosa have all been proposed.<sup>[10]</sup> Addition of ions such as magnesium, zinc, potassium, and bicarbonate to saline has shown to have positive effects such as promoting cell repair, reducing apoptosis, and mucus viscosity.<sup>[12]</sup>

## MATERIALS AND METHODS

The main objectives of the study are as follows:

1. To study the effectiveness of the use of SNI in routine primary care for chronic or recurrent sinus symptoms
2. Also to study the safety of SNI, incidence of any complication, and improvement in the QOL in these patients.

### Study Design

This was a prospective observational study.

### Study Setting and Duration

The study was conducted at Government T D Medical College, Alappuzha, Kerala, in the Ear, Nose, and Throat (ENT) Department during the period of 1 year after obtaining ethical clearance.

### Study Subjects

Patients presenting with symptoms of CRS attending the ENT outpatient department (OPD) were enrolled during the study period, as per the RSTF criteria.

### Inclusion Criteria

All patients in the age group between 16 and 76 years with 2 major symptoms/one major +2 minor symptoms persisting for more than 12 consecutive weeks were included in the study. The symptoms of CRS are less in patients below 16 years and compliance to SNI would be less in patients below 16 years and above 76 years.

### Exclusion Criteria

Patients presenting with the following conditions were excluded from the study.

- Marked deviated nasal septum
- Extensive nasal polypsis
- Atrophic rhinitis
- Severe facial trauma
- History of nasal surgery in the past.

The sample size was calculated by noting the prevalence of CRS in Alappuzha. A total of 400 patients who attended the ENT OPD were enrolled as per the inclusion and exclusion criteria.

The selected patients were randomly divided into two groups.

Group I – those receiving SNI in addition to oral medication for CRS.

Group II – those receiving oral medication alone for CRS.

Symptoms were assessed using the RSDI scoring system.

### Study Procedure

This study was conducted on the patients attending the ENT OPD, at T D Medical College, Alappuzha, Kerala, from January 2015 to December 2015.

After getting clearance from the Institutional Research and Ethical Committees, 400 patients diagnosed with CRS were enrolled as per the inclusion and exclusion criteria. Signed written informed consent was obtained from all the 400 patients included in the study. Detailed evaluation was done which included ENT examination and systemic examination. Diagnostic nasal endoscopy was done for all patients. At the initial visit, a baseline RSDI score was calculated for all and it was recorded [Table 2]. Both groups were asked to fill a questionnaire and grade their symptoms. This was called as the pre-treatment score. The 200 patients under Group I received SNI daily in addition to oral medication for symptomatic relief with antibiotics, decongestants, and antihistamines, while the remaining 200 belonging to Group II were given oral antibiotics, decongestants, and antihistamines alone. All patients were asked to review after 4 weeks.

Those in Group I were given a detailed class on the method of SNI. Each patient was given a 20 cc plastic

syringe with a cannula, measuring spoon, non-iodized salt, and a container. The patients were asked to prepare the saline solution in the following manner.

- Put 1 teaspoon of salt into the container
- Add 500 ml of lukewarm water
- Add a pinch of sodium bicarbonate to make it physiological
- Mix the contents.

Instructions were also given as to the method of saline irrigation as detailed below

- Lean over the sink. Turn your head to one side
- Insert the cannula tip into the uppermost nostril and breathe through your mouth
- Push gently the piston of the syringe so that the solution flows into the upper nostril
- In a few moments, the solution will begin to drain from the lower nostril
- Continue until the syringe is empty, then exhale gently through both nostrils
- Refill the syringe, turn your head to the opposite side, and repeat on the other nostril
- Do this 2 times daily for 4 weeks.

The patients were told to clean the syringe and cannula with warm water and a mild detergent. The unused saline solution was to be kept in a sealed container at room temperature for the next 48 h.

The same questionnaire was filled at the end of 4 weeks of treatment, and the total score was calculated. This was called the post-treatment score. Qualitative variables were expressed in percentages or proportion, and quantitative variables summarized in mean with standard deviation. Chi-square test was used for testing the significance. Paired *t*-test was used to find the significance of the post-treatment score between the two groups.

## RESULTS

There were 400 patients with a diagnosis of CRS and fitting within the inclusion criteria. During the course of the study, all were followed up for 4 weeks. A total of 200 patients were given symptomatic treatment with oral antibiotics, decongestants, and antihistamines, while the rest 200 received daily SNI in addition to the oral medications. At the initial visit a baseline RSDI score was calculated for all and recorded. They were given respective treatment randomly and asked to review after 4 weeks. The main focus of the study was to find out whether SNI would improve the symptoms in CRS.

Age wise, the youngest patient was 18 years old and the oldest 60. Most numbers of patients belonged to the

30–40 years of age group. The mean age was 39.91 with a standard deviation of 11.685 [Table 3].

Males constituted 47.2% and females constituted 52.8% of the study population [Table 4]. Any gender-based difference in RSDI score after treatment was analyzed but showed no statistical significance (Chi-square – 0.973).

The main clinical symptoms were tabulated [Table 5]. The most frequent symptom was nasal block (45.8%), and the least frequent symptom was anosmia (0.5%).

The association between the educational status and the post-treatment score in the two groups was analyzed, but was not significant with a Chi-square value of 0.011, implying that the method of using nasal irrigation was simple and easily practicable to all patients irrespective of their educational status [Table 6].

On analyzing the pre-treatment symptoms and post-treatment symptoms of patients with CRS of Group I and Group II, Group I patients who were treated with SNI in

**Table 3: Age distribution of the study population**

Age group (years)	Frequency (number)
<30	95
30–40	136
40–50	51
50–60	118

**Table 4: Sex distribution in the sample population**

Gender	Frequency	%
Male	189	47.2
Female	211	52.8
Total	400	100

**Table 5: Clinical symptoms of the study group**

Complaints	Frequency	%
Headache	27	6.8
Facial pain	92	23
Nasal discharge	45	11.2
Nasal block	183	45.8
Hyposmia	41	12.8
Anosmia	2	0.5
Total	400	100

**Table 6: Educational status of the study population**

Education	Frequency	%
Elementary schooling	116	29
Graduate	143	35.8
Postgraduate	141	35.2
Total	400	100

addition to oral medication showed much more relief in the symptoms of headache, facial pain, and nasal discharge than those in Group II who were on oral medication alone, which was statistically significant with  $P$  value of  $< 0.001$  in all. This implies that patients with these symptoms pertaining to CRS are very well benefitted by SNI [Table 7].

Furthermore, there was a statistically significant difference between the mean pre-test and post-test scores between the two groups with  $P$  value of  $< 0.001$  and with  $t$ -value of 51.942 using the paired  $t$ -test.

About 77% of the patients in Group I were strictly using SNI which means satisfactory compliance and the improvement in post-treatment scores in them was statistically highly significant with  $P$  value of  $< 0.001$  [Table 8].

Side effects were few, mainly nasal irritation (17%), pooling of saline (11%), headache (3%), and epistaxis (1%), while 68% of the study population did not have any adverse effect on using nasal irrigation [Table 9].

## DISCUSSION

Saline irrigation has gained popularity in relieving the symptoms of chronic sinusitis, and there have been several randomized controlled trials showing objective and subjective efficacy of saline irrigation in sinonasal disease.<sup>[12]</sup>

**Table 7: Efficacy of saline nasal irrigation**

Efficacy of treatment by SNI	Group I (SNI+oral medication)	Group II (oral medication alone)
Improvement	127	59
No improvement	72	142

SNI: Saline nasal irrigation

**Table 8: The use of SNI in the study population**

Usage of SNI	Frequency	%
Occasional use	46	23
Strict use	154	77
Total	200	100

SNI: Saline nasal irrigation

**Table 9: Adverse effect profile of saline nasal irrigation**

Adverse effects	Frequency	%
Nil	136	68
Nasal irritation	34	17
Pooling of saline	22	11
Headache	6	3
Epistaxis	2	1
Total	200	100

The main aim of the study was to find out if SNI improved the symptoms of CRS, increased QOL thereby reducing the overall morbidity of the disease. Moreover, saline being cheap and physiological are highly safe and have very minimal side effects; thus, it could be practised in our setting and thereby decrease the recurrences and duration of medications for CRS. About 0.9–3% saline solutions have been most often used. Although optimal pH and temperature are not known,<sup>[14]</sup> 4.5–7 pH is recommended.<sup>[12]</sup>

Harvey *et al.* were the first to analyze the clinical relevance of the therapeutic use of nasal saline irrigation in CRS which was published in a Cochrane review in 2007.<sup>[12]</sup> This included eight randomized controlled trials. These studies could not be standardized as there were differences in the selection of patients, methods used for nasal irrigation and in evaluating the outcome measures. Efficacy of nasal irrigation with saline solution was compared with a placebo, with no treatment or as an adjunct with other treatment. Comparison between hypertonic saline solution and isotonic solution was also done. Patients had similar improvement with both hypertonic and isotonic saline solutions, but radiological scores seemed better in patients after hypertonic saline therapy.

On comparing nasal irrigation with hypertonic and isotonic saline irrigation in 40 patients using 200 ml of solution twice a day, Bachman *et al.* noted similar clinical improvement in both the groups but Hauptman and Ryan who studied on 80 patients found that nasal airway improvement was better with isotonic SNI.<sup>[12]</sup>

The mode of saline administration is also important where large volume low-pressure isotonic saline irrigation was found to be more effective than saline nasal spray in reducing the use of medication and thereby improving the QOL.<sup>[17]</sup>

Similarly, in the prospective RCT comparing nasal spray and nasal irrigation by Pynnonen *et al.*<sup>[17]</sup> symptom, severity and disease-specific QOL were assessed with the sinonasal outcome test (SNOT-20) which is a 20-item survey that measures physical problems, emotional consequences, and functional limitations of sinusitis.<sup>[18]</sup> The conclusion was that the saline irrigation group had lower SNOT-20 scores than the nasal spray group.

However, the addition of isotonic saline irrigation after 3 months in the post-operative cases did not reduce the crusting, edema, adhesions, and polyps in the study of 23 patients conducted by Freeman *et al.*<sup>[12]</sup> Khianey *et al.* reported that nasal irrigation could reduce the use of medicines and therefore minimize resistance to antibiotics.<sup>[19]</sup>

In the study group of 400 patients, 189 were males and 211 females. The different age and sex distributions were studied, but it showed no significant association with the outcome. The educational status of the population also did not affect the outcome thereby favoring easy use of SNI in all. About 77% of the patients in the second group were strictly using SNI which means satisfactory compliance and the improvement in post-treatment scores in them was statistically highly significant with  $P$  value of  $< 0.001$ .

SNI, among all the complaints, could maximally improve the symptoms of nasal block, facial pain, and headache. The relationship between various symptoms and post-treatment score was analyzed, and the results were statistically significant in those with headache, facial pain, and nasal discharge with  $P$  value of  $< 0.001$  in all implying that patients' symptoms pertaining to CRS benefitted by SNI.

There was a statistically significant difference between the mean pre-test and post-test scores of the two groups with  $P$  value of  $< 0.001$  with  $t$ -value of 51.942 using the paired  $t$ -test. The study was successful in this regard by getting a statistically significant difference between the two groups after treatment which was comparable to previous similar studies. The study also analyzed the side effect profile of SNI which showed nasal irritation as the major adverse effect in 17.2% of the total population others being pooling of saliva, headache, and epistaxis.

Among the 400 patients who took part in the study, all received some form of treatment and both were successful in improving the symptoms of CRS which was comparable to various studies done before and hence SNI is established for adjuvant therapy in CRS.

Other than CRI, SNI is also recommended as adjunctive therapy in acute upper respiratory tract infections, allergic rhinitis, rhinitis of pregnancy, and Wegener's granulomatosis.<sup>[16]</sup>

SNI is also advocated in certain other conditions like in elderly people with sinusitis,<sup>[20]</sup> rhinitis medicamentosa,<sup>[21]</sup> infants with nasolacrimal duct obstruction,<sup>[22]</sup> in decontaminating the nose following industrial accidents,<sup>[23]</sup> after nasal tumour removal<sup>[24]</sup> and choanal atresia repair.<sup>[25]</sup>

Looking into the emerging trends in topical therapy, surfactants which reduce water surface tension may be used to dissolve biofilms. About 1% baby shampoo in normal saline has been used in inhibiting the biofilm formation of *Pseudomonas* species *in vitro*. Xylitol and sodium hypochlorite are the newer additives for nasal irrigation. Both are tolerated well and give good symptomatic relief, disease clearance as well as in endoscopic appearance.<sup>[11]</sup>

## Limitations

All data were obtained from the patients and hence subjected to recall bias.

The patients were followed up only for 4 weeks. The long-term efficacy of SNI in CRS was not studied.

QOL assessment was done indirectly using symptom index and the impact of CRS on the subjects' productivity was not entirely measured, as no information was available on daily work performance.

Effectiveness of SNI was not studied in the pediatric age group who are at a high risk of frequent upper respiratory tract infections.

## CONCLUSION

Rhinosinusitis is a worldwide health issue causing significant morbidity. SNI is a very useful, yet inexpensive method with little complications to alleviate the symptoms related to CRS. The method of irrigation also has high compliance. The technique of SNI should be standardized and should be considered in all patients with CRS along with the medical and surgical management for maximum benefit. The easily prepared solution of saline douche can also be used as a home remedy, thereby, avoiding prolonged hospital stay. This is one technique which can be used widely regardless of the age or comorbidities of the general population with CRS.

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# A Clinical and Demographic Study on Oropharyngeal Malignancies

M Ravikumar<sup>1</sup>, P Lavanya<sup>2</sup>, B Divyareka<sup>2</sup>

<sup>1</sup>Associate Professor, Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, India, <sup>2</sup>Junior Resident, Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, India

## Abstract

**Background:** The aim of the study was to determine the distribution of oropharyngeal malignancies in terms of age, sex, personal habits, symptoms, site, histopathological type, and differentiation; and the modes of treatment adopted and its results.

**Materials and Methods:** A total of 68 patients treated previously in the Department of Ear, Nose, and Throat of MNR Medical College and Hospital were included in this study. Patients of all age groups and gender were included in the study. Patients with persistent mass of the neck or throat or with symptoms suggesting oropharyngeal cancer were included in the study. Patients with symptoms of chronic throat pain, difficulty swallowing, weight loss, earache, voice change, and blood-tinged saliva were included in the study. Patients with severe cardiac, renal and pulmonary diseases were excluded from the study. Patients with immunodeficiency diseases were excluded from the study. All the patients were initially evaluated by a detailed medical history and comprehensive head and neck examination, which included flexible endoscope examination of the pharynx and larynx in an outpatient department setting. Patients with suspicious looking lesions (tumors) of the oropharynx were biopsied for histopathological evaluation. All patients with a confirmed diagnosis of oropharyngeal squamous cell carcinoma were subjected to evaluation by a multidisciplinary treatment team. Imaging was done to evaluate the primary tumor, involvement of lymph nodes in the neck, and for evidence of metastatic cancer spread beyond the head and neck. The patients were subjected to either computed tomography scan or magnetic resonance imaging of the neck to evaluate the pharynx and lymph nodes in the neck.

**Observations and Results:** Among the 68 patients, there were 41 males (60.29%) and 27 females (39.70%), with a male to female ratio of 1.51: 1. The mean age was  $55.63 \pm 5.70$  years. Thirty-seven patients (54.41%) were in 55–65 years, 24 patients (35.29%) in 45–55 years, and 7 patients (10.29%) were aged above 65 years. Malignant tumors of the tonsil were observed in 21/68 (30.88%), posterior one-third of the tongue in 17/68 (25%), soft palate in 10/68 (14.70%), valleculae in 10 (14.70%), and suprahoid epiglottis in 6 (8.82%), and posterior pharyngeal wall in 4 (105.88%) of the patients.

**Conclusions:** Oropharyngeal cancers are one of the most common malignant tumors of the aero-digestive tract. Males are more commonly affected than females and usually in the 5<sup>th</sup>–6<sup>th</sup> decade of life. The incidence is rising in females also because of using smokeless tobacco products. The most common site was tonsil followed by posterior one-third of the tongue; the least common site was posterior pharyngeal wall. Well-differentiated carcinoma was the most common histopathological finding.

**Key words:** Malignancies, Oropharynx, Radiotherapy and chemotherapy, Staging, TNM classification

## INTRODUCTION

The risk factors causing oropharyngeal malignant tumors are habits, social customs, diet, occupational exposure, climate, geography, and difference in race and

genetic factors.<sup>[1]</sup> Even though the malignant neoplasms of the oral cavity, oropharynx, and hypopharynx put together account for 45% of all cancers in India, the prevalence of only oropharyngeal malignancies is least forthcoming in the literature.<sup>[2]</sup> The incidence of oropharyngeal malignant tumors is not only common in India but also in the populations of Indian origin elsewhere; especially it was reported in Malaysia.<sup>[3]</sup> The malignant tumors of oropharynx are easily diagnosed by ear, nose, and throat (ENT) clinical examination but more than 80% of these patients report at a very late stage. Direct bone involvement takes place early and is

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**Corresponding Author:** Dr. M Ravikumar, Department of ENT, MNR Medical College and Hospital, Sangareddy, Telangana, India.

seen in nearly two-third of the cases.<sup>[3]</sup> Multicentricity of the tumors and field cancerization in the mucosa has been noted by several workers.<sup>[4]</sup> Human papillomavirus (HPV) infection was found to be responsible for onset of oropharyngeal cancers that arise predominantly from the lingual and palatine tonsils within the oropharynx.<sup>[5]</sup> Gillison stated that oral HPV infection has recently been associated with sexual behavior; particularly with number of multiple oral sex partners.<sup>[6]</sup> The vast majority of primary oropharyngeal tumors are squamous cell carcinomas (SCCs) on histopathological examination, but other varieties arising from minor salivary tumors (adenomas/adenocarcinomas), primary lymphoid tumors, undifferentiated tumors, various sarcomas, and “mixed cellularity” neoplasms occurring primarily in the oropharynx are not uncommon.<sup>[7]</sup> Review of recent literature shows that many of these tumors (at least in the United States) are associated with HPV infection and potentially more amenable to curative treatment.<sup>[8]</sup> Literature also shows in retrospective studies that nearly 60% of oropharyngeal SCCs are found to be moderately differentiated, 20% well differentiated, and 20% poorly differentiated.<sup>[7]</sup> Genomics and proteomics are likely to modify the methods of sub-classification of many cancers, including SCCs of the head and neck, as increasingly specific molecular markers and patterns of gene expression are identified.<sup>[9]</sup> The etiological agents of oropharyngeal SCC are tobacco use and excess alcohol use. Alcohol abuse acts not only independently as a risk factor for oropharyngeal SCC but also seems to potentiate the carcinogenic nature of tobacco smoke in the oropharynx. Moreover, the carcinogenic effects of both alcohol and tobacco smoke on the oropharynx appear to function in dose-dependent manners.<sup>[10]</sup> The change in the trends of occurrence of SCC of oropharynx among the younger age groups in USA is mainly attributed to HPV seropositivity, oral HPV infection, or both. For reasons not yet understood, most HPV-associated oropharyngeal SCCs originate in the tonsil. Although HPV18 and HPV-16 are associated with genital cancers, the vast majority (84%) of HPV-associated head and neck cancers are associated with HPV-16 only.<sup>[11-13]</sup> Few authors have suggested that HPV associated oropharyngeal cancers may be less aggressive than those not associated with the virus; specifically, HPV association tends to confer much better survival rates. The biologic/molecular reasons for these clinical observations have not been clearly elucidated.<sup>[14,15]</sup> In this context, the present study is undertaken to determine the distribution of oropharyngeal malignancies in terms of age, sex, personal habits, symptoms, site, histopathological type, and differentiation; and the modes of treatment adopted and its results.

## MATERIALS AND METHODS

Sixty-eight patients treated previously in the Department of ENT of MNR Medical College and Hospital was included in this study. The medical records of these patients were retrieved from the medical records section and analyzed. An Institutional Ethical Clearance was obtained before commencement of the study.

### Inclusion Criteria

(1) Patients of all age groups and gender were included in the study. (2) Patients with persistent mass of the neck or throat or with symptoms suggesting oropharyngeal cancer were included in the study. (3) Patients with symptoms of chronic throat pain, difficulty swallowing, weight loss, earache, voice change, and blood-tinged saliva were included in the study.

### Exclusion Criteria

(1) Patients with severe cardiac, renal, and pulmonary diseases were excluded from the study. (2) Patients with immunodeficiency diseases were excluded from the study. All the patients were initially evaluated by a detailed medical history and comprehensive head and neck examination, which included flexible endoscope examination of the pharynx and larynx in an outpatient department (OPD) setting. Patients with suspicious looking lesions (tumors) of the oropharynx were biopsied for histopathological evaluation. In those patients, where it was not possible to perform biopsy in OPD, and if a lesion was not easily accessible either directly through the mouth or through flexible endoscopy, an additional examination and biopsy under general anesthesia in an operating room was done. In patients presenting with neck masses an adequate tissue for diagnosis through a needle biopsy (fine-needle aspiration, or FNA) was done. All patients with a confirmed diagnosis of oropharyngeal SCC were subjected to evaluation by a multidisciplinary treatment team. Imaging was done to evaluate the primary tumor, involvement of lymph nodes in the neck, and for evidence of metastatic cancer spread beyond the head and neck. The patients were subjected to either computed tomography scan or magnetic resonance imaging of the neck to evaluate the pharynx and lymph nodes in the neck. These scans were done with intravenous contrast in nearly all cases, with the exception of patients with impaired kidney function or an allergy to contrast dye. CT scan of the chest was also done in most cases, to evaluate for the presence of metastatic cancer in the lungs or lymph nodes of the chest. Positron emission tomography scan was done 6 patients for pretreatment evaluation, particularly for patients with advanced-stage disease. All the data were analyzed and tabulated using standard statistical methods.

## OBSERVATIONS AND RESULTS

Sixty-eight patients attending the Department of ENT in MNR Medical College and Hospital, Sangareddy, Telangana, who were diagnosed with malignancy of oropharynx, were included in this study. There were 41 males (60.29%) and 27 females (39.70%), with a male to female ratio of 1.51: 1. The patients belonged to the age group of 45 to above 65 years with a mean age of  $55.63 \pm 5.70$  years. There were 37 patients (54.41%) in the age group of 55–65 years, 24 patients (35.29%) in the age group of 45–55 years, and 7 patients (10.29%) were aged above 65 years. The youngest patient was aged 56 years and the eldest patient was aged 69 years [Table 1].

The personal habits of the study group were studied and found that 38/41 (92.68%) of the males and 8/27 (29.62%) of the females had the habit of smoking. Alcohol consumption was observed in 27/41 (65.85%) of the males and 16/27 (59.25%) of the females. Tobacco in the form of gutkha or chewing pan was noted in 34/41 (82.92%) of the males and 22/27 (81.48%) of the females. Consumption of alcohol and tobacco in the form of smoking or chewing was noted in 14/41 (34.14%) of the males and 12/27 (44.44%) of the females. About 3/41 (7.31%) of the males and 2/27 (7.40%) of the females had no risk factors as habits [Table 2].

About 54/68 (79.41%) patients showed ulceroproliferative growths as the presenting lesions in this study followed by 12/68 (17.64%) of the patients showed ulcerative lesions, and 2/68 (2.94%) of them showed infiltrative type of lesions. The incidence of site of lesions of various subsites is tabulated in Table 3. Malignant tumors of the tonsil were observed in 21/68 (30.88%), posterior one-third of the tongue in 17/68 (25%), soft palate in 10/68 (14.70%), valleculae in 10 (14.70%), and suprahyoid epiglottis in 6 (8.82%), and posterior pharyngeal wall in 4 (105.88%) of the patients [Table 3].

Histopathological study of all the biopsy specimens was done and it was observed that well-differentiated SCC was reported in 49/68 (72.05%) of the patients followed by poorly differentiated SCC in 11 (16.17%) and anaplastic carcinoma was observed in the remaining 8 (11.76%) of the patients.

## DISCUSSION

In India malignant tumors of the oropharynx and oral cavity account for the third most common cancer in men and women but when only oropharynx is considered it is the 7<sup>th</sup> most common cancer among both the genders.<sup>[16]</sup> In the present study, the male to female ratio was 1.5:1 which

**Table 1: The age and gender incidence of the study (n=68)**

Age group	Male – 41	Female – 27
45 – 55 years – 24	15	9
55 – 65 years – 37	23	14
Above 65 years – 7	3	4

**Table 2: The incidence of risk habits in the study group (n=68)**

Personal habits	Male – 41 (%)	Female – 27 (%)	P value
Smoking	38 (92.68)	8 (29.62)	0.031
Alcohol	27 (65.85)	16 (59.25)	Not significant
Tobacco chewing (Pan, Gutka)	34 (82.92)	22 (81.48)	Not significant
Alcohol and tobacco (smoking, pan, gutka)	14 (34.14)	12 (44.44)	Not significant
None of the above	3 (7.31)	2 (7.40)	Not significant

**Table 3: The site of lesions according to the gender in the study group (n=68)**

Site of lesion	Male – 41 (%)	Female – 27 (%)
Tonsil – 21 (30.88%)	13 (19.11)	8 (11.76)
Posterior one-third tongue – 17 (25%)	11 (16.17)	6 (8.82)
Soft palate – 10 (14.70%)	7 (10.29)	3 (4.41)
Valleculae – 10 (14.70%)	5 (12.51)	5 (18.51)
Supra-hyoid epiglottis – 6 (8.82%)	3 (4.41)	3 (4.41)
Posterior pharyngeal wall – 4 (5.88%)	2 (2.94)	2 (2.94)

is comparable to other parts of India; in one report from Kerala the incidence in males was 57.8% in males and 42.2% in females.<sup>[17]</sup> The higher incidence of oropharyngeal malignancies in males may be as a result of increase in the consumption of tobacco and alcohol. Tobacco is consumed by males in both smoking and chewing form in India, whereas native females usually do not smoke. This difference can also be attributed to more males seeking early medical consultation.<sup>[18]</sup> In the present study, it was found that 38/41 (92.68%) of the males and 8/27 (29.62%) of the females had the habit of smoking which is statistically significant with  $P = 0.031$  ( $P$  significant at  $<0.05$ ). There were 41 males (60.29%) and 27 females (39.70%), with a male to female ratio of 1.51: 1. The patients belonged to the age group of 45 to above 65 years with a mean age of  $55.63 \pm 5.70$  years. There were 37 patients (54.41%) in the age group of 55–65 years, 24 patients (35.29%) in the age group of 45–55 years, and 7 patients (10.29%) were aged above 65 years. The youngest patient was aged 56 years and the eldest patient was aged 69 years [Table 1]. Ahluwalia *et al.*<sup>[19]</sup> reported from their study that the peak incidence of oropharyngeal malignancy was among males in the 6<sup>th</sup> decade of life (40.89%), while in females it was 5<sup>th</sup> decade comprising 37.31%. Patel and Pandya reported that 12.9%



of oropharyngeal malignancies were below 35 years of age, 23.8% between 35 and 45, and 63.3% cases over 45 years of age.<sup>[20]</sup> The mean age in the present study was  $55.63 \pm 5.70$  years when compared to the study done by Durazzo *et al.* was 57.4 years, and only 8.6% of the patients were 40 years or less.<sup>[21]</sup> In the present study, 38/41 (92.68%) of the males and 8/27 (29.62%) of the females had the habit of smoking. Alcohol consumption was observed in 27/41 (65.85%) of the males and 16/27 (59.25%) of the females. Tobacco in the form of gutkha or chewing pan was noted in 34/41 (82.92%) of the males and 22/27 (81.48%) of the females. Consumption of alcohol and tobacco in the form of smoking or chewing was noted in 14/41 (34.14%) of the males and 12/27 (44.44%) of the females. About 3/41 (7.31%) of the males and 2/27 (7.40%) of the females had no risk factors as habits [Table 2]. It was reported that women have substantially high level of chewing habits than men in many rural areas, as they believe that tobacco has magical and medicinal properties.<sup>[16,17]</sup> In comparison to this study in the study by Dias and Almeida, 57.8% were tobacco users, 50% were alcoholics, and 43.8% were both alcoholics and smokers.<sup>[22]</sup> In another study by Durazzo *et al.*<sup>[21]</sup> reported tobacco smoking in 80.8% of the patients, history of alcohol intake was observed in 56.6% of the patients. More recently in Western world, HPV infection is emerging as a common etiological factor for oral and oropharyngeal malignancies, mostly as a result of oral sex.<sup>[11]</sup> However, in India, alcohol and tobacco usage are still the most common risk factor. Risk of oral and oropharyngeal malignancy is higher for hard liquor and beer.<sup>[23]</sup> It is presumed that alcohol may act as a solvent to enhance mucosal exposure to carcinogens, apart from being a direct carcinogen. Acetaldehyde, an alcohol metabolite, can form DNA adducts that interfere with DNA synthesis and repair.<sup>[24]</sup> Rodu and Jansson<sup>[25]</sup> postulated a relationship between use of smokeless tobacco products and oral cancers as a complicated phenomenon due to the heterogeneity in smokeless tobacco, containing tobacco-specific nitrosamines. However, in India, smokeless tobacco is often mixed with other carcinogenic substances such as betel, areca nut, and lime making the smokeless tobacco products much stronger and in dose-response relationships with increased intensity, and when used for longer durations resulting in the risk of premalignant and malignant lesions of the oral cavity and oropharynx.<sup>[26]</sup> Malignant tumors of the tonsil was observed in 21/68 (30.88%), posterior one-third of the tongue in 17/68 (25%), soft palate in 10/68 (14.70%), valleculae in 10 (14.70%), and suprahyoid epiglottis in 6 (8.82%), and posterior pharyngeal wall in 4 (5.88%) of the patients [Table 3]. Lin *et al.*, observed 70–80% of oropharyngeal SCC originate in the tonsillar complex as similar to the present study tonsillar tumors (30.88%) were the most common. They concluded that although these tumors are often asymptomatic initially,

the majority of patients report odynophagia, dysphagia, or both.<sup>[9]</sup> Late symptoms include otalgia, bleeding, decreased tongue mobility, and trismus (usually due to invasion of the pterygoid plate).<sup>[9]</sup> Lin *et al.* observed that SCC of the tongue base was second most frequent sub-site to develop tumors and tends to be locally, regionally, and systemically aggressive and they are poorly differentiated. The incidence in their study was 29.30% which is similar to the present study of 25%. Malignant tumors of the soft-palate are also relatively uncommon but tend to be diagnosed at early stages, because the soft palate is the most amenable oropharyngeal subsite to direct visual inspection and manual palpation.<sup>[17]</sup> In the present study, the incidence of soft palate was 14.70% the third most common site. Cohan *et al.*<sup>[27]</sup> observed that tumors originating from the posterior pharyngeal wall are rare because they tend to remain asymptomatic until they gain considerable bulk. In the present study, the incidence of posterior pharyngeal wall tumors was 5.88% which was least common tumor. It was observed in this study that well-differentiated SCC was reported in 49/68 (72.05%) of the patients, followed by poorly differentiated SCC in 11 (16.17%) and anaplastic carcinoma was observed in the remaining 8 (11.76%) of the patients. similarly, Mehrotra *et al.*<sup>[28]</sup> also noticed moderately differentiated SCC as the most prevalent type in males (13%), and well-differentiated was common in females (5.3%). However, there are several studies reporting well-differentiated SCC as the most prevalent.<sup>[19,22,29,30]</sup>

## CONCLUSIONS

Oropharyngeal cancers are one of the most common malignant tumors of the aero-digestive tract. Males are more commonly affected than females and usually in the 5<sup>th</sup>–6<sup>th</sup> decade of life. The incidence is rising in females also because of using smokeless tobacco products. The most common site was tonsil followed by posterior one-third of the tongue; the least common site was posterior pharyngeal wall. Well-differentiated carcinoma was the most common histopathological finding.

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# Clinical Profile of Stroke Patients in South Tamil Nadu Tertiary Care Hospital – A Cross-sectional Study

Y Kingsly Jebasingh<sup>1</sup>, P Sivanesan<sup>2</sup>

<sup>1</sup>Professor, Department of Neurology, Kanyakumari Government Medical College, Kanyakumari, Tamil Nadu, India, <sup>2</sup>Junior Resident, Department of Medicine, Kanyakumari Government Medical College, Kanyakumari, Tamil Nadu, India

## Abstract

**Introduction:** There are 15 million people worldwide who suffer a stroke each year. According to the World Health Organization, stroke is the second leading cause of death for people above the age of 60 years, and the fifth leading cause in people aged 15–59 years old.

**Aim:** This study aims to study the clinical profile of patients presenting with stroke in South Tamil Nadu.

**Materials and Methods:** The cross-sectional study was conducted in the Department of Medicine at Kanyakumari Government Medical College from September 2018 to June 2019. A total of 140 patients who presented with symptoms of stroke were assessed, for the relative frequency of ischemic and hemorrhagic stroke separately.

**Results:** The incidence of stroke is maximum in the age group of 51–60 years comprise 34.28% with a mean age of 56 years. Cerebral infarction was more than hemorrhage. Hypertension was among leading risk factors for both types comprise 48.5%. Hemiplegia was the most common presentation followed by speech involvement and facial palsy. In ischemic stroke, the most common site was internal (20.71%) followed by parietal (9.28%). In hemorrhage, the most common site was capsuloganglionic (7.85%) followed by thalamus (5.0%).

**Conclusion:** Developing countries like India are facing a double burden of communicable and non-communicable diseases. Stroke is one of the leading causes of death and disability in India.

**Key words:** Hemorrhagic stroke, Hypertension, Ischemic stroke, Tertiary health-care center

## INTRODUCTION

Stroke is one of the devastating and disabling diseases which is one of the leading causes of morbidity and mortality that rank the top three causes of death after cardiovascular and cancer.<sup>[1]</sup> It is defined as a rapidly developing sign of focal (or global) disturbance of cerebral function with symptoms lasting for  $\geq 24$  h or leading to death with no apparent cause other than vascular origin.<sup>[2]</sup> It is a collection of clinical syndromes resulting from cerebral

ischemia to intracranial hemorrhage. Hypertension, alcoholism, smoking, diabetes mellitus, and dyslipidemia are the most common causes of stroke.<sup>[3]</sup>

Stroke is an important and leading cause of morbidity and mortality worldwide. The consequences of stroke can be severe, leading annually to 5 million deaths and being left permanently disabled.<sup>[4]</sup> A stroke study conducted in Kolkata<sup>[5]</sup> showed a prevalence of 147 cases per 100,000 population and an annual incidence of 36/100,000 in the year 1998–99. At present, the stroke fact sheet of 2012 estimates 84–262/100,000 in rural and 334–424/100,000 in urban areas. In a stroke, the hemorrhagic cause is high in Asian countries due to the high prevalence of hypertension which may have been masked or treated without sufficient control of blood pressure. The estimated percentage of hemorrhagic stroke in the western population is around 10% of all stroke cases, and in India, it is 17.7–32% of all strokes.<sup>[6]</sup>

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**Corresponding Author:** Dr. P Sivanesan, Department of Medicine, Kanyakumari Government Medical College, Kanyakumari, Tamil Nadu, India.

## Aim

This study aims to study the clinical profile of patients presenting with stroke in South Tamil Nadu.

## MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Medicine at Kanyakumari Government Medical College from September 2018 to June 2019. A total of 140 patients who presented with symptoms of stroke were assessed the past year, for the relative frequency of ischemic and hemorrhagic stroke separately. All the patients who presented with the clinical diagnosis of acute stroke were subjected to a detailed clinical history, particularly for alcohol, smoking, hypertension, diabetes, previous stroke, transient ischemic attack, physical examination, serial neurological examination, and computed tomography (CT) magnetic resonance imaging scan of the brain.

### Inclusion Criteria

The following criteria were included in the study:

1. All patients above the age of 18 years
2. All the having clinical and CT confirmed diagnosis of stroke.

### Exclusion Criteria

The following criteria were excluded from the study:

1. Patients below 18
2. Stroke due to trauma
3. Patients medical records which were not showing CT confirmed diagnosis.

All patients included in the study after getting consent were taken with a detailed history regarding age, sex, occupation, time of occurrence of the event, and comorbid factors such as pre-existing hypertension, diabetes, dyslipidemia, and drug intake including alcohol. The patients were clinically assessed for vital parameters and detailed neurological examination and other systems examination were conducted. Concurrently, the patients were also worked up for complete hemogram, coagulation profile, and basic biochemical parameters including random blood sugar and renal/lipid profiles/electrolyte profile, urine albumin/sugar/deposits, electrocardiogram, chest X-ray, and CT brain, and in needed cases, collagen vascular disease profile was done. All these parameters were collected by detailed history as with patients/relatives/attenders as appropriate in a standard hospital approved pro forma.

## RESULTS

In our study, the age range was from 30 to 80 years with a mean age was 56 years. In this study, the youngest patient

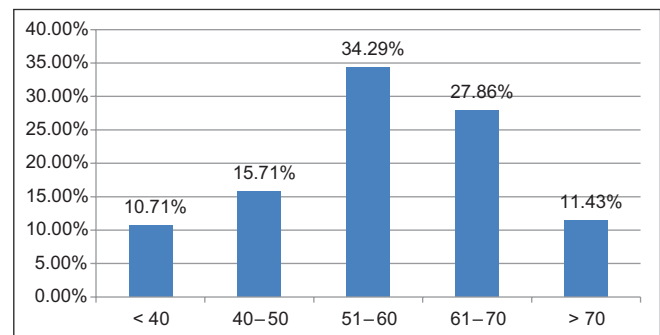
was 32 years old and the oldest was 76 years old. The incidence of cerebrovascular accident is maximum in 51–60 years of the age group which comprises 34.28% of total patients and young stroke (age <40 years) comprised 10.71% of all patients [Figure 1].

The male-to-female ratio was 1.6:1. From the observation, it can be concluded that the incidence of stroke is more common in the male sex [Figure 2].

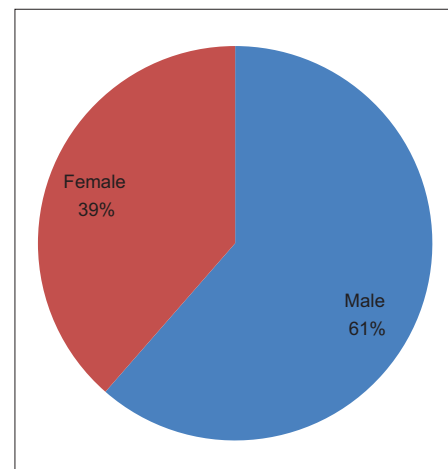
In our study as shown in Table 1, the most common clinical presentation was hemiplegia which was 54.2% followed by

**Table 1: Topographic distribution of hemorrhage**

Areas involved	Ischemic stroke
	Number of cases (%)
Thalamus	7 (5.0)
Basal ganglia	5 (3.57)
Internal capsule	11 (7.85)
Pons	3 (2.14)
Midbrain	2 (1.42)
Cerebellar	3 (2.14)
Frontal	2 (1.42)
Parietal	3 (2.14)
Temporal	2 (1.42)
Occipital	2 (1.42)



**Figure 1: Age-wise distribution of cases**



**Figure 2: Gender distributions of stroke patients**

upper motor neuron facial palsy (16.4), speech involvement (15%), vomiting and headache (10%), unsteadiness of gait (6.4%), giddiness (5%), convulsions (5.7%), and altered sensorium (3.5%) [Figure 3].

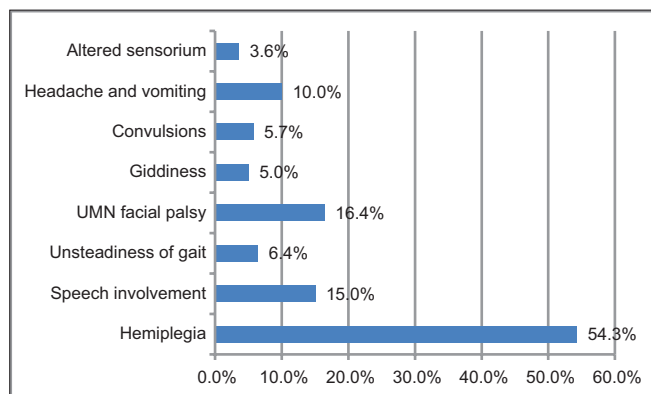
In our study, the most common risk factor was hypertension (68 patients) with 48.5%, followed by diabetes mellitus (52 patients) 37.14%, dyslipidemia (36 patients) 25.7%, 44.2% smoker (62 patients), alcohol (58 patients) 41.4%, 4 patients had past H/o of malignancy, and 8 patients were having rheumatic valvular disease.

In our study, 102 patients (72.8%) suffered ischemic stroke and 38 patients (27.1%) suffered a hemorrhagic stroke. Hence, the most common type of stroke is cerebral infarction. Of 102 ischemic stroke patients, 62 (44.2%) were male and 40 (28.6%) were female. Of 38 hemorrhagic stroke patients, 24 (17.1%) were male and 14 were female (10%) [Figures 4 and 5].

In our study, the most common site of infarct was capsuloganglionic (20.71%), followed by parietal (9.28%), cerebellar (8.57%), and frontal lobe (5.71%) as shown in Table 2.

**Table 2: Topographic distribution of ischemic stroke**

Areas involved	Hemorrhage Number of cases (%)
Thalamus	8 (5.71)
Basal ganglia	4 (2.85)
Internal capsule	29 (20.71)
Pons	9 (6.42)
Midbrain	4 (2.85)
Cerebellar	12 (8.57)
Frontal	8 (5.71)
Parietal	13 (9.28)
Temporal	8 (5.71)
Occipital	7 (5.0)



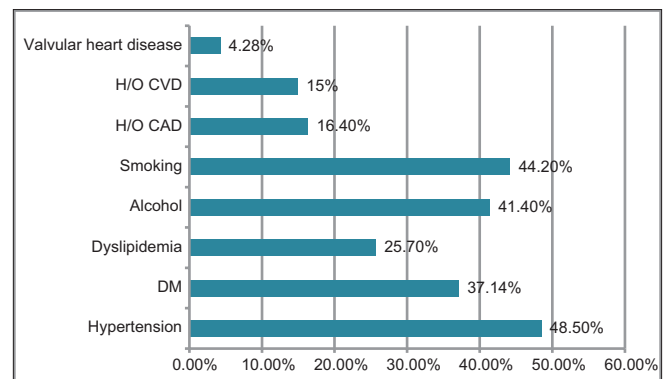
**Figure 3: Clinical presentation of stroke patients**

In our study, thrombotic stroke mostly involves the middle cerebral artery territory. In our study, the most common site of hemorrhage was capsuloganglionic (7.85%) followed by thalamus (5.0%) as shown in Table 1.

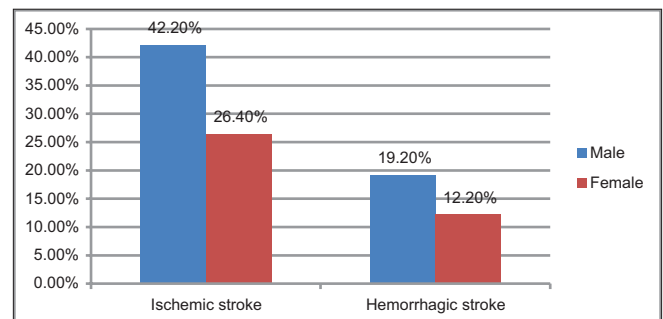
## DISCUSSION

The effects of stroke can vary enormously, depending on the area of the brain that has been damaged and the extent of the damage. Clinical features vary from paralysis communication difficulties (problems with speaking, reading, writing, and understanding) with mental processes such as learning, concentration, and memory. Some patients can present with visual disturbances, urinary incontinence, swallowing difficulties and emotional problems, etc. It can take time for the full implications of a stroke to sink in. It has a physiological, economical, and psychological impact on the patients.<sup>[7]</sup> Stroke ranks first among all central nervous system diseases both in frequency and gravity. Approximately 20 million people each year suffer from stroke and of these 5 million do not survive.<sup>[8]</sup> Older population-based studies in India conducted in Vellore and Rohtak quoted annual incidence of stroke as 13 per lac and 33 per lac persons, respectively.<sup>[9,10]</sup> Strokes form nearly 1.5% of all hospital admissions, 4.5% of all medical, and 20% of neurological cases.<sup>[11]</sup>

Mehndiratta *et al.* showed a ratio of 1:08 in North India, whereas El Zunni *et al.* demonstrated a similar ratio of 1.2:1



**Figure 4: Prevalence of risk factors in stroke patients**



**Figure 5: Gender-wise distribution of different types of stroke**

in Africa. The mean age of all the patients in our study was 31.92 years, a study in North India by Mehndiratta *et al.* showed a similar mean age of 31.97 years.<sup>[12,13]</sup>

Nagaraja *et al.*<sup>[14]</sup> had shown an incidence of smoking associated with stroke to be 15%, Dalal<sup>[8]</sup> 40%, Bogousslavsky and Pierre<sup>[15]</sup> 36.6%, and Alvarez *et al.*<sup>[16]</sup> 56.7%. In meta-analysis of 32 separate studies of relation between smoking and stroke analyzed by Shinton and Beevers,<sup>[17]</sup> there was a strong association between smoking and incidence of stroke. Our study showed 36%. In the study of Nagaraja *et al.*, the frequency of alcohol consumption was 15%, Alvarez *et al.*<sup>[18]</sup> 37.8%, and Dalal<sup>[15]</sup> 40%, the present study had 30%. In the study by Nagaraja *et al.*,<sup>[14]</sup> the incidence of diabetes was 11%, Dalal<sup>[15]</sup> 20%, Grindal *et al.*<sup>[19]</sup> 5.2%, El Zunni *et al.*<sup>[13]</sup> 14.8%, and Alvarez *et al.*<sup>[18]</sup> 10.9%, whereas in our study, it was 24%. In the present study, 16 patients (32%) had hypertension; Dalal<sup>[15]</sup> showed an incidence of 46.7%, Alvarez *et al.*<sup>[18]</sup> 23%, Nagaraja *et al.*<sup>[14]</sup> 22.6%, and Grindal *et al.*<sup>[19]</sup> 17.2%.

In the present study, the most common type of stroke was ischemic that is cerebral infarction (68.6%) which correlated with studies done by Aiyar, in which infarction was in 70%, in Eapen *et al.* was 68%, and in Devich and Karoli was 75%. The second most common type of stroke was hemorrhagic (31.4%) which correlated with a study done by Eapen *et al.* was 32%, Aiyar was 26%, and Devich and Karoli was 25%.<sup>[3,20,21]</sup>

In the present study, the most common site of hemorrhage was capsuloganglionic (20.71%), followed by parietal (9.28%), cerebellar (8.57%), and frontal lobe (5.71%). A study was done by Eapen *et al.* and Aiyer *et al.* where it has been concluded that in multiple hematoma sites, the most common was thalamic ganglionic region.

## CONCLUSION

In India, the incidence of stroke is increasing nowadays. There is a huge burden of stroke with significant regional variations of stroke in our county. The incidence of stroke is maximum in the age group of 51–60 years comprise 34.28%. Young patients who are affected with stroke were 10.71% of patient. Cerebral infarction was more than hemorrhage. Males were more affected than females in ischemic stroke as well as hemorrhagic. Hypertension was among leading risk factors for both types comprise

48.5% of patients followed by diabetes mellitus 37.14% and dyslipidemia 25.7% of patients. Hemiplegia was the most common presentation followed by speech involvement and facial palsy. In ischemic stroke, the most common site was internal (20.71%) followed by parietal (9.28%). In hemorrhage, the most common site was capsuloganglionic (7.85%) followed by thalamus (5.0%). We need holistic approach and more research to fight against this deadly and disabling disease.

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# Functional Outcome of Comminuted Fracture Shaft of Humerus Operated by Minimally Invasive Anterior Plate Osteosynthesis – A Prospective Study

V A Prabhu<sup>1</sup>, D Sanjay Kanth<sup>2</sup>

<sup>1</sup>Senior Assistant Professor, Department of Orthopaedics and Traumatology, Madurai Medical College, Government Rajaji Hospital, Madurai, Tamil Nadu, India, <sup>2</sup>Postgraduate, Department of Orthopaedics and Traumatology, Madurai Medical College, Government Rajaji Hospital, Madurai, Tamil Nadu, India

## Abstract

**Introduction:** Minimally invasive plate osteosynthesis (MIPO) has been advocated as a safe approach to humeral shaft fracture management.

**Aim:** This study aims to analyze and evaluate the functional outcome of surgical management of comminuted shaft of humerus by minimally invasive anterior plate osteosynthesis.

**Materials and Methods:** In this prospective study, patients with humeral shaft fractures were included in the study. All the patients with a comminuted diaphyseal fracture of humerus underwent MIPO technique. Constant–Murley score for shoulder and Mayo Elbow Performance Score (MEPS) for elbow were assessed postoperatively at 3 months, 6 months, and 2 years follow-up and score calculated at each visit.

**Results:** In 15 patients, the mean Constant score was 87 on the affected side and 90.67 on the unaffected side. The mean MEPS was 97.33 ranging from 85 to 100. The mean surgical time with MIPO was 69 min (range: 60–90 min). The average blood loss with MIPO was 109 ml (range: 75–150 min).

**Conclusion:** MIPO of the humerus gives good functional and cosmetic results and should be considered one of the management options in the treatment of humeral diaphyseal fractures.

**Key words:** Diaphyseal fracture, Humerus, Minimally invasive plate osteosynthesis

## INTRODUCTION

Humeral shaft fractures make up approximately 1% of all fractures. Typically, they are the result of direct trauma but also occur in sports where rotational forces are greater, for example, baseball or arm wrestling. Fractures of the middle or distal third of the shaft put the radial nerve at risk. In a small percentage of cases, humeral shaft fractures

are associated with a vascular injury. Open fractures are uncommon but can represent serious injuries, particularly if associated with crushing in industrial injuries.<sup>[1]</sup>

Non-operative treatment of diaphyseal humeral fractures can be accomplished with various techniques such as Velpeau bandage, a sling and body bandage, abduction cast or splint, coaptation splint or u-slab, hanging arm cast, and functional bracing. Functional bracing, as described by Sarmiento *et al.*, is widely used by orthopedic practitioners for the management of acute diaphyseal humeral fractures. Sarmiento *et al.* have also presented the largest series of 620 patients treated with functional bracing with adequate follow-up.<sup>[2]</sup>

By 1996, the previous list was enriched with segmental fractures, pathological fractures, bilateral fractures, floating

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**Corresponding Author:** Dr. D Sanjay Kanth, Department of Orthopaedics and Traumatology, Madurai Medical College, Government Rajaji Hospital, Madurai, Tamil Nadu, India.



elbow, polytrauma cases, neurologic loss after penetrating injury, associated vascular injury, and intra-articular fracture extension while some of the previous indications, such as open fractures or fractures associated with radial nerve palsy, were reassessed.<sup>[1]</sup>

Over the past 10–20 years, surgeons have paid attention to the details and secondary characteristics of fracture patterns and although the basic list of indications for operative treatment has not changed, more “relative” indications have been added.

Plating enables the surgeon to reduce and hold the critical articular or periarticular fragments. Although plating can be technically demanding, the results are predictable. Associated shoulder or elbow stiffness is infrequent, unless there is a periarticular or intra-articular extension of the fracture planes. Plating is also best for holding corrected malunion cases following osteotomy and remains the treatment of choice for non-union of the humerus.<sup>[3]</sup>

Another option for managing humeral fractures is intramedullary nailing. Recent designs include nails with smaller diameters, which are more flexible, have multiple locking options, and can compress the fracture. Humeral nails can be inserted either antegrade or retrograde in a reamed or unreamed manner.<sup>[4]</sup>

Minimally invasive approaches should be considered to plate a multifragmentary humeral shaft fracture and are usually performed with a pair of incisions, one distal and one proximal. Minimally invasive plate osteosynthesis (MIPO) techniques are challenging and have the benefit of reducing soft tissue damage but are not without their risks.<sup>[5]</sup>

### Aim

This study aims to analyze and evaluate the functional outcome of surgical management of comminuted shaft of humerus by minimally invasive anterior plate osteosynthesis.

## MATERIALS AND METHODS

Patients attending the Department of Orthopaedics in Government Rajaji Hospital and Madurai Medical College from November 2016 to October 2018 who are diagnosed with comminuted shaft of humerus fracture and willing for surgery.

### Inclusion Criteria

The following criteria were included in the study:

1. Fractures of the shaft of humerus
2. Age of more than 18 years

3. Simple injury
4. Mid-third comminuted fracture
5. Spiral fractures
6. Osteoporotic fractures.

### Exclusion Criteria

The following criteria were excluded from the study:

1. Patients who not fit for surgery
2. Patients below 18 years of age
3. Compound fractures
4. Vascular injury.

At the time of admission, fractures were classified according to the Orthopaedic Trauma Association classification. Nature of the injury was also noted. All the patients with comminuted diaphyseal fracture of humerus underwent MIPO technique. In the post-operative radiographs, humerus malalignment was measured. The degree of the angulation (varus or valgus), anteroposterior, rotational, and shortening were evaluated radiologically and clinically.

Constant–Murley score for shoulder and Mayo Elbow Performance Score (MEPS) for elbow were assessed postoperatively at 3 months, 6 months, and 2 years follow-up and score calculated at each visit.

## RESULTS

Among the 15 patients studied, the highest number of patients was seen in 40–60 years (53.3%) age group. Among the 15 cases, there were 9 male and 6 female patients with predominant male distribution. Among the patients studied, most of the patients had affected left side compared with right. Most cases were due to road traffic accidents (73.3%). The other mechanisms are accidental fall (26.6%). Among the 15 cases, 6 cases had no angulation and 5 cases did have minimum angulation of  $<10^\circ$  of varus or valgus angulation. Three cases had varus angulation ( $>10^\circ$ ) which showed no significant functional impairment and no cases had valgus angulation. One case had reported posterior angulation due to excessive plate contouring. None of the patients had any amount of rotational malalignment or shortening [Figures 1 and 2]. The mean union time is 11.9 weeks, ranging from 8 to 20 weeks. With respect to shoulder range of motion, among the 15 patients; 9 patients (60%) had excellent results, 4 patients (26.7%) had good result, 2 (13.3%) had fair result, and no poor result. With respect to elbow range of motion, among the 15 patients; 12 patients (80%) had excellent results, 3 patients (20%) had good result, no fair result, and no poor result [Table 1]. Shoulder function is assessed by Constant–Murley score. The mean

Constant score was 87 on the affected side and 90.67 on the unaffected side. Shoulder function was assessed by Constant–Murley score. Among the 15 patients, 14 patients had excellent results and 1 patient had good result [Table 2]. The mean MEPS was 97.33 ranging from 85 to 100. Elbow function score was assessed by MEPS. Among the 15 patients, all patients had excellent elbow

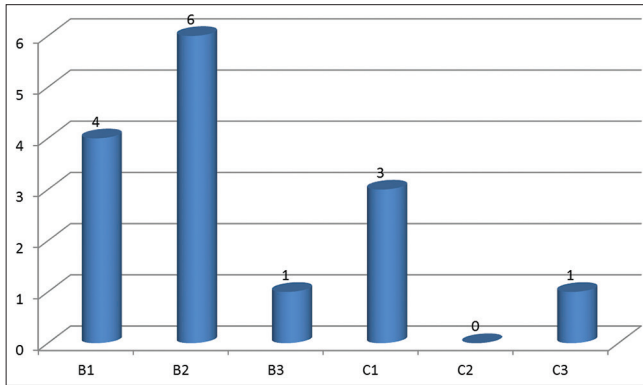


Figure 1: OTA classification

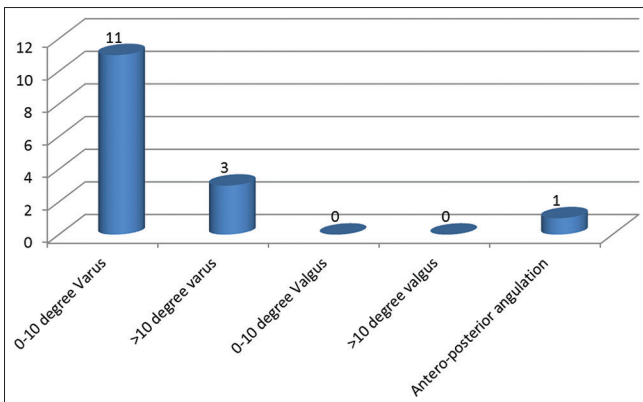


Figure 2: Radiological valgus/varus angulation

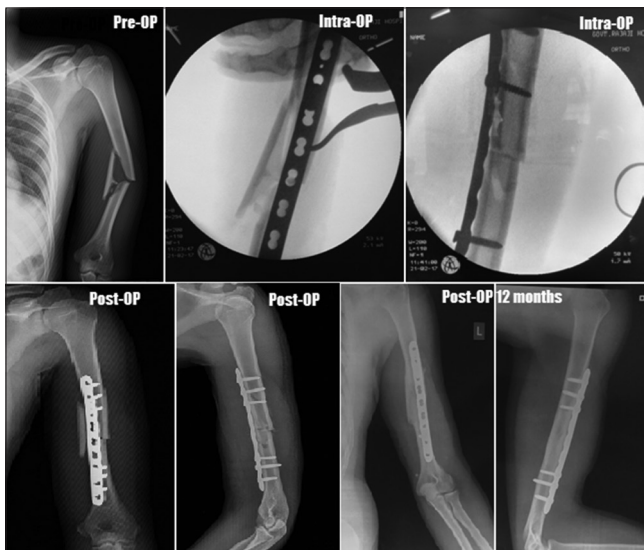


Figure 3: Simple #shaft of humerus left mid-third comminuted

function score. The mean surgical time with MIPO was 69 min (range: 60–90 min). The average blood loss with MIPO was 109 ml (range: 75–150 min). Two of 15 had radial nerve palsy postoperatively. Postoperatively, these cases are given with cock-up splints, preferably dynamic cock-up splints. Nerve conduction study was done in these two cases by 6 weeks. Recovery was assessed at every follow-up by sensory and motor examination. One case had full recovery by the end of 6 months and the other case showed no recovery by the end of 1 year for which tendon transfer planned. One case showed delayed union by 20 weeks. The fracture was fixed in distraction [Figure 3].

## DISCUSSION

Minimally invasive surgical treatment of skeletal injuries aims to preserve the biology of soft tissue and bone. The rationale for performing mechanical stabilization through fracture fixation is the obvious need to restore anatomy and mechanical function of the bone. Optimal bone healing requires a balance between mechanics and biology and is aided by modern osteosynthesis. In open reduction internal fixation (ORIF), the problem was that, all too often, precise reduction and absolute stable fixation were achieved at the expense of extensive soft tissue trauma caused by the surgery.

MIPO scores over open reduction and plate fixation of humerus fractures by decreasing the surgical trauma to the soft tissue and maintaining the periosteal circulation. Application of the plate on the bone by an open technique interferes with the local vascularization, leading to osteonecrosis beneath the implant, which can cause delayed healing or non-healing (the reported rate of non-union being 5.8%). The primary bone healing without callus formation is not very strong and there exists a real risk

Table 1: Shoulder/elbow range of motion

Range of motion	Shoulder	Elbow
Excellent (100%)	9	12
Good (75–100%)	4	3
Fair (50–75%)	2	-
Poor (<50%)	-	-
Total	15	15

Table 2: Functional outcome

Outcome	Constant score	MEPS
Excellent	14	15
Good	1	0
Fair	0	0
Poor	0	0

MEPS: Mayo Elbow Performance Score

for refracture after removal of the implant in the open technique. MIPO is that it is devoid of the entry point problems of intramedullary nailing such as rotator cuff impingement.<sup>[6]</sup>

The average union time for fractures in our study was 11.9 weeks (range: 8–20 weeks) and the union rate was 93.7%. One case showed delayed union by 20 weeks. The fracture was fixed in distraction at fracture site due to excessive traction after initial proximal screw placement. The results were good compared to Concha *et al.* study where union rate was 91.5% (32/35) at an average of 12 weeks. All the cases showed union without primary or secondary bone grafting.<sup>[7]</sup>

ORIF for comminuted fractures draws the need for lag screw fixation or bone grafting which prolongs the surgery time, blood loss, and post-operative morbidity. Nevertheless, the risk of non-union rate is higher than MIPO due to extensive soft tissue stripping according to literature around 5.8%. MIPO gains advantage over ORIF in these issues.

Esmailiejah *et al.* found better results with MIPO when compared to open reduction and plating as regard to the time of surgery and iatrogenic radial nerve injury (3% vs. 12%) and the rate of infection (0% vs. 6%), patients managed with the MIPO technique had also shorter time for union and earlier return to their previous level of activities.<sup>[8]</sup>

Of the 15 cases, 4 cases had more than 10° angulation which does not show any functional impairment. Hence, near-normal biological reduction in MIPO does not compromise on functional outcome of the patient.

The mean surgical time with MIPO was 69 min (range: 60–90 min) which was less compared to Shetty *et al.* study which was 91.5.<sup>[6]</sup>

Shoulder function was assessed by Constant–Murley score which was 87 on affected side and 90.67 on healthy side and better compared to Apivatthakakul *et al.* study which reported 85.8 on affected side and 90.6 on the healthy side.<sup>[9]</sup>

The mean MEPS for the elbow is 97.66 which was comparable to other studies.

No cases reported infection postoperatively which was better compared to Concha *et al.* study which reported two cases of infection.<sup>[7]</sup>

Post-operative iatrogenic radial nerve palsy was reported in two cases which were higher compared to Deepak *et*

*al.*<sup>[10]</sup> study and Hadhoud *et al.*;<sup>[11]</sup> one case recovered by 6 months follow-up and one case did not show recovery at 1 year for which tendon transfer planned subsequently. These nerve injuries occurred earlier in the study probably due to plate offset and unicortical drilling with chance of drill bit slippage into the neural structures posteriorly. Hence, plate position should be visualized digitally and radiologically before drilling. Take care to be in the proper intermuscular plain and the plate advanced gently in close contact to bone over the anterior surface in a proximal to distal direction to protect deltoid insertion. The forearm must be positioned in supination; pronation brings the radial nerve closer to plate according to Apivatthakakul *et al.*<sup>[9]</sup> study. The scar was cosmetically acceptable when compared to ORIF. The average blood loss was less compared to ORIF and all the patients showed early return of activities due to decreased post-operative morbidity.

## CONCLUSION

MIPO offers excellent functional outcome for the comminuted shaft of humerus with better union rate and decreased risk of non-union compared to ORIF. Near-normal biological reduction in MIPO offers equally good functional outcome with better union rate compared to anatomical reduction in ORIF, more so for comminuted fractures. There is decreased post-operative morbidity with early return to function. The operating time and blood loss are less compared to ORIF. The chance of infection is negligible due to decreased surgical exposure. Risk of radial nerve palsy is there to start with, but with experience can be neglected.

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# A Study of Correlation of Clinical Variables with Presenting Stage and Type of Endometrial Cancer at a Tertiary Care Hospital - A Retrospective Study

B Sravanthi<sup>1</sup>, K V S Latha<sup>2</sup>

<sup>1</sup>Postgraduate, Department of Medical Oncology, Madras Medical College, Chennai, Tamil Nadu, India, <sup>2</sup>Associate Professor, Department of Medical Oncology, Madras Medical College, Chennai, Tamil Nadu, India

## Abstract

**Introduction:** The prevalence of gynecological cancers has been increasing in the Asian population. With the recent changing trend in lifestyle and reproductive profile of women, the number of cases being diagnosed with endometrial cancer is increasing.

**Aim:** The aim of this study is to evaluate the correlation of various clinical risk factors of endometrial carcinoma on the histopathology and presenting stage of the disease.

**Materials and Methods:** A hospital-based, retrospective study included 100 patients of endometrial carcinoma presented at the Institute of Obstetrics and Gynaecology, Chennai, India, between January 2016 and June 2019. The correlation of age ( $\leq 40$  years and  $> 40$  years), parity status (parous and nulliparous), menstrual status (premenopause and postmenopause), diabetes, hypertension, duration of complaint ( $\leq 6$  months and  $> 6$  months), and body mass index (BMI) with the stage of the disease (clinical/radiological and pathological stages) and histological class was analyzed.

**Results:** The mean age of patients was  $56.4 \pm 11.3$  years. Among the 100 patients, a total of 62 (63.6%) patients had presented with clinical/radiological stage-I, of which 6 patients had defaulted for treatment and 6 patients had the stage-IV disease. Of the 88 patients who underwent staging laparotomy, 59 (67%) patients had pathological stage-I carcinoma and 3, 18, and 8 patients presented in stage II, III, and IV disease, respectively. Histopathological evaluation revealed endometrioid adenocarcinoma as the most common type, in 79 patients (79%). No significant correlation of any of the risk factors on clinical/radiological, pathological as well as on histopathology was observed.

**Conclusion:** The study did not state the statistically significant association of age, parity status, menopause, diabetes, hypertension, BMI, and the duration of complaints with the histological class of endometrial carcinoma and presenting clinical and pathological stages of endometrial carcinoma.

**Key words:** Clinical factors, Endometrial cancer, Pathological correlation

## INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in the Western world and is the second-most common gynecological malignancy in developing countries.<sup>[1,2]</sup> Anciently, endometrial carcinoma was a disease of developed countries, but due to changing trends in the lifestyle and

reproductive profile of women, the prevalence of endometrial carcinoma is increasing in developing countries as well. The etiological factors responsible for the development of endometrial carcinoma are increasing age ( $> 55$  years), obesity, hypertension, diabetes, nulliparity, menopause, high level of estrogen/endometrial hyperplasia, genetic mutation, and tamoxifen use (breast cancer).<sup>[2-4]</sup> Abnormal uterine bleeding (e.g., menometrorrhagia and postmenopausal bleeding) is a typical presenting symptom in women with endometrial carcinoma. Endometrial carcinoma is primarily a disease of postmenopausal women and only 20–25% of cases occur in the premenopausal population (age  $< 45$  years).<sup>[2,3]</sup>

Conventionally, endometrial carcinomas have been classified on the basis of clinical, endocrine, and epidemiological

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**Corresponding Author:** Dr. K V S Latha, Department of Medical Oncology, Madras Medical College, Chennai, Tamil Nadu, India.



characteristics as Type-I tumors (estrogen-dependent, and associated with endometrial hyperplasia) and Type-II tumors (estrogen-independent and associated with endometrial atrophy). Histopathological characteristics of endometrial carcinoma categorize it into different subtypes such as endometrioid adenocarcinoma, serous adenocarcinoma, serous endometrioid intraepithelial carcinoma, clear-cell carcinoma, mixed epithelial carcinoma, mucinous adenocarcinoma, endometrial stromal sarcoma, papillary serous carcinoma, squamous cell carcinoma, and malignant mixed Müllerian tumor.<sup>[4,5]</sup> There are lack of data on correlation of various etiological factors with clinic-pathological stages and with the histopathological class of endometrial carcinoma.

### Aim

The aim of this study is to study the effect of various clinical variables on the histopathological and clinical/pathological stages of endometrial carcinoma.

## MATERIALS AND METHODS

This hospital-based, retrospective study was conducted at the Institute of Obstetrics and Gynaecology, Chennai, India. The study included 100 patients who were diagnosed and treated for endometrial carcinoma between January 2016 and June 2019. The baseline demographic details, clinical, staging, and a histopathological class of endometrial carcinoma of all the patients were collected in a retrospective manner from the medical records of the oncology department of the hospital. The demographic details such as age, medical history, body mass index (BMI), marital and parity status, age of menopause, and family history of cancer; and clinical signs and symptoms reported during presentation were also identified from the records the stages of endometrial cancer were derived according to the International Federation of Gynaecology and Obstetrics (FIGO) 2009 classification as clinical/radiological stages (by computed tomography chest and abdomen) and pathological stages (by staging laparotomy). The details of histopathological type with grade were also derived.

The correlation of age ( $\leq 40$  years and  $> 40$  years), parity status (parous and nulliparous), menstrual status (premenopause and postmenopause), coexisting illnesses such as diabetes, hypertension, duration of complaint ( $\leq 6$  months and  $> 6$  months), and BMI with the stage of the disease (clinical/radiological and pathological stages), and histological class was analyzed. BMI was classified as per the Asian criteria for BMI into eight groups – underweight:  $< 18.5$  kg/m<sup>2</sup>, normal: 18.5–22.9 kg/m<sup>2</sup>, overweight: 23–24.9 kg/m<sup>2</sup>, preobese: 25–29.9 kg/m<sup>2</sup>, obese

type-1: 30–40 kg/m<sup>2</sup>, obese type-2: 40.1–50 kg/m<sup>2</sup>, and obese type-3:  $> 50$  kg/m<sup>2</sup>.

The statistical analyses were performed using the SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA). The Chi-square, Gamma Statistic, and Fisher's exact tests were used when appropriate to assess the relationships between clinic-pathologic variables and clinical variable and two-sided  $P < 0.05$  was considered statistically significant. Quantitative data are presented as a mean and standard deviation, and qualitative data are presented as frequency and percentage.

## RESULTS

The study included retrospective data of 100 patients who were diagnosed with endometrial carcinoma. The mean age of patients was  $56.4 \pm 11.3$  years. Among all, 91 (91%) patients were diagnosed with endometrial carcinoma after the age of 40 years. The disease was diagnosed after an average of  $15.3 \pm 7.5$  years postmenopause. Total 6 cases had other malignancies along with endometrial carcinoma, which includes two cases of ovarian carcinoma, 2 cases of breast carcinoma, 1 case of cervical carcinoma, and 1 case of ovarian and cervical carcinoma. Table 1 displays the demographic details of the patients. Among all clinical presentation, abnormal vaginal bleeding was found as the most common sign of endometrial carcinoma in 63 (85.1%) postmenopausal and 18 (69.2%) premenopausal women. Other complaints observed in patients with endometrial carcinoma were white discharge, abdominal pain, and abdominal mass.

The staging of endometrial carcinoma was observed as: (i) clinical/radiological stage and (ii) pathological stage. A total of 62 (62.6%) patients were presented with clinical/radiological stage-I carcinoma and 59 (67%) patients with pathological stage-I carcinoma.

Histopathological evaluation of the present study revealed endometrioid adenocarcinoma in 78 patients, among which 39 (49.4%) patients diagnosed with well-differentiated (Grade-1), 22 (27.8%) with moderately-differentiated (Grade-2), and 17 (21.5%) with poorly-differentiated (Grade-3). Three patients were diagnosed with clear-cell adenocarcinoma. Seven patients were diagnosed with endometrial stromal sarcoma with 6 low-grade well-differentiated sarcomas and 1 high-grade undifferentiated sarcoma. Mucinous endometrial adenocarcinoma was discovered in 3 patients, of which 2 were well-differentiated (Grade-1) and 1 was moderately-differentiated (Grade-2). Only 1 case of poorly-differentiated squamous cell carcinoma was observed. Furthermore, staging laparotomy

was performed in 88 patients and among them, >50% myometrial invasion was observed in 62 (70.5%) patients and <50% myometrial invasion in 26 (29.5%) patients.

Furthermore, we have analyzed the correlation of baseline demographic criteria (age, parity status, menstrual status,

diabetes, hypertension, BMI, and duration of complaints) with clinical/radiological stage [Table 2], pathological stage [Table 3] and histo-pathological class of endometrial carcinoma [Table 4]. However, no significant association of any of the risk factors on clinical/radiological, pathological as well as on histopathological type was observed. As endometrioid adenocarcinoma has been found as a most common type of endometrial carcinoma, we have also analyzed the association of baseline demographics with the occurrence of well, moderately, and poorly differentiated adenocarcinoma of the endometrium. No significant association of any of the parameter was found in our study [Table 5].

## DISCUSSION

The present study evaluated the correlation of various etiological parameters (age, parity status, menopause, diabetes, hypertension, BMI, and duration of complaint) of endometrial carcinoma with histopathological class and stages of the disease. Approximately 75% of patients were clinically diagnosed with early-stage disease (FIGO stage-I and -II).<sup>[1]</sup> Age is considered the main risk factor, with most cases occurring in women over the age of 50 years. Women with age >55 years have 1.4 relatively higher risks of the development of endometrial carcinoma.<sup>[6,7]</sup> In our study,

**Table 1: Baseline demographic details of all the patients**

Characteristics	Number of patients=100
Age, years (mean±SD)	56.4±11.3
Age group, n (%)	
≤40 years	9 (9%)
>40 years	91 (91%)
Diabetes mellitus, n (%)	30 (30%)
Hypertension, n (%)	45 (45%)
BMI, kg/cm <sup>2</sup> (n=97) (mean±SD)	26.5±6.0
Marital status, n (%)	
Married	92 (92%)
Unmarried	8 (8%)
Parity	
Parous, n (%)	85 (85%)
Age of parous (mean±SD)	57.0±10.8
Nulliparous, n (%)	15 (15%)
Age of nulliparous (mean±SD)	53.3±13.5
Menopause, n (%)	
Yes	74 (74%)
No	26 (26%)
Menopause years (mean±SD)	15.3±7.5

SD: Standard deviation

**Table 2: Correlation of various etiological variables with clinical/radiological stages of endometrial carcinoma**

Characteristics	Clinical/radiological stages (n=99)								P-value	Gamma correlation
	I n=62 (%)	II n=6 (%)	III-A n=8 (%)	III-B n=3 (%)	III-C1 n=13 (%)	III-C2 n=1 (%)	IV-A n=1 (%)	IV-B n=5 (%)		
Age										
≤40 years	4 (6.5)	1 (16.7)	1 (12.5)	0	3 (23.1)	00	00	0	0.326	-0.269
>40 years	58 (93.5)	5 (83.3)	7 (87.5)	3 (100)	10 (76.9)	1 (100)	1 (100)	5 (100)		
Parity										
Parous	50 (80.6)	5 (83.3)	7 (87.5)	3 (100)	13 (100)	0	1 (100)	5 (100)	0.072	-0.435
Nulliparous	12 (19.4)	1 (16.7)	1 (12.5)	0	0	1 (100)	0	0		
Menopause										
Premenopausal	16 (25.8)	0	6 (75.0)	0	3 (21.4)	1 (100)	0	0	0.929	0.018
postmenopausal	46 (74.2)	6 (100)	2 (25.0)	2 (100)	11 (78.6)	0	1 (100)	5 (100)		
Diabetes										
No	44 (71.0)	3 (50.0)	6 (75.0)	0	10 (71.4)	1 (100)	1 (100)	4 (80.0)	0.965	0.009
Yes	18 (29.0)	3 (50.0)	2 (25.0)	2 (100)	4 (28.6)	0	0	1 (20.0)		
Hypertension										
No	31 (50.0)	3 (50.0)	6 (75.0)	0	10 (71.4)	1 (100)	1 (100)	2 (40.0)	0.25	-0.201
Yes	31 (50.0)	3 (50.0)	2 (25.0)	2 (100)	4 (28.6)	0	0	3 (60.0)		
BMI range (kg/m <sup>2</sup> )										
Underweight <18.5	3 (5.0)	1 (16.7)	0	0	1 (7.1)	0	1 (100)	0	0.071	-0.225
Normal: 18.5–22.9	11 (18.3)	1 (16.7)	2 (28.6)	1 (50.0)	2 (14.3)	1 (100)	0	1 (20.0)		
Overweight: 23–24.9	9 (15.0)	1 (16.7)	1 (14.3)	1 (50.0)	3 (21.4)	0	0	1 (20.0)		
Preobese: 25–29.9	15 (25.0)	3 (50.0)	3 (42.9)	0	5 (35.7)	0	0	2 (40.0)		
Obese type-1:30–40	20 (33.3)	0	1 (14.3)	0	3 (21.4)	0	0	1 (20.0)		
Obese type-2: 40.1–50	2 (3.3)	0	0	0	0	0	0	0		
Duration of complaint										
≤6 months	44 (73.3)	5 (83.3)	8 (100)	1 (33.3)	9 (69.2)	1 (100)	1 (100)	3 (60.0)	0.966	0.009
>6 months	16 (26.7)	1 (16.7)	0	2 (66.7)	4 (30.8)	00	0	2 (40.0)		

BMI: Body mass index

**Table 3: Correlation of various etiological variables with pathological stages of endometrial carcinoma**

Characteristics	Pathological stages (n=88)								P-value	Gamma correlation
	I-A n=23 (%)	I-B n=36 (%)	II n=3 (%)	III-A n=8 (%)	III-B n=2 (%)	III-C1 n=8 (%)	IV-A n=1 (%)	IV-B n=7 (%)		
Age										
≤40 years	2 (8.7)	1 (2.8)	0	1 (12.5)	0	1 (12.5)	0	2 (28.6)	0.393	-0.288
>40 years	21 (91.3)	35 (97.2)	3 (100.0)	7 (87.5)	2 (100)	7 (87.5)	1 (100)	5 (71.4)		
Parity										
Parous	21 (91.3)	26 (72.2)	3 (100.0)	8 (100.0)	2 (100)	8 (100)	1 (100)	4 (57.1)	0.751	0.068
Nulliparous	2 (8.7)	10 (27.8)	0	0	0	0	0	3 (42.9)		
Menopause										
Premenopausal	9 (39.1)	5 (13.9)	0	5 (62.5)	0	2 (25.0)	0	2 (28.6)	0.623	0.089
postmenopausal	14 (60.9)	31 (86.1)	3 (100)	3 (37.5)	2 (100)	6 (75.0)	1 (100)	5 (71.4)		
Diabetes										
No	18 (78.3)	24 (66.7)	2 (66.7)	6 (75.0)	1 (50.0)	4 (50.0)	1 (100)	5 (71.4)	0.353	0.16
Yes	5 (21.7)	12 (33.3)	1 (33.3)	2 (25.0)	1 (50.0)	4 (50.0)	0	2 (28.6)		
Hypertension										
No	14 (60.9)	15 (41.7)	1 (33.3)	5 (62.5)	1 (50.0)	4 (50.0)	1 (100.0)	5 (71.4)	0.860	-0.028
Yes	9 (39.1)	21 (58.3)	2 (66.7)	3 (37.5)	1 (50.0)	4 (50.0)	0	2 (28.6)		
BMI range (kg/m <sup>2</sup> )										
Underweight: <18.5	2 (8.7)	1 (2.9)	0.0	1 (14.3)	0	0	1 (100)	1 (14.3)	0.333	-0.124
Normal: 18.5–22.9	3 (13.0)	8 (23.5)	0.0	1 (14.3)	1 (50.0)	1 (12.5)	0	3 (42.9)		
Overweight: 23–24.9	5 (21.7)	4 (11.8)	1 (33.3)	1 (14.3)	0	2 (25.0)	0	0		
Preobese: 25–29.9	4 (17.4)	11 (32.4)	2 (66.7)	3 (42.9)	1 (50.0)	2 (25.0)	0	1 (14.3)		
Obese type-1: 30–40	8 (34.8)	10 (29.4)	0	1 (14.3)	0	3 (37.5)	0	1 (14.3)		
Obese type-2: 40.1–50	1 (4.3)	0	0	0	0	0.0	0	1 (14.3)		
Duration of complaint										
≤6 months	16 (72.7)	27 (77.1)	2 (66.7)	8 (100)	0	5 (62.5)	1 (100)	7 (100)	0.514	-0.12
>6 months	6 (27.3)	8 (22.9)	1 (33.3)	0.0	2 (100)	3 (37.5)	0	0		

BMI: Body mass index

**Table 4: Correlation of various etiological variables with the histological class of endometrial carcinoma**

Characteristics	Histopathology (n=99)									P-value	Gamma correlation
	EA n=78 (%)	ESS n=7 (%)	CCA n=3 (%)	MEA n=3 (%)	PSC n=3 (%)	EAV n=2 (%)	MMT-CH n=1 (%)	MEC (EA+PSC) n=1 (%)	SCC n=1 (%)		
Age											
≤40 years	5 (6.3)	2 (28.6)	0	1 (33.3)	0	1 (50.0)	0	0	0	0.183	-0.454
>40 years	74 (93.7)	5 (71.4)	3 (100)	2 (66.7)	3 (100)	1 (50.0)	1 (100)	1 (100)	1 (100)		
Parity											
Parous	67 (84.8)	7 (100)	2 (66.7)	2 (66.7)	3 (100)	1 (50.0)	1 (100)	1 (100)	1 (100)	0.968	-0.009
Nulliparous	12 (15.2)	0	1 (33.3)	1 (33.3)	0	1 (50.0)	0	0	0		
Menopause											
Premenopausal	19 (24.1)	4 (57.1)	0	1 (33.3)	1 (33.3)	0	0	0	1 (100)	0.545	-0.167
postmenopausal	60 (75.9)	3 (42.9)	3 (100)	2 (66.7)	2 (66.7)	2 (100)	1 (100)	1 (100)	0		
Diabetes											
No	53 (67.1)	7 (100)	2 (66.7)	2 (66.7)	3 (100)	1 (50.0)	0.0	0	1 (100)	0.264	-0.283
Yes	26 (32.9)	0	1 (33.3)	1 (33.3)	0	1 (50.0)	1 (100)	1 (100)	0		
HTN											
No	42 (53.2)	6 (85.7)	0.0	2 (66.7)	2 (66.7)	1 (50.0)	0	1 (100)	1 (100)	0.541	-0.145
Yes	37 (46.8)	1 (14.3)	3 (100)	1 (33.3)	1 (33.3)	1 (50.0)	1 (100)	0	0		
BMI range (kg/m <sup>2</sup> )											
Underweight: <18.5	3 (3.9)	3 (50.0)	0	0	0	0	0	0	0	0.107	-0.254
Normal: 18.5–22.9	15 (19.5)	0	2 (66.7)	1 (33.3)	0	1 (50.0)	0	1 (100)	0		
Overweight: 23–24.9	13 (16.9)	1 (16.7)	0	0	0	1 (50.0)	1 (100)	0	0		
Preobese: 25–29.9	22 (28.6)	2 (33.3)	1 (33.3)	2 (66.7)	1 (33.3)	0	0	0	0		
Obese type-1: 30–40	22 (28.6)	0	0	0	2 (66.7)	0	0	0	1 (100)		
Obese type-2: 40.1–50	2 (2.6)	0	0	0	0	0	0	0	0		
Duration of complaint											
≤6 months	57 (74.0)	6 (85.7)	2 (66.7)	3 (100)	2 (66.7)	1 (50.0)	1 (100)	1 (100)	0	0.946	-0.018
>6 months	20 (26.0)	1 (14.3)	1 (33.3)	0	1 (33.3)	1 (50.0)	0	0	1 (100)		

HTN: Hypertension, BMI: Body mass index, EA: Endometrioid adenocarcinoma, ESS: Endometrial stromal sarcoma, CCA: Clear cell adenocarcinoma, MEA: Mucinous endometrial adenocarcinoma, PSC: Papillary serous carcinoma, EAV: Endometrial adenocarcinoma villoglandular type, MMT-CH: Malignant mixed mullerian tumor - carcinosarcoma of homologous type, MEC: Mixed epithelial carcinoma, SCC: Squamous cell carcinoma

**Table 5: Correlation of various etiological variables with development endometrioid adenocarcinoma**

Characteristics	Endometrioid adenoca (n=78)			P-value	Gamma correlation
	WD (Grade-1) n=39 (%)	MD (Grade-2) n=22 (%)	PD (Grade-3) n=17 (%)		
Age					
≤40 years	1 (2.6)	1 (4.5)	3 (17.6)	0.122	-0.629
>40 years	38 (97.4)	21 (95.5)	14 (82.4)		
Parity					
Parous	32 (82.1)	21 (95.5)	13 (76.5)	0.961	-0.014
Nulliparous	7 (17.9)	1 (4.5)	4 (23.5)		
Menopause					
Premenopausal	10 (25.6)	4 (18.2)	5 (29.4)	0.985	-0.004
postmenopausal	29 (74.4)	18 (81.8)	12 (70.6)		
Diabetes					
No	29 (74.4)	11 (50.0)	12 (70.6)	0.349	0.178
Yes	10 (25.6)	11 (50.0)	5 (29.4)		
Hypertension					
No	22 (56.4)	9 (40.9)	10 (58.8)	0.784	0.052
Yes	17 (43.6)	13 (59.1)	7 (41.2)		
BMI range (kg/m <sup>2</sup> )					
Underweight: <18.5	1 (2.7)	0 (0.0)	2 (11.8)	0.886	-0.02
Normal: 18.5–22.9	8 (21.6)	3 (13.6)	3 (17.6)		
Overweight: 23–24.9	7 (18.9)	4 (18.2)	2 (11.8)		
Preobese: 25–29.9	9 (24.3)	8 (36.4)	5 (29.4)		
Obese Type-1: 30–40	10 (27.0)	7 (31.8)	5 (29.4)		
Obese Type-2: 40.1–50	2 (5.4)	0	0		
Duration of complaint					
≤6 months	25 (65.8)	14 (66.7)	12 (70.6)	0.75	-0.065
>6 months	13 (34.2)	7 (33.3)	5 (29.4)		

BMI: Body mass index, WD: Well differentiated, MD: Moderately differentiated, PD: Poorly differentiated

only 9% of women with age <40 years were diagnosed with endometrial carcinoma. No statistically significant correlation of patient's age with histopathological class and clinical and pathological stage were found in our study.

Obesity is considered as a key factor which leads to the development of about 30% of all cancers in humans and increasing BMI has strong associated with endometrial cancer incidences and mortality. A recent meta-analysis revealed that with each increase in BMI of 5 kg/m<sup>2</sup>, the woman's risk of developing endometrial cancer significantly increase by 1.59.<sup>[8,9]</sup> In obese women, the exposure of estrogen to endometrial tissue is more due to excessive estrogen production by the conversion of androgens in the fat. A study by Cauley *et al.*<sup>[10]</sup> also proved in that obese (BMI >30) postmenopausal women have >40% increases in both circulating estrone and estradiol levels compared to normal (BMI <27) postmenopausal women. Literature states that high-BMI has good prognostic features, including low-grade tumor, endometrioid histology, and presentation at the early stage. However, patients with low BMI are expected to have high-grade tumors, nonendometrioid histology and may present at advanced stages of endometrial carcinoma with poorer clinical outcomes.<sup>[7]</sup> In our study also, 22 patients with BMI ≥30 kg/m<sup>2</sup> were presented with clinical stage I of endometrial carcinoma, 19 patients presented with pathological stage IA and IB.

Most of the patients ( $n = 24$ ) with BMI of ≥30 kg/m<sup>2</sup> were diagnosed with endometrial adenocarcinoma. However, no significant correlation between BMI and obesity was observed with histological class and clinical/pathological stages of endometrial carcinoma.

Nulliparity is associated with a two-fold increase in the risk of development of endometrial carcinoma. The reason behind this might be related to the absence of progesterone in women who are infertile, which resulting in continuous unopposed estrogen stimulation. However, multiple factors might be involved in this, and it might be related to the individual's hormonal profile during life. It has been found that nulliparous women have a significantly increased number of endometrial shedding events during their menstrual lives compared to parous women which might increase the risk of endometrial carcinoma in such women.<sup>[2–4]</sup> In our study, we tried to establish correlate nulliparity with the stages of endometrial carcinoma and histological grades, but no such association was found between them which guided toward conduction of larger studies to prove this. Diabetes and hypertension were also found to increase the risk of development of endometrial carcinoma by 1.8–2.0-fold and 1.5-fold, respectively.<sup>[3]</sup> The present study also analyzed the correlation between diabetes and hypertension with histological class and clinical and pathological stages, but no significant correlation has been

proved. It was also found that premenopausal women were presented with early stage of endometrial carcinoma and with less complexly differentiated tumors, but in our study, it was not established.<sup>[2,3]</sup>

Among all histological subtypes of endometrial carcinoma, endometrial adenocarcinoma is the most common type diagnosed in around 50–60% of cases. Endometrial adenocarcinoma is further graded into three types depending on the differentiation of tumor as well-differentiated, moderately differentiated, and poorly differentiated carcinoma. Here, in this study, we also analyzed the role of various risk factors of endometrial carcinoma (age, parity status, menopause, diabetes, hypertension, BMI, and duration of complaint) with tumor differentiation in endometrial adenocarcinoma. However, no significant association was noted of each risk factor with the differentiation of tumor cells in endometrial adenocarcinoma.

## CONCLUSION

From the results of the present study, it can be concluded that age, parity status, menopause, diabetes, hypertension, BMI, and duration of complaints have no association with the histological class of endometrial carcinoma and

also with clinical and pathological stages of endometrial carcinoma. However, larger trials are required to prove this with more number of patients of endometrial carcinoma.

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# Utility of Global Longitudinal Strain in Predicting Obstructive Coronary Artery Disease in Intermediate Risk Patients

Jahangeer Basha Shaik<sup>1</sup>, V S Bharathi Lakshmi<sup>2</sup>, L S R Krishna<sup>3</sup>

<sup>1</sup>Senior Resident, Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India, <sup>2</sup>Assistant Professor, Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India, <sup>3</sup>Professor, Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

## Abstract

**Introduction:** Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in the world and has nearing its epidemic proportions. Although CAD mortality rates worldwide have declined over the past four decades, CAD remains responsible for about one-third or more of all deaths in individuals overage.

**Aims and Objectives:** The primary objective of the study is to see the correlation between global longitudinal strain assessed by tissue Doppler imaging or two-dimensional (2D) speckle tracking echocardiography and CAD as assessed by coronary angiography in intermediate-risk patients.

**Materials and Methods:** This was a prospective clinical study, Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad. Patients admitted with symptoms of stable CAD during the period June 12 to November 30, 2017 were studied.

**Results:** Total number of patients with a clinical diagnosis of stable angina at intermediate risk of CAD as per Framingham Risk Score admitted to the hospital during the study period is 50. Out of 50 patients, five patients refused coronary angiogram.

**Conclusion:** Global longitudinal strain (GLS) assessed by 2D-STE at rest is a predictor of significant CAD. GLS has high sensitivity for early detection of significant CAD in intermediate risk patients. 2D-STE has the potential to improve the value of echocardiography in the detection of the CAD, identifying high-risk patients.

**Key words:** Intermediate risk patients, Longitudinal Strain, Significant CAD

## INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in the world and has nearing its epidemic proportions. Although CAD mortality rates worldwide have declined over the past four decades, CAD remains responsible for about one-third or more of all deaths in individuals overage 35.<sup>[1-3]</sup> CAD causes 9.4% of total deaths (25 lakhs) in underdeveloped countries and 16.3% (13 lakhs) of all deaths in developed countries.<sup>[1]</sup> The World

Health Organization has calculated the year of 2002 alone, 12.6% of deaths in the world were because of CAD.<sup>[2]</sup> The proportion of CAD is expected to increase as it is the disease of aging and the world population getting older.

India has a similar scenario. Indian studies have revealed that cardiovascular diseases (CVD) cause about 40% of deaths in the urban areas and 30% of deaths in rural areas in India.<sup>[3]</sup> Prevalence of CVD in the adult population has multiplied in urban areas from around 2% in early 1960s to 6.5% in late 1970s, 7% during the year 1980, to close 10% in 1990, and to a critical 10.5% in the year 2000. At the same time in rural areas, it is increased to a smaller extent from about 2% during 1970 to 2.5% in late 1980s, and to calculate 4% in 1990, at last the prevalence has reached 4.5% in 2000.

Hence, prevention of CVDs among people is more important. If CVD occurs, the earlier detection and

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**Corresponding Author:** Dr. V S Bharathi Lakshmi, MD DM, Assistant Professor, Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. Mobile: 9052633996. E-mail: bharathivanaparty@gmail.com

treatment are required for the prevention of complications and death. Moreover, identification of risk factors and prevention of CAD are more important than treatment itself. Early detection of CAD among people with or without symptoms is main task to reduce morbidity and mortality. There are various invasive and non-invasive methods to detect CAD among people with symptoms. Always invasive methods have their own advantages and disadvantages, so non-invasive tests are low-cost modalities of CAD detection and are need of the hour. Various non-invasive methods used are electrocardiogram (ECG), echocardiogram (ECHO), computed tomography (CT), magnetic resonance imaging, and nuclear imaging. Exercise stress testing such as treadmill test, stress echocardiography, and stress single-photon emission computed tomography is routinely used for the non-invasive assessment of CAD and is considered safe procedures.

In recent years, it has become increasingly apparent that a large number of patients classified as low risk or intermediate risk for acute coronary syndrome (ACS) and without diagnostic cardiac biomarkers represent the most prevalent group of patients admitted to hospital with chest pain.<sup>[4,5]</sup> Up to one-third of patients with chest pain who are referred to coronary angiography have no significant coronary artery stenosis.<sup>[6]</sup> Although this investigation is generally safe, it has well-known risk of complications and is also costly. Exercise testing is widely used for selecting patients for coronary angiography but has its clear limitations as emphasized in the European guidelines for stable CAD.<sup>[7]</sup> In stable CAD, coronary CT angiography (CTA) is a non-invasive alternative to assess coronary anatomy, but according to expert consensus only selected patients should be considered for CTA.<sup>[7]</sup> Thus, we are in need of a simple, non-invasive method to improve the selection of patients who are referred for coronary angiography.

Recently, quantification of left ventricular (LV) longitudinal strain and strain rate using two-dimensional (2D) speckle tracking echocardiography (2D STE) was shown to be a sensitive method for identifying significant CAD, transmural myocardial infarction<sup>[8,9]</sup> as well as acute or subacute ischemia.<sup>[10,11]</sup>

The present study is done to see the correlation between global longitudinal strain (GLS) and CAD as assessed by coronary angiography in intermediate risk patients admitted in Nizam's Institute of Medical Sciences, Hyderabad, between June 1, 2017, and November 30, 2017.

### Aims and Objectives

The primary objective of the study is to see the correlation between GLS assessed by tissue Doppler imaging or 2D STE and CAD as assessed by coronary angiography in

intermediate risk patients so that strain imaging can be used as a reliable non-invasive tool to predict obstructive CAD, and invasive coronary angiography and its complications can be avoided in selected patients.

## MATERIALS AND METHODS

### Design

This was a prospective clinical study.

### Setting

This study was conducted at Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad.

### Subjects

Patients admitted with symptoms of stable CAD during the period June 1, 2017–November 30, 2017.

### Inclusion Criteria

Adult patients (age > 18 years) who presented to the hospital by clinically suspected stable CAD (symptoms felt to be related to CAD such as angina or angina equivalents) were included in the study.

Patients with no regional wall motion (WM) abnormality and preserved LV ejection fraction (LVEF) on conventional 2D echocardiography.

Patients at intermediate risk of CAD based on Framingham Risk Score (10-year risk of MI or death of 10–20%) who underwent coronary angiogram were included in the study.

### Exclusion Criteria

The following criteria were excluded from the study:

- ACSs
- Known ischemic heart disease
- Congestive heart failure
- Significant valvular disease
- Rhythm other than sinus rhythm
- LVEF <50% or regional WM abnormalities at rest as detected by echocardiography
- Prior history of percutaneous coronary intervention or coronary artery bypass grafting
- Patients who refused coronary angiogram.

### Investigations

- Complete blood picture
- Blood urea, serum creatinine
- Serum electrolytes
- Fasting lipid profile
- ECG
- Cardiac biomarkers (LDH, CPK-MB)
- Chest X-ray
- 2D ECHO including strain imaging.

After the clinical evaluation, including review of medical history, relevant physical examination, and relevant investigations as detailed above, all the patients who gave consent underwent coronary angiogram in the same hospital admission.

All echocardiographic examinations are obtained using Philips HD11XE machine. LV diameters and wall thicknesses are measured in the left parasternal long axis at the level of the mitral valve tips, ensuring a measurement perpendicular to the long axis of the ventricle. Pulsed wave Doppler is used to record transmitral flow at the tips of the mitral leaflets in the four-chamber (4-CH) apical view as well as the trans-aortic flow in the five-chamber apical view. Peak velocity of early (E) and atrial (A) diastolic filling of the Doppler mitral flow and E/A ratio is calculated. LVEF was determined using modified biplane Simpson's method in the 4-CH and the two-chamber (2-CH) apical views as recommended by the American Society of echocardiography.

### Strain Analysis

Two consecutive heart cycles at rest, from the three standard apical planes (4-CH, 2-CH, and long-axis), are considered by conventional 2D grayscale echocardiography. In each of the apical views, the endocardial contour was manually drawn and tracking of deformation was automatically performed by the software, once visual confirmation of good quality tracking was given by the operator. The software algorithm automatically segmented the LV into six equidistant segments and selected suitable speckles in the myocardium for tracking. The software algorithm then tracked the speckle patterns on a frame by frame basis using the sum of absolute difference algorithm. Regional longitudinal peak systolic strain was measured in all views between aortic valve opening and closing for the six basal, six midventricular, and four apical segments and 17<sup>th</sup> segment was apical cap and averaged from the 17 segments to provide Global Longitudinal peak systole strain (GLSS).

Coronary angiography is performed by either a radial or femoral approach. A reduction in arterial lumen area of >50% of left main coronary artery (LMCA) and >70% of any other coronary artery is considered significant.

### Statistical Analysis

All analyses were made using the Minitab 16 software package. Continuous variables are expressed as mean  $\pm$  standard deviation; categorical variables are expressed as percentages. Independent *t*-test is used to compare means, ANOVA to compare multiple groups.

The research protocol is approved by the Institutional Ethics Committee, Nizam's Institute of Medical Sciences, Hyderabad. Written, informed consent is obtained from each patient.

## RESULTS

A total number of patients with clinical diagnosis of Stable Angina at intermediate risk of CAD as per Framingham Risk Score admitted to the hospital during the study period is 50. Out of 50 patients, five patients refused coronary angiogram so they are excluded from the data analysis.

### Clinical Data

Most of the patients fell in the age groups of 41–50 years and 51–60 years (22 and 24, respectively) Table 1. Three patients were in the age group of 31–40 years and one patient in the age group of 61–70 years.

The relative frequency of males and females presenting with stable angina and intermediate risk of CAD is 54% (27 patients) and 46% (23 patients), respectively Table 2.

Out of 50 patients, 27 (54%) were smokers Table 3. Forty-four (88%) patients had hypertension. Of them, 37 were on medical therapy for hypertension. Thirty-four patients had dyslipidemia and 22 (44%) had family history of CAD.

All the patients underwent a coronary angiogram Table 4. Twenty-nine patients (58%) had normal coronaries or nonobstructive CAD. Fifteen patients (30%) had single-vessel disease and four patients (8%) had double vessel disease. One patient had triple vessel disease, and one patient had left main coronary disease with bifurcation

**Table 1: Age distribution of patients**

Age group (in years)	Total	Percentage
31–40	3	6
41–50	22	44
51–60	24	48
61–70	1	2
All	126	100

**Table 2: Sex distribution of the patients**

Sex	No. of patients	Percentage
Male	27	54
Female	23	46
Total	50	100

**Table 3: Other baseline characteristics**

	Number of patients	Percentage
Smoking	27	54
Hypertension	44	88
Hypertension on treatment	37	74
Diabetes mellitus	24	48
Family history of CAD	22	44
Dyslipidemia	34	68

CAD: Coronary artery disease

lesion (distal LMCA with ostial left anterior descending [LAD] and ostial LCX).

The difference in the mean age of presentation between patients with and without significant CAD is not statistically significant ( $P = 0.40$ ). There is also no difference among patients with single-vessel disease, double-vessel disease, triple vessel disease, and LMCA disease in respect to mean age of presentation. Similarly, there is no statistically significant difference between the patients with and without significant CAD with regard to body mass index (BMI) ( $P = 0.99$ ).

All the baseline characteristics are relatively comparable among the different patient groups as depicted in Table 5.

**Table 4: Coronary angiography results**

	No. of patients	Percentage
Normal coronaries/Non obstructive CAD	29	58
Single vessel disease	15	30
Double vessel disease	4	8
Triple vessel disease/LMCA disease	2	4

CAD: Coronary artery disease, LMCA: Left main coronary artery

There were no statistically significant differences between the normal, single vessel, two vessels and three vessels disease groups as regard of septal wall thickness ( $P = 0.39$ ), posterior wall thickness ( $P = 0.31$ ), LV end diastolic diameter ( $P = 0.44$ ), LV end systolic diameter ( $p = 0.07$ ), ejection fraction ( $P = 0.77$ ), E wave velocity ( $P = 0.63$ ), A wave velocity ( $P = 0.82$ ) and E/A ratio ( $P = 0.89$ ) as shown in Table 6.

There is a statistically significant difference in mean of GLPSS between those with normal coronaries versus patients with CAD ( $P$  value 0.00). Mean GLPSS is  $-20.4 \pm 0.83$ ,  $-18.33 \pm 0.5$ ,  $-17.32 \pm 0.41$  and  $-16 \pm 0.14$  for normal, single vessel, two vessels and three vessels disease respectively (Table 7) (Fig. 11). There is also a statistically significant difference in mean of peak systolic global longitudinal strain rate between those with normal coronaries versus patients with CAD ( $P$  value 0.00). Mean GLPSS is  $1.5 \pm 0.22$ ,  $0.7 \pm 0.17$ ,  $0.65 \pm 0.17$  and  $0.4 \pm 0$  normal, single vessel, two vessel and three vessel disease respectively Table 7.

## DISCUSSION

Many patients who are at intermediate risk for CAD present with stable angina or angina equivalents. Patients

**Table 5: Demographic data as regard to extent of cad**

	Normal coronaries/non-obstructive CAD (%)	SVD (%)	DVD (%)	TVD/LMCA disease (%)
Males	14 (51.85)	9 (33.33)	2 (7.4)	2 (7.4)
Females	15 (65)	6 (26)	2 (8.6)	0 (0)
Smoking	14 (51.85)	10 (37.03)	2 (7.40)	1 (3.7)
Hypertension	26 (59.09)	13 (29.54)	3 (6.8)	2 (4.5)
Dyslipidemia	22 (64.7)	9 (26.4)	3 (8.8)	0 (0)
Diabetes	17 (70.83)	5 (20.83)	1 (4.16)	1 (4.16)
Family H/o CAD	12 (54.54)	5 (22.72)	3 (13.63)	2 (9.09)

**Table 6: Echocardiographic data according to extent of coronary artery disease**

	Normal coronaries/non-obstructive CAD	SVD	DVD	TVD/LMCA Disease	One way anova test	
					F	P value
SWT (cm)	1.05±0.13	1±0.06	1.07±0.09	1.05±0.07	1.01	0.39
PWT (cm)	1.07±0.13	1±0.07	1.07±0.09	1±0	1.21	0.31
LVEDD (cm)	4.64±0.48	4.53±0.33	4.47±0.39	5±0	0.9	0.44
LVESD (cm)	2.78±0.32	2.56±0.22	2.6±0.21	3±0.28	2.7	0.07
EF (%)	61.75±3.67	61.8±3.78	60.5±3.41	59.5±2.12	0.37	0.77
E WAVE (cm/s)	0.85±0.10	0.86±0.14	0.89±0.08	0.95±0.06	0.57	0.63
A WAVE (cm/s)	0.96±0.15	0.94±0.16	1.04±0.35	0.96±0.19	0.3	0.82
E/A RATIO	0.90±0.16	0.91±0.16	0.93±0.33	1±0.14	0.21	0.89

**Table 7: Global longitudinal peak systolic strain in the studied population**

	Normal coronaries/Non-obstructive CAD	SVD	DVD	TVD/LMCA disease	One way anova	
					F	P value
PS GLS (%)	-20.40±0.83	-18.33±0.5	-17.32±0.41	-16±0.14	8.11	0.00
PS GLSR (s <sup>-1</sup> )	1.50±0.22	0.70±0.17	0.65±0.17	0.4±0	73.83	0.00



with regional WM abnormality on echocardiography do not pose a problem in diagnosis. The subset of patients without regional WM abnormality on echocardiography needs to be further evaluated before subjecting them to invasive procedures like coronary angiography.

We generally have a higher threshold for investigation as long as the patient has good LV function. Questions persist regarding the appropriateness and cost effectiveness of screening for CAD along with the optimal approach to screening. GLS measured by 2D STE at rest has been recognized as a sensitive parameter in the detection of significant CAD.

In the present study, the value of GLPSS at rest to predict the presence, extent, and severity of CAD in patients with suspected stable angina pectoris has been evaluated. The present study included 50 patients with suspected stable angina pectoris without regional WM abnormality and with normal systolic function. These patients were subjected to 2D-STE and coronary angiography. Global LPSS are calculated and are correlated to the results of coronary angiography for each patient.

Of the 50 patients included in the present study, 29 patients had normal coronary arteries or mild non-obstructive CAD and 21 had significant CAD. Fifteen patients had single-vessel disease, four patients had two-vessel diseases, one patient had three-vessel diseases, and one patient had distal LMCA bifurcation lesion involving the ostia of LAD artery and left circumflex artery. There was statistically insignificant difference between the groups of patients with non-obstructive CAD and obstructive CAD (LMCA >50% stenosis and other coronary arteries >70% stenosis) as regard to the conventional echo parameters (dimensions, ejection fraction, and mitral E and A velocities) which were concordant with Biering-Sørensen *et al.*, Montgomery *et al.*, and Nicola *et al.* who showed statistically insignificant difference between the two groups with and without CAD in terms of EF and LV internal diameters. However, the present study is not in agreement with Radwan *et al.* study where there was a lower EF in the group of CAD ( $59.3 \pm 3.2\%$  vs.  $65.7 \pm 4.7\%$ ;  $P < 0.000$ ).

In the present study, there is a statistically significant lower GLSS and strain rate in patients with CAD compared to those with normal coronary arteries or mild non-obstructive CAD ( $P = 0.00$ ). There are no statistically significant differences in terms of age and BMI with  $P = 0.40$  and  $0.99$ , respectively. There are no significant differences in respect to other baseline demographic variables such as diabetes mellitus, hypertension, smoking, dyslipidemia, or family history of CAD.

There is a statistically significant difference in mean of GLPSS between those with normal coronaries or mild non-

obstructive CAD and patients with CAD ( $P = 0.00$ ). There is also a statistically significant difference in mean of peak systolic GLS rate between those with normal coronaries or mild non-obstructive CAD and patients with CAD ( $P = 0.00$ ). These observations are in agreement and consistent with the studies of Biering-Sørensen *et al.*, Montgomery *et al.*, Nicola *et al.*, Radwan *et al.*, Smedsrud *et al.*, and Shimoni *et al.*

Biering-Sørensen *et al.* studied 296 consecutive patients with clinically suspected stable angina pectoris, no previous cardiac history, and normal LVEF. GLSS was significantly lower in patients with CAD compared with patients without CAD ( $17.1 \pm 2.5\%$  vs.  $18.8 \pm 2.6\%$ ;  $P < 0.001$ ). They concluded that in patients with suspected stable angina pectoris, GLSS assessed at rest is an independent predictor of significant CAD.

In the study conducted by Montgomery *et al.*, 2D STE characteristics of 123 consecutive patients who underwent stress echocardiography and subsequently coronary angiography within 10 days were assessed. In this study, in 56 patients with significant CAD<sub>>50</sub>, GLS was  $216.77 \pm 3.18\%$  compared with  $219.05 \pm 3.43\%$  in the 67 patients without CAD<sub><50</sub> ( $P = 0.0002$ ). They concluded that non-obstructive CAD was identified by a reduced GLS measured by 2D STE in rest images with similar accuracy to the traditional WM score index measured in stress echocardiography.

Nicola *et al.* studied 82 patients who are referred for stress echocardiography. GLS was measured by STE in all the patients. Patients in the CAD group had significantly reduced rest GLS ( $-19 \pm 2.4$  vs.  $-22.7 \pm 2.4$ ,  $P = 0.001$ ). They concluded that rest GLS demonstrated high accuracy in the detection of obstructive CAD, not different from, and possibly superior to, the visual assessment of regional WM during stress echocardiography. Rest GLS is synergistic with stress WM assessment, leading to the highest accuracy of detecting whether a patient is affected by obstructive CAD or not.

Radwan *et al.* studied 80 patients with suspected stable angina pectoris and no regional wall motion abnormalities with normal ejection fraction. There was a significant decrease in GLS in patients with obstructive CAD compared to patients without CAD ( $-11.86 \pm 2.89\%$  vs.  $-18.65 \pm 0.79\%$ ,  $P < 0.000$ ). The optimal cutoff value of GLS for prediction of significant CAD was  $-15.6\%$  (AUC 0.88, 95% CI 0.78–0.96  $P < 0.000$ ). The sensitivity, specificity, and accuracy of GLS for detecting significant CAD were 93.1%, 81.8%, and 90%, respectively. There was a significant positive correlation between GLS and EF ( $r = 0.33$ ;  $P = 0.036$ ). There was incremental significant decrease in GLS with increasing number of coronary



vessels involved. From these observations, they concluded that measurement of GLS using 2D STE is sensitive and accurate tool in the prediction of severe CAD.

Smedsrud *et al.* observed that 86 patients with suspected CAD referred to elective diagnostic coronary angiography. Global systolic strain was significantly lower in patients with CAD ( $-17.7 \pm 3.0\%$  vs.  $-19.5 \pm 2.6\%$ ,  $P = 0.003$ ).

Shimoni *et al.* observed that there are significant differences in all strain parameters between patients with and without CAD. They concluded that in patients hospitalized with angina who have significant CAD on coronary angiography, longitudinal systolic function is impaired.

Gopinath *et al.* concluded from their study that strain imaging has high sensitivity and high negative predictive value when compared to CAG (gold standard) in identifying obstructive CAD, making this a good test to rule out obstructive CAD in a low-risk population.

Moustafa *et al.* studied 200 patients with stable angina and normal conventional echocardiography. There was a statistically significant difference in the mean of GLSS between normal coronaries and different degrees of CAD ( $-20.11 \pm 0.8$  for normal,  $-18.34 \pm 2.52$  for single vessel,  $-16.14 \pm 2.85$  for two vessels,  $-14.81 \pm 2.12$  for three vessels, and  $-13.01 \pm 2.92$  for left main disease). GLPSS showed high sensitivity for the diagnosis of single-vessel CAD (90%, specificity 95.1%, cutoff value:  $-18.44$ , AUC: 0.954); two vessels disease (90%, sensitivity 88.9%, cutoff value  $-17.35$ , AUC: 0.906), and for three vessels CAD (cutoff value  $-15.33$ , sensitivity 63%, and specificity 72.2%, AUC 0.681). They concluded that 2D STE has good sensitivity and specificity to predict the presence, extent, and severity of CAD.

Bakhom *et al.* studied 82 patients and found that GLS, global longitudinal strain rate, global radial strain, global radial strain rate, mid circumferential strain, and mid circumferential strain rate were significantly lower in patients with significant CAD compared to normal coronary arteries group (all  $P = 0.000$ ).

## CONCLUSIONS

GLS assessed by 2D-STE at rest is a predictor of significant CAD. GLS has high sensitivity for early detection of significant CAD in intermediate risk patients. 2D-STE has

the potential to improve the value of echocardiography in the detection of the CAD, identifying high-risk patients.

Patients who are at intermediate risk for CAD who have normal or inconclusive ECG findings and normal conventional 2D echocardiography should be assessed by strain imaging. This approach helps in selecting the patients for invasive coronary angiography which in turn helps to decrease the risks and costs associated with coronary angiography. Patients who are stratified as low risk by strain imaging can be discharged earlier further decreasing the health-care costs. At the same time, early detection of subclinical LV dysfunction based on abnormal strain findings helps in evaluating such patients with a more aggressive approach such as coronary angiography and early appropriate revascularization if appropriate.

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# Functional Outcome of Internal Fixation of Fibula by Closed Tens Nailing in Addition to Tibia in Distal Both Bone Leg Fractures

V A Prabhu<sup>1</sup>, M Kishore Kumar<sup>2</sup>

<sup>1</sup>Senior Assistant Professor, Department of Orthopaedics and Traumatology, Madurai Medical College, Government Rajaji Hospital, Madurai, Tamil Nadu, India, <sup>2</sup>Post Graduate, Department of Orthopaedics, Madurai Medical College, Madurai, Tamil Nadu, India

## Abstract

**Introduction:** Treatment of adult tibiofibular fractures, especially severely comminuted fractures, is technically challenging due to the lack of reduction markers and difficulty in restoring the alignment. Fixation of the fibula can facilitate the reduction of the tibia fracture and restoration of the lower extremity alignment.

**Aim:** This study aims to study the functional outcome of internal fixation of fibula by closed tens nailing in addition to tibia in distal both bone leg fractures.

**Materials and Methods:** Patients with distal both bone leg fractures for whom fibular fixation was done in addition to tibia nailing in Government Rajaji Hospital, Madurai from July 2016 to September 2018 with a minimum 1-year follow-up were included in the study.

**Results:** In this study among 15 patients, 9 patients did not have any angulation, 6 patients had varus angulation with mean varus of 2°, and none of the patients had valgus angulation. The mean range of movements in patients with fibula fixation was 96%. The mean time of union in these patients was 5 months (minimum of 4 months and a maximum of 7 months). Johner and Wruch's criteria: Among the 15 patients, 12 patients (80%) had excellent results and 3 (20%) had good results. There were no fair and poor results.

**Conclusion:** Treatment of distal third both bone leg fractures by fixation of fibula by closed tens nailing in addition to the tibia is useful in anatomical reduction of tibia and reduced malalignment of tibia with good ankle functions. Further randomized control studies are needed to assess the long-term functional outcome in these patients.

**Key words:** Ankle functions, Fibula fixation, Imil nailing, Tens nail, Tibial malalignment

## INTRODUCTION

Tibial diaphyseal fractures are one of the most common long bone fractures encountered.<sup>[1,2]</sup> The distal third region accounts for about 20–30%.<sup>[1,3-5]</sup> Fractures in the distal third of both bones leg when treated by conservative line of management, there are high chances of malunions,<sup>[1,2]</sup> ankle stiffness due to prolonged immobilization, delayed union, valgus or varus malalignment.

Schoot *et al.* followed up 88 patients with fracture of the distal third of leg with attention to angular deformity,

osteoarthritis of the knee, ankle, and any other residual complaints.<sup>[6]</sup> They showed positive relation between the degeneration process in knee and ankle with malalignment of tibia.<sup>[7-10]</sup> They opined that fractures of the distal third of the leg should be managed so that the possibility of angular deformity should be minimized and thereby minimize late arthritis.

Intramedullary interlocking nailing appears to be one of the good treatment options available due to various advantages such as fewer wound complications, less malunion, early weight-bearing, and early motion.

The anatomical reduction seems to be needed to reduce malaligned tibia which results in ankle and knee arthritis. As the deformity approaches either of the joints, malalignment leads to maldistribution of articular surface pressures that may predispose to premature osteoarthritis.<sup>[11]</sup>

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**Corresponding Author:** Dr. M Kishore Kumar, Department of Orthopaedics, Madurai Medical College, Madurai, Tamil Nadu, India.

To study the clinical relevance of fibular fixation by closed tens nailing in addition to the tibia in distal third fractures of both bones of leg and in an effort to outline the advantage and benefits of fixation of the fibula, this study was undertaken.

### Aim

This study aims to study the functional outcome of internal fixation of fibula by closed tens nailing in addition to tibia in distal both bone leg fractures.

## MATERIALS AND METHODS

This prospective study was conducted in the Department of Orthopaedics at Madurai Medical College and Rajaji Hospital. Patients with distal both bone leg fractures for whom fibular fixation was done in addition to tibia nailing from July 2016 to September 2018 with a minimum of 1-month of follow-up were included in this study.

### Inclusion Criteria

The following criteria were included in the study:

- Simple distal both bone leg fractures
- Compound Grade I fractures
- Age of more than 18 years
- Both sexes.

### Exclusion Criteria

The following criteria were excluded from the study:

- Age <18 years
- Compound Grades II, IIIa, IIIb, and IIIc fracture
- The patient did not fit for surgery due to comorbid conditions
- Procedure: Fracture fibula was addressed first.

### Pre-operative Assessment

- X-ray of the affected leg including one joint above and one joint below; including the ipsilateral knee and ankle joints
- Minimum two views are necessary: Anteroposterior and lateral views
- Pre-operative nail length is measured clinically
- The diameter of the nail is measured using the pre-operative X-rays at the level of the isthmus.

### Post-operative Protocol

- Static quadriceps and ankle pump exercises started at the end of 48 h
- Active knee range of motion (ROM) exercises were started
- EOT has done on the 3<sup>rd</sup>, 6<sup>th</sup>, and 9<sup>th</sup> post-operative days
- Suture removal was done on the 11<sup>th</sup> post-operative day
- Full ROM of knee at discharge on the 12<sup>th</sup> post-operative day

- Non-weight-bearing for 6 weeks; the first visit after 6 weeks
- Partial weight-bearing started after evidence of callus formation (6 weeks–3 months) and
- Full weight-bearing started when there is the radiological union of three cortices.

Postoperatively, patients were followed up clinically and radiologically at 6 weeks, 3 months, 6 months, and 1 year and then yearly intervals until the fracture heals completely.

Orthopedic trauma association classification was used at the time of admission and fractures were classified according to it. The nature of the injury was also noted.

Post-operative radiographs were taken to assess the tibial malalignment. The degree of the tibial angulation (varus or valgus), (anteroposterior), and (rotational) and shortening were evaluated radiologically and clinically.

At the end of 1 year, the range of movement (dorsiflexion and plantar flexion) at the ankle was determined. The functional assessment of ankle function is done by “Ankle evaluation rating system” by Merchant and Deitz. “Johner and Wruch’s Criteria” were used for final evaluation.

## RESULTS

Among the 15 patients who studied, 12 were male; the highest number of patients was seen in 20–40 years (53.3%) age group. The average was 37.2 years. Most cases were due to road traffic accidents (73.3%). The other mechanisms being accidental fall from height (26.6%) [Table 1]. In this study, 80% of cases were closed fractures and 20% were open fractures of the tibia. In open fractures, three were of compound Grade I (20%) according to Gustilo and Anderson’s classification.

In this study among 15 patients, 9 patients did not have any angulation, 6 patients had varus angulation with mean varus of 2°, and none of the patients had valgus angulation. None of the patients had anteroposterior angulation. None of the patients had rotational malalignment and shortening. The mean range of movements in patients with fibula fixation

**Table 1: Classification (OTA classification)**

Classification	Frequency	Percentage
A1	2	13.3
A2	4	26.6
A3	5	33.3
B2	2	13.4
B3	2	13.4
Total	15	100

OTA: Orthopedic Trauma Association

was 96%. Among the 15 patients, 11 patients (73.3) had excellent results and 4 patients (26.7) had a good result, with no fair and poor results [Table 2]. Ankle evaluation rating system score showed 66.4% of patients got 100 points [Table 3]. Meantime of union in these patients was 5 months (minimum of 4 months and a maximum of 7 months) [Table 4 and Figures 1 and 2].

One of 15 patients had wound complications at the fibular tens nail incision site. It was a superficial infection which was treated with intravenous antibiotics.

Among the 15 patients, 12 patients (80%) had an excellent result and 3 (20%) had good results. There were no fair and poor results in Johner and Wruch's criteria [Table 5].

## DISCUSSION

In the fractures of both bones of leg involving the distal third region, the importance of fixing of fibular fracture has not yet been clearly analyzed. This study was conducted in 15 patients to analyze the results of fixing the fibula fracture in fractures of the lower third of the shaft of tibia

**Table 2: Ankle range of motion**

Range of motion	Frequency	Percentage
Excellent (100%)	11	73.3
Good (75–100%)	4	26.7
Fair (50–75%)	-	-
Poor (<50%)	-	-
Total	15	100

**Table 3: Pattern of clinical AERS score**

Ankle evaluation score (total 100 points)	Frequency	Percentage
<60	-	-
60–80	1	13.3
>80	5	33.3
100	9	66.4
Total	15	100

AERS: Ankle evaluation rating system

**Table 4: Pattern of time of union**

Time of union (in months)	Frequency	Percentage
≤5	10	66.6
>5	5	33.3
Total	15	100



**Figure 1: (a) Pre-operative anteroposterior (AP) view, (b) pre-operative lateral view, (c) 2 weeks AP view, (d) 2 weeks lateral view, (e) 1-year follow-up AP view, (f) 1-year follow-up lateral view**



**Figure 2: (a) Range of motion (ROM) – dorsiflexion (0–20°), (b) thigh foot axis (7°), (c) ROM – plantar flexion (0–45°), (d) no varus/valgus malalignment (Johner and Wruch's criteria: Excellent)**



**Table 5: Johner and Wruch's criteria**

Type	Excellent (number of PTS)	Good (number of PTS)	Fair (number of PTS)	Poor (number of PTS)
Non-union	None (15)	None (nil)	None (nil)	Yes (nil)
Deformity (varus/valgus)	None (12)	2–5° (3)	6–10° (nil)	>10° (nil)
Mobility at ankle (%)	Normal (12)	>75% (3)	50–75% (nil)	<50% (nil)
Gait	Normal (15)	Normal (nil)	Insignificant limp (nil)	Significant limp (nil)

and fibula. In all of the cases, the fractured tibia was treated with interlocking intramedullary nailing.

In 12 of 15 patients, there was a mild amount of valgus/varus angulation at the fracture site within the acceptable range. The average valgus angulation was 2.8° and average varus angulation was 4.3°. Only one patient had a varus angulation of 8°. In comparison to the previous studies, where fibula was treated conservatively in fractures of distal third of tibia and fibula, the valgus and varus angulation in our study were significantly less. Acceptable angulation was 5°.

Fibular plate fixation increased the initial rotational stability after distal tibial fracture compared with that provided by tibial intramedullary nailing alone. However, there was no difference in rotational structural stiffness between the specimens treated with and without plate fixation as applied torque was increased.

Comparing the results of this study with the above-mentioned literature, when the fixation of fibula<sup>[12]</sup> is done before nailing of tibia, it helps in alignment of the proximal and distal tibial fragments and maintains the length of lateral column,<sup>[13]</sup> thereby reducing the incidence of varus/valgus malalignment at the fracture site.

Merchant and Deitz<sup>[5]</sup> in their clinical study of 3717 patients followed up for 29 years had a mean ankle evaluation score of 88.4 points for patients with a distal third of the shaft of the tibia. All of the patients in their series were treated non-operatively with a cast.

In our study, the less mean score when compared to the study by Merchant and Deitz may be accounted to the shorter duration of the follow-up (the longest duration of follow-up being 1 year, 6 months with a mean duration of 11.3 months).<sup>[5]</sup>

One of 15 patients treated with fixation of fibula developed superficial wound infections over the fibular incision site. It was controlled by appropriate dressing and antibiotics.

The average union time was 5 months; a minimum of 4 months and a maximum of 6 months. There were no non-unions. Comparing our results with the previous studies conducted by Richmond *et al.*,<sup>[14]</sup> in 2004, the time

of union was not influenced by the fixation of fibula. All fractures united within the acceptable duration for union.

The final analysis of results according to Johner and Wruch's criteria showed excellent to good outcomes in most of the patients (12 patients, 80%) and favorable in 3 (20%) of the patients.

## CONCLUSION

Treatment of distal third both bone leg fractures by fixation of fibula by closed tens nailing in addition to the tibia is useful in anatomical reduction of tibia and reduced malalignment of tibia with good ankle functions. Further randomized control studies are needed to assess the long-term functional outcome in these patients.

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# Dermatological Manifestations of Internal Malignancies

S Athilakshmi, M Vairaprabha Devi

Assistant Professor, Department of Dermatology, Kilpauk Medical College, Chennai, Tamil Nadu, India

## Abstract

**Introduction:** The skin is said to be the mirror of internal organs. Cutaneous manifestations may occur in many internal malignancies. It may precede, follow, or occur concurrently with the onset of internal malignancy.

**Aim:** This study aims to assess the frequency and significance of dermatological manifestations in patients with internal malignancies.

**Methods:** A total of 125 proven patients with various internal malignancies presenting to our outpatient department with skin lesions were included in the study.

**Results:** According to our study, males were more commonly affected than females and the common age group was 40–60 years. The most common skin manifestations observed were cutaneous infections followed by cutaneous metastasis.

**Conclusion:** Skin reflects the course of any internal disease. Identification of these skin manifestations may aid in both early diagnosis and treatment of internal malignancies.

**Key words:** Internal malignancies, Diagnosis, Skin changes

## INTRODUCTION

Skin, the largest organ of our body, reflects the changes in the internal organs. Skin manifestations in internal malignancies are diverse and may be specific or non-specific.<sup>[1]</sup>

Curth proposed criteria for the causal relationship between skin manifestations and internal malignancy.<sup>[2]</sup>

- Both conditions should begin simultaneously
- Development of a parallel course
- The dermatoses are not a part of any genetic syndrome
- The dermatoses are uncommon in general population
- There is a high frequency of association between both conditions.

Hebra first pointed cutaneous hyperpigmentation as a part of internal malignancy in 1868.<sup>[3]</sup> Since then, more than

50 skin conditions have been reported in association with internal malignancies.<sup>[4]</sup>

- The underlying malignancy may produce cutaneous manifestations either by direct invasion of skin or spread through lymphatics or blood, producing metastasis in skin.
- Carcinogen exposure and certain inherited disorders with internal malignancies may be associated with skin lesions.<sup>[3]</sup>
- Radiotherapy and chemotherapy instituted for treating malignancies may lead to cutaneous manifestations.<sup>[4]</sup>
- Identification of cutaneous lesions in patients with internal malignancies may be helpful in assessing the extent of disease, disease progress, and its response to treatment.

## MATERIALS AND METHODS

### Materials

This study includes 125 patients with proven internal malignancy presenting to our outpatient department with skin lesions, observed over a period of 6 months from January 2019.

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**Corresponding Author:** Dr. M Vairaprabha Devi, Assistant Professor, Department of Dermatology, Kilpauk Medical College, Chennai, Tamil Nadu, India

### Methodology

1. A detailed history was taken and systemic and dermatological examination were done
2. Basic laboratory investigations were done
3. In some patients, investigations pertaining to particular conditions were done which include scraping for the diagnosis fungus and acarus, and skin biopsy as done to confirm the diagnosis.

### Inclusion Criteria

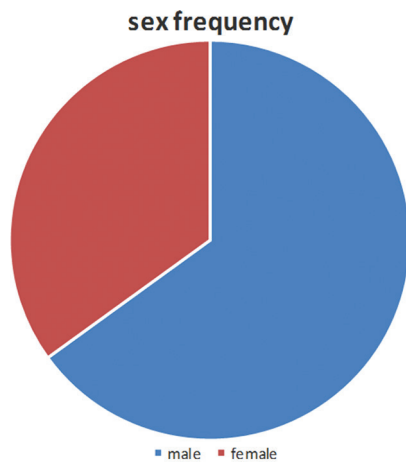
Patients with internal malignancy presenting with dermatological manifestations were included in the study.

### Exclusion Criteria

Patients unwilling for our study and patients who were treated for their skin lesions were not included in the study.

## RESULTS

A total of 125 patients with various types of malignancies presenting with skin manifestations were included in this study. Of this, 78 were male (62.4%) and 47 were female (33.6%).



The frequency of various internal malignancies observed in our study is as below:

Internal malignancy	Number of patients	Percentage
Carcinoma breast	26	20.8
Carcinoma buccal mucosa	24	19.2
Carcinoma tongue	3	2.4
Carcinoma cervix	8	6.4
Carcinoma oropharynx	9	7.2
Osteosarcoma	4	3.2
Malignant melanoma	2	1.6
Lymphoma	4	3.2
Gastric carcinoma	14	11.2
Squamous cell carcinoma	4	3.2
Cutaneous T-cell lymphoma	1	0.8
Bronchogenic carcinoma	7	5.6
Renal cell carcinoma	3	2.4

Basal cell epithelioma	6	4.8
Hepatocellular carcinoma	3	2.4
Carcinoma prostate	3	2.4
Secondaries neck with primary unknown	4	3.2
Total	125	100

Carcinoma breast was the most common malignancy found in 26 (20.8%) patients followed by carcinoma buccal mucosa which was present in 24 patients (19.2%). Eight patients presented with carcinoma cervix. Out of seven patients with basal cell epithelioma, three were diagnosed in our department and biopsy was done to confirm the diagnosis.

The age of the patients ranged from 10 to more than 80 years. The maximum number of patients was in the age group of 60–80 years (48%).

Age group	Frequency	Percentage
<20	5	4
20–40	6	4.8
40–60	45	36
60–80	60	48
>80	9	7.2
Total	125	100

There were six patients in 20–40 years age group. Forty-five patients in 40–60 years age group and nine patients in 40–60 years age group and nine patients were above 80 years of age.

The incidence of cutaneous manifestations in various internal malignancies is listed below:

Skin manifestations	Frequency	Percentage
Herpes zoster	20	16
Dermatophytosis	15	12
Scabies	5	4
Pyoderma	8	6.4
Mucosal pigmentation	7	5.6
Acanthosis nigricans	2	1.6
Seborrheic keratosis	7	5.6
Acquired ichthyosis	10	8
Pruritus	11	8.8
Erythroderma	1	0.8
Secondary lymphedema	3	2.4
Lymphangioma	2	1.6
Vasculitis	2	1.6
Cutaneous metastasis	15	12

Patients presented with cutaneous manifestations either due to disease *per se* or as a consequence to therapy or both.

The most common skin lesions were herpes zoster. It was observed in 20 patients (16%) followed by dermatophytosis (12%). The increased incidence may be attributed to immunosuppression in these patients.

Cutaneous metastasis was observed in 15 patients (12%). The most common site of cutaneous metastasis was chest followed by head and neck. The most common cause of cutaneous metastasis was carcinoma breast in females and carcinoma buccal mucosa in males.

#### Cutaneous Manifestations Due to Therapy

Drug reaction	6	4.8
Alopecia	5	4
Nail changes	3	2.4
Radiation dermatitis	3	2.4

The most common chemotherapeutic agents attributing to drug reaction were capecitabine, sorafenib, cisplatin, and 5-fluorouracil. Hand-foot syndrome was observed in a patient related with capecitabine for carcinoma breast and in another patient on sorafenib for hepatocellular carcinoma.

Pigmentation of lips was noted in seven patients. Of five patients with alopecia, three had diffuse hair loss and two had alopecia totalis.

Three patients presented with nail changes including onychodystrophy and koilonychia.

## DISCUSSION

As there is a rising trend in the occurrence of internal malignancies, early recognition is possible by identification of the cutaneous lesions which may precede or occur concurrently with the onset of malignancy.

- The skin lesions occurring in internal malignancy are called dermadromes of internal malignancy.<sup>[5]</sup> According to Rajagopal *et al.*, dermatological manifestations occur in 237.35 patients.<sup>[6]</sup>
- In malignancies, metastasis skin is rare.<sup>[7]</sup> Cutaneous metastasis usually occur after the fifth decade.<sup>[8]</sup> In our study, cutaneous metastasis was observed in 12% of patients. In a study by Browstein *et al.*, the most common malignancy producing cutaneous metastasis was carcinoma lungs followed by carcinoma colon in males and carcinoma breast in females.<sup>[9]</sup> In our study, carcinoma lungs in males and carcinoma breast in females similar to a study by Tharakram *et al.*<sup>[10]</sup>
- Most frequent cutaneous infection encountered was herpes zoster which was mostly multidermatomal in contrast to the study conducted by Kiliç *et al.* which reported fungal infections to be the most common.<sup>[11]</sup> The occurrence of herpes zoster in patients on remission may indicate recurrence of malignancy.<sup>[12]</sup>
- There is an increased incidence of infections in patients with internal malignancies which may be attributed to immunocompromised status of the patient due to

disease *per se* or chemotherapy.<sup>[13]</sup>

- According to our study, middle-aged (40–60 years) people were most commonly affected. Similar observation was reported by Gül *et al.*<sup>[14]</sup>
- In our study, drug reaction was observed to be the most common chemotherapy-induced dermatoses, whereas Kanti *et al.* reported hair loss to be the common dermatoses due to chemotherapeutic agents.<sup>[15]</sup>

Pruritus was found to be associated with lymphoma and is seen only in later stages of disease.<sup>[16]</sup> As per the study by Hassan *et al.*, 2.4% of patients presented with ichthyosis but in our study 8% presented with ichthyosis.

- Radiation dermatitis was found in three patients of 68 patients on radiotherapy. It may take weeks to months for the occurrence of skin manifestations following completion of radiotherapy.<sup>[17]</sup>

Vasculitis was observed in two patients. One patient with renal cell carcinoma presented with necrotizing ulcer and another patient with gastric carcinoma had purpuric lesions both lower limbs. Hematological malignancies are more commonly reported to be associated with cutaneous vasculitis.<sup>[18]</sup>

- In addition, cutaneous manifestations such as scabies, pyoderma, acanthosis nigricans, lymphedema, and lymphangioma were also noted in our study.

## CONCLUSION

Skin is the mirror of internal organs. Cutaneous manifestations may precede, occur concurrently, or may follow after the occurrence of internal malignancies. Any patient with unusual cutaneous manifestations who do not respond to therapy should be thoroughly investigated for underlying immunosuppression including internal malignancies. Prompt identification of these cutaneous manifestations will help in early diagnosis and treatment of internal malignancies.

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# A Study of Angiographic Profile and Clinical Outcomes in Women with Acute Coronary Syndrome

E Anil Kumar<sup>1</sup>, V S Bharathi Lakshmi<sup>2</sup>, L S R Krishna<sup>3</sup>

<sup>1</sup>Senior Resident, Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India, <sup>2</sup>Assistant Professor, Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India, <sup>3</sup>Professor, Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

## Abstract

**Introduction:** Cardiovascular disease (CVD) is the leading cause of mortality for women in India and globally. Coronary artery disease (CAD) has traditionally been considered a disease of men.

**Aims and Objectives:** The aim of the study was to study the clinical profile, risk factors, and extent of CAD in women with an acute coronary syndrome.

**Materials and Methods:** A total of 50 patients fulfilling the inclusion criteria will be a part of this study. Patients admitted in the Cardiology Department of Nizam's Institute Of Medical Sciences, Telangana.

**Observations and Results:** A total of 50 subjects were enrolled in the study after meeting the inclusion criteria. The enrollment period was from November 2018 to December 2018. Out of these 36 (72%) had ST segment elevation myocardial infarction (STEMI), 9 (18%) were non-STEMI, and 5 (10%) were diagnosed as unstable angina.

**Conclusions:** The incidence of CAD increases with age in females with more adverse outcomes in elderly females. Risk scoring systems such as Killip's Class and TIMI score were fairly accurate in female patients in predicting adverse outcomes and complications.

**Key words:** Acute Coronary Syndrome, Angiogram, Unstable angina

## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality for women in India and globally.<sup>[1]</sup> Coronary artery disease (CAD) has traditionally been considered a disease of men. The Global Burden of Disease Study reported that the disability-adjusted life year lost by CAD in India during 1990 was 5.6 million in men and 4.5 million in women; the projected figures for 2020 were 14.4 million

and 7.7 million in men and women, respectively.<sup>[2]</sup> The annual CVD mortality rate has remained greater for women than for men.

There are important sex differences in the pathophysiology, clinical presentation, and clinical outcomes of CAD in women.<sup>[2]</sup> Women's health involves two aspects Sex differences resulting from biological factors and gender differences affected by broader social, environmental, and community factors.

Obstructive atherosclerotic disease of the epicardial coronary arteries remains the basic cause of acute myocardial infarction (AMI) in both sexes, plaque characteristics differ for women, and recent data have suggested a greater role of microvascular disease in the pathophysiology of coronary events among women.<sup>[3]</sup>

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**Corresponding Author:** Dr. V S Bharathi Lakshmi, MD DM, Assistant Professor, Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. Mobile: 9052633996. E-mail: bharathivanaparty@gmail.com

Women are often older when they present with their first AMI, at an average age of 71.8 years compared with 65 years for men.<sup>[4]</sup> Recently, an increase in CAD incidence and deaths among women 45–54 years of age have been observed in various studies. Asian Indian women have greater proportionate mortality burden from CAD compared with non-Hispanic White women, particularly at a younger age because of more comorbidities (e.g., diabetes mellitus [DM], Hypertension [HTN], heart failure [HF], and obesity) at the time of presentation with AMI.<sup>[5]</sup>

Certain risk factors are more potent in women, include tobacco abuse, type 2 DM, depression, and other psychosocial risk factors. The INTERHEART study data identified nine potentially modifiable risk factors (smoking, HTN, DM, waist-hip ratio, dietary patterns, physical activity, alcohol consumption, plasma apolipoproteins, and psychosocial factors) that account for 96% of the population attributable risk of AMI in women.<sup>[6]</sup>

Compared with men, women are more likely to have high-risk presentations and less likely to manifest central chest pain.<sup>[6]</sup> Women are undertreated with guideline-based recommendations, leading to worse outcomes and increased rates of readmission, reinfarction, and deaths in the 1<sup>st</sup> year after AMI.

Despite their substantial burden of CVD, women have been underrepresented in clinical trials of CVD, generally making up only ≈20% of enrolled patients. Thus, a considerable research gap exists in the knowledge of sex-specific examination of coronary pathophysiology; optimal diagnostic strategies; effective lifestyle, pharmacological, and invasive interventions.<sup>[7]</sup>

Women's heart health is not only solely a medical issue but also involves economic, legal and regulatory, psychosocial, ethical, faith-based, cultural, environmental, community, health systems, and political and public policy issues locally and globally.

Considering the high burden of CAD in women there is a need for sex-specific data about pathophysiology of atherosclerotic disease, risk factor stratification, causes of treatment delay, rate of complications, angiographic profile, and treatment strategies.<sup>[8]</sup> Hence, the present study is undertaken to improve the knowledge about presentation of acute coronary syndrome (ACS) in women in an urban tertiary care setting.

### Aims and Objectives

The aim of the study was to study the clinical profile, risk factors, and extent of CAD in women with an ACS and to evaluate the in-hospital course and outcome of therapies in women with ACS.

## MATERIAL AND METHODS

### Study Site

Patients admitted to the Cardiology Department of Nizam's Institute of Medical Sciences, Telangana.

### Study Population

The subjects will be female patients, who would present the first time with a diagnosis of ACS within a week of symptoms onset at our hospital. Once the patients will meet the inclusion and exclusion criteria as defined, they will be enrolled in the study after signing the informed consent.

### Study Design

This was a prospective observational study.

### Sample Size

A total of 50 patients fulfilling the inclusion criteria will be a part of this study.

### Study Duration

The study will be performed from November 2018.

### Inclusion Criteria

The following criteria were included in the study:

1. Female patients with symptoms of ACS within 7 days of presentation
2. Women with age 18 years or older
3. Women with first-time presentation with ACS
4. Women willing and able to provide informed, written consent.

### Exclusion Criteria

Women with prior HF and prior ischemic heart disease were excluded from the study.

### Methodology

Data is collected. During the in-hospital stay of the patient, and there will be no follow-up of patient after being discharged from the hospital. The data is collected from the patients and recorded in a prepared case report form. Demographic details, medical history, risk factors, investigations, complications rate, treatment, and hospitalisation details are collected.

ACS will be defined as a spectrum of conditions compatible with acute myocardial ischemia and/or infarction that are usually due to an abrupt reduction in coronary blood flow. Patients will be divided into three categories the diagnosis of acute MI will be done by third universal definition of acute myocardial infarction. As having unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), or ST-elevation MI.

The absence of persistent ST-elevation is suggestive of NSTEMACS. NSTEM-ACS will be further subdivided on the basis of cardiac biomarkers of necrosis. If cardiac biomarkers are elevated, and the clinical context is appropriate, the patient is considered to have NSTEMI; otherwise, the patient is deemed to have UA.

The following data will be included for analysis:

1. Patients demographic profile:
2. Clinical presentation and physical examination Symptoms of ACS (Typical Symptoms or Atypical Symptoms) Time to presentation
3. CAD risk factor profile:
  - a. Current cigarette/bidi smoking or tobacco use
  - b. Dyslipidemia defined as the presence of any of the following Patients on lipid-lowering drugs or total cholesterol >240 mg/dl, TG >150 mg/dl, low-density lipoprotein (LDL) >130 mg/dl, and high-density lipoprotein (HDL) <50 mg/dl for females.

Diabetes mellitus Symptoms of diabetes and plasma glucose concentration  $\geq 200$  mg/dl or fasting blood sugar  $\geq 126$  mg/dl or 2-h postprandial  $\geq 200$  mg/dl.

- a. Hypertension (SBP  $\geq 140$  and/or DBP  $\geq 90$  mmHg and/or on anti-hypertensive treatment)
- b. Family history of CAD (first-degree relatives with CAD before the age of 55 years in men and 65 years in women),
- c. Obesity (defined using the body mass index (BMI) with a value  $>30$ . BMI was calculated using Quetlet's formula (weight in kg/height in  $m^2$ ).
- d. Psychosocial risk factors
- e. Physical inactivity (people who do not get the recommended level of regular physical activity).
4. Hematology investigations (CBC, renal function tests, lipid profile, and cardiac biomarkers)
5. ECG: On admission and regular intervals
6. Imaging studies
  - a. 2D echo was done within 24 hours of admission, chest Xray was done.
7. Coronary angiographic findings
  - a. Selective coronary angiogram will be done using the standard technique during hospital admission unless patient is not willing for CAG or has significant renal disease
  - b. Significant CAD is defined as diameter stenosis  $>50\%$  in each major epicardial artery
  - c. Normal vessels were defined as the complete absence of any disease in the left main coronary artery (LMCA), left anterior descending (LAD), right coronary artery (RCA), and left circumflex (LCX) as well as in their main branches
  - d. Patients will be classified as having single-vessel disease (SVD), double-vessel disease (DVD) or triple vessel disease (TVD) accordingly.

8. Treatment received:
  - a. STEMI reperfusion strategies: Thrombolysis/percutaneous coronary intervention (PCI)/coronary artery bypass grafting (CABG) standard pharmacotherapy for STEMI as per guidelines
  - b. NSTEMI revascularization strategies: PCI/CABG Standard pharmacotherapy for NSTEMI as per guidelines.
9. Complications due to primary disease:
  - a. Cardiogenic shock
  - b. Mechanical complications (acute MR/ventricular septal rupture/left ventricular free wall rupture and tamponade)
  - c. Congestive cardiac failure/Left ventricular failure
  - d. Arrhythmias
  - e. Bleeding complications (major/minor bleeding)
  - f. In hospital death.

### Statistical Methods

Continuous variables are presented as mean  $\pm$  SD or median if the data are unevenly distributed. Categorical variables are expressed as frequencies and percentages. The comparison of continuous variables between the groups was performed using student's *t* test. The data were summarized in the form of percent population.

## RESULTS

A total of 50 subjects were enrolled in the study after meeting the inclusion criteria. The enrollment period was from November 2018 to December 2018. Out of these 36 (72%) had STEMI, 9 (18%) were NSTEMI, and 5 (10%) were diagnosed as UA.

### Age

Most patients were in 61–70 years of age group across all ACS subtypes. The mean age was  $62.1 \pm 10$  years.

### Clinical Presentation

#### Chest pain

A total of 42 (84%) patients presented with chest pain Table 1. Out of these 31 (62%), patients presented with typical chest pain and 11 (22%) had atypical chest pain on presentation. Chest pain was absent in 8 (16%) patients. They had other associated symptoms.

**Table 1: Associated symptoms in women**

Symptoms	Number of patients	Percentage
Dyspnea	16	32
Sweating	13	26
Palpitations	2	4
Syncope	2	4
Vomiting	1	2

### Time to Presentation

The average time from onset of symptoms to first medical contact was 24 h. In the STEMI group, patients who presented within 12 h were 27 (74.07%) and 9 (25.92%) patients came after 12 h of symptom onset.

### Risk Factor Profile

**Table 2: Risk factor distribution in ACS subtypes**

	Overall (%)	UA (%)	NSTEMI (%)	STEMI (%)
HTN	35 (70)	3 (60)	8 (88.8)	24 (66.6)
DM	29 (58)	2 (40)	5 (57)	22 (60.6)
Obesity	17 (34)	1 (20)	2 (22.2)	14 (38.8)
Physical inactivity	19 (38)	2 (40)	4 (44.1)	13 (36.4)
Tobacco abuse	3 (4.3)	-	2 (22.2)	1 (4.1)
CVA/PVD	1 (3)	-	-	1 (7)
Family history	14 (30)	1 (20)	2 (6.7)	11 (33.3)

ACS: Acute coronary syndrome, HTN: Hypertension, DM: Diabetes mellitus, NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, UA: Unstable angina, CVA: Cerebrovascular accident, PVD: Peripheral vascular disease

### Type of ACS

Out of these, 36 (72%) had STEMI, 9 (18%) were NSTEMI, and 5 (10%) were diagnosed as UA.

**Table 3: Type of ACS**

Type of ACS	Total	Percentage
UA	5	10
NSTEMI	9	18
STEMI	36	72

ACS: Acute coronary syndrome, NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, UA: Unstable angina

### Echocardiography

Echocardiography revealed moderate mitral regurgitation (MR) in 3 (5.6%) patients, and all these patients had STEMI. Mild MR was present in 11 (22%) patients. The average ejection fraction was 47%.

**Table 4: Echocardiographic findings in ACS subtypes**

	UA	NSTEMI	STEMI
LVEF (%)	59.1 (SD±1.8)	57 (SD±3)	45 (SD±6)
Mild MR	-	4	7
Moderate MR	-	-	3
VSR	-	-	-

LVEF: Left ventricular ejection fraction, MR: Mitral regurgitation, ACS: Acute coronary syndrome, NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, UA: Unstable angina, SD: Standard deviation

### Coronary Angiography

Coronary angiogram was done in 50 (100%) patients as per standard protocol.

**Table 5: Coronary angiogram findings in ACS subtypes**

Findings	Total (%)	UA	NSTEMI	STEMI
Single vessel disease	22 (44.0)	2	2	18
Two vessel disease	13 (26)	1	2	10
Triple vessel disease	13 (26)	-	5	8
LMCA disease	4 (6.3)	-	2	2
Normal/mild disease	2 (4)	2	-	-

LCMA: Left main coronary artery, ACS: Acute coronary syndrome, NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, UA: Unstable angina

### Treatment Received

All 50 study patients received aspirin dose of 325 mg.

Furthermore, high dose statins (atorvastatin 40 mg/80 mg or Rosuvastatin 20 mg/40 mg) were used in all 50 study population. The second antiplatelet was used in 48 patients.

Clopidogrel was used in 20 (42%), prasugrel was used in 9 (18%), and ticagrelor was used in 19 (39%) study population.

### Mortality

In the study population, 2 (4%) patients died during a hospital stay. Both women were above 60 years of age and average age was 71 years. Both patients had STEMI. The average time from onset of symptoms to first medical contact was 20 h. Out of these, both patients had DM, both patients had hypertension, and 1 patient was obese.

In both these patients, Killip's class was >3 and TIMI risk score was >9. Both of these underwent coronary angiography. One patient had TVD and 1 patient had DVD with LMCA. One patient underwent primary PCI.

One patient had ventricular tachycardia, and the other had a complete heart block requiring temporary pacemaker support. Out of 2 patients, 1 died due to cardiogenic shock and 1 patient died due to ventricular tachycardia.

## DISCUSSION

Gender disparity in cardiac diagnosis and treatment has been investigated thoroughly in multiple trials Table 2. This study highlights the clinical features of ACSs in women, an underemphasized study group.

Most patients in our study belonged to 61–70 years stratified age groups across all ACS subtypes. The mean age was  $62.1 \pm 10$  years Table 3.

Older the age, higher was the odds of in-hospital mortality. Both the 2 patients who died were more than 60 years of age. The average age was 71 years Table 4.



### Clinical Presentation

In all the ACS subtypes, 42 (84%) patients presented with chest pain. Out of these, 31 (62%) patients presented with typical chest pain and 11 (22%) had atypical chest pain on presentation. Chest pain was absent in 8 (16.0%) patients Table 5.

In a study by Canto *et al.*, 28.2% of women presented without typical chest discomfort and gender-specific differences in MI presentation without chest discomfort became progressively smaller with advancing age. The in-hospital mortality rate was 14.6% for women and 10.3% for men. Younger women presenting without chest pain had greater hospital mortality than younger men without chest pain, and these sex differences decreased or even reversed with advancing age, with adjusted OR for 65–74 years, 0.91 (95% CI, 0.88–0.95), and 75 years or older, 0.81. Out of 2 patients who died in our study both had typical chest pain Table 6.

**Table 6: Comparison of patients with chest pain**

	With chest pain %	Without chest pain %
Our study	84	16
Canto <i>et al.</i>	71.8	28.2
Milner <i>et al.</i>	83.4	16.6

In our study, dyspnea was the presenting symptom in 16 (32%) patients with 4 of them had only dyspnea without any chest pain. Other associated symptoms were sweating 13 (26%), palpitations 2 (4%), syncope 2 (4%), and vomiting 1 (2%).

Milner *et al.* studied 127 men and 90 women with CAD. They concluded, among patients presenting to the emergency department with symptoms of coronary disease other than chest pain, there were several sex-related differences in symptoms. Dyspnea, nausea/vomiting, indigestion, fatigue, sweating, and arm or shoulder pain as presenting symptoms in the absence of chest pain were more frequent among women than men. Many cases of myocardial infarction in women go unrecognized, particularly at younger ages due to these atypical symptoms.

### Time to Presentation

The average time from onset of symptoms to first medical contact was 24 h.

In the STEMI group, patients who presented within 12 h were 27 (75%) and 9 (25%) patients came more than 12 h of symptom onset.

In a similar study done by Veena Nanjappa *et al.*,<sup>19</sup> in South Indian women, 16.7% women presented within 4 h after symptom onset and 58.3% presented more than 12 h after

symptom onset in the NSTEMI group; 18.1% patients in STEMI group presented within 4 h of symptom onset and 38.6% after 12 h. About 64.3% patients in UA group presented 12 h after symptom onset Table 7.

**Table 7 : Comparison of patients on time to presentation**

	<12 h %	>12 h %
Our study	75	25
Veena Nanjappa <i>et al.</i>	61.4	38.6

Compared with young men with AMI in the VIRGO trial, young women who were eligible for and received reperfusion therapy were more likely to present >6 h after symptom onset (35% vs. 23%;  $P = 0.002$ ).

In our study, the average time from onset of symptoms to the first medical contact was 24 h in patients who had in-hospital mortality. This delay in seeking medical attention likely contributes to adverse outcomes in women. This delay is often due to lack of awareness of risk, passivity, inaccurate symptom attribution, and barriers to self-care.

### Risk Factor Profile

The percentage of subjects with diabetes mellitus (55.5% in NSTEMI, 61.1% in STEMI, and 40% in UA) was much higher than in both CREATE registry (30.4%) and the INTERHEART study (30.2%) Table 8.

The percentage of hypertensives (88.8% of NSTEMI, 66.6% of STEMI, and 60% of UA) was also high when compared to the CREATE registry (37.7%) and the INTERHEART study (53.6%).

Obesity and physical inactivity were the next most common risk factors found in this study.

The mean BMI was  $28.9 \pm 3.23$  kg/m<sup>2</sup>. About 65.33% patients had BMI between 25 and 30 kg/m<sup>2</sup> and 28.66% patients fell into the obese category (i.e., BMI > 30 kg/m<sup>2</sup>).

Physical inactivity was present in 9 (18%) patients. Physical inactivity is associated with higher blood pressure, worse cholesterol levels, poorer glucose metabolism, poorer mental health, and obesity. Physical inactivity, quantified by a prolonged sitting time, has been shown to be an independent risk factor for CVD in women beyond leisure-time physical activity.



**Table 8: Comparison of risk factors between our study and interheart study**

	Our study %	Interheart study %
HTN	70	58
DM	58	30.6
Smoking	4.3	20.1
Obesity	34	45.6

HTN: Hypertension, DM: Diabetes mellitus

Tobacco abuse was found in only 3 (6%) patients. This justifies the fact that the overall rate of smoking is low among Indian women, particularly in urban areas Table 9. Only 8% of the women in Asian countries smoke compared to 60% men who smoke.

Associated CVDs like Cerebrovascular accident (CVA)/ Peripheral vascular disease (PVD) were present in 1 (2%) patient that patient presented with STEMI. Associated CVDs have more severe presentation and poorer outcomes.

### Dyslipidemia

The mean total cholesterol level was higher in our study (191.4 mg/dl) than that found among MI cases in Tirupati, India (177.07 mg/dl). The same was noticed for mean LDL level also (163.9 mg/dl). However, the levels of the protective HDL were also found to be lower in our study (40.6 mg/dl) than in the earlier study (46 mg/dl).

The lipid abnormalities were present in 61.5% in the INTER-HEART study and in 38.75% in a study by Bhasin *et al.* It suggests a high prevalence of dyslipidemia in the female population.

### Type of ACS

In our study, 36 (72%) had STEMI, 9 (18%) were NSTEMI, and 5 (10%) were diagnosed as UA.

In our study, the majority of patients were STEMI (72%) which is different from the data from developed countries, in which NSTEMI was the predominant presentation Table 10.

In the STEMI subgroup, 18 (50% of STEMI population) had anterior wall myocardial infarction (AWMI), 15 (41.3% of STEMI population) had inferior wall myocardial infarction (IWMI), 1 (2.9% of STEMI population 2.3%) had Living with Mental Illness (LWMI), and 2 (5.8% of STEMI population) had people LWMI (PLWMI).

In a similar study done by Veena Nanjappa *et al.*, 45% had AWMI, 34% had IWMI, and 17 % had LWMI/PLWMI.

**Table 9: Comparison of ACS in developed and developing countries**

	STEMI %	NSTEMI %
Our study	72	18
Veena Nanjappa <i>et al.</i>	62.4	27.1
Create128	61	39
Global registry of ACS	30–40	60–70
European heart surveys	42	51

ACS: Acute coronary syndrome, NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction

### Risk Assessment

#### Killip's class

In our study, 4.6% of STEMI patients presented in Killip's Class III and 4.2% of STEMI patients presented in Killip's Class IV. The majority of STEMI patients were in Killip's Classes I or II (76.4% and 14% of STEMI population, respectively). In all the patient death patients, Killip's class was more than 3.

In a similar study by Veena Nanjappa *et al.*, 12% of STEMI presented in Killips Class III and 15.7% of STEMI patients presented in Killips Class IV.

About 21.7% in Kerala ACS registry had Killips Class >1. About 38.6% of women had Killips Classes II–IV in SWEDEHEART study.

#### TIMI Score

The mean TIMI score across all subtypes were 5. The mean TIMI risk score in UA was 3 (SD  $\pm$  1) and 4.3 (SD  $\pm$  1.4) in NSTEMI subgroups.

The mean TIMI score for STEMI patients was 5.2 (SD  $\pm$  2).

The TIMI risk score was a good predictor of disease severity, as most complications were associated with higher scores. In STEMI patients who died during hospital stay, TIMI risk score was >9.

As these scores were developed in patient populations that were at least two-thirds male, so their performance in women is not well established. However, still, the TIMI risk score has performed well in both men and women for the prediction of death or MI at 30 days.

### Echocardiography

Echocardiography revealed moderate mitral regurgitation in 3 (6%) patients and all these patients had STEMI. In VeenaNanjappa *et al.* study, echocardiogram finding of moderate MR is seen in 6% of STEMI population.

The average ejection fraction was 47 %.

The STEMI group showed the worse left ventricular ejection fraction ( $45 \pm 6\%$ ).

### Coronary Angiography

Coronary angiogram was done in 50 (100%) patients out of the study population. Single vessel disease was most commonly found across the spectrum of ACS 22 (44%).

Triple vessel disease was found in 13 (26%) patients. About 4% in NSTEMI, 22.2% in STEMI, and none in UA group had TVD.

Left main involvement was seen in 4 (8%) patients of which 2 patients had STEMI and 2 patients had NSTEMI.

Normal or mild disease was found in 2 (4%) patients. All were having UA.

UA was more commonly associated with normal coronaries as compared to NSTEMI and STEMI. In UA group, many patients may have been over diagnosed, false-positive as ACS. In a similar study by Veena Nanjappa *et al.*, single-vessel disease was most common finding. About 13.9% in UA group had NSTEMI, 10.8% in UA group had STEMI, and 14.3% in UA group had TVD. Left main involvement was seen in 3 patients each of STEMI and NSTEMI group.

In a study done by Rajni Sharma *et al.*, single-vessel disease was present in 127 (46.02%) of female patients whereas 603 (51.67%) of male patients ( $P < 0.001$ ). 2VD was present in 44 (15.94%) female patients in comparison to 220 (18.85%) male patients. TVD was seen in 27 (9.78%) female patients but 89 (7.62%) male patients. LMCA disease was seen in 3 (1.09%) female patients whereas in 20 (1.71%) male patients ( $P > 0.05$ ). Normal or mild disease was present in 75 (27.17%) of female patients compared with 235 (20.15%) of male patients.

### Treatment

All 50 study patients received aspirin and statins during hospitalization or on discharge. The second antiplatelet was used in 48 patients. Clopidogrel was used in 20 (40%), prasugrel in 9 (18 %), and ticagrelor in 19 (38%).

In a similar study by Veena Nanjappa *et al.*, all patients received aspirin across all ACS groups. Ticagrelor use was 11.1% in NSTEMI, 8.4% in STEMI, and 21.4% in UA group. About 42.2% of STEMI patients received prasugrel and 30.6% in NSTEMI group. Clopidogrel was used in 94.4% NSTEMI and 94% of STEMI patients. About 39.9% of patients had a switch over. All patients initially received statins, and in 1 patient, it was later discontinued because of raised liver enzymes in patient with normal coronaries.

The use of ticagrelor as a second antiplatelet agent is steadily increasing due to its superior efficacy and better safety profile.

A total of 44 (88%) patients received adjuvant anticoagulation in our study. LMWH was most commonly used 29 (58%). Unfractionated heparin was used in 15 (30%) patients, especially in patients who had associated AKI.

### Emergency Revascularization

Of the 36 patients who were eligible for primary revascularization, 20 patients (55.5%) underwent either thrombolysis or primary PCI.

### Thrombolysis

Thrombolysis was done in 8 (22.2%) STEMI patients. Most patients had time to presentation  $< 12$  h. All 8 patients received streptokinase. No patient had a risk of IC bleed during or post-thrombolysis with streptokinase.

In a similar study by Veena Nanjappa *et al.*, 10.8% received thrombolysis in STEMI group.

### Primary PCI

In our study, 12 (33.3% of STEMI population) underwent primary revascularization with PCI.

Out of these, primary PCI to RCA was the most common with 6 patients. Primary PCI to LAD was done in 5 patients and 1 patient had primary PCI to LCx.

In a similar study by Veena Nanjappa *et al.*, 68.7% of patients in STEMI group underwent primary angioplasty.

A pooled analysis of 22 trials that randomized 6763 STEMI patients to primary PCI versus thrombolytics found that women had lower 30-day mortality with primary PCI. Despite this beneficial effect, women are less subjected to primary PCI, especially in Indian scenarios.

In a study by Mady Moriel *et al.* in STEMI-patients, acute reperfusion was less frequent in women than in men (53% vs. 63%, respectively,  $P = 0.01$ ); reperfusion by thrombolysis was done in 30% patients and PAMI in 70% of STEMI.

### Elective Revascularization

Out of the 50 women, 36 patients received elective revascularization. The majority underwent PCI 30 (60 %), while 6 (12%) patients had CABG surgery.

In the PCI group, single-vessel PCI was most common in all ACS subtypes. Most of the two vessels or multivessel PCI was done in NSTEMI and STEMI group.

In a study done by Veena Nanjappa *et al.*, 69.4% in NSTEMI group underwent PCI, 42.9% patients in UA group underwent PCI. Multivessel PCI was done in 8.3% NSTEMI and 6% STEMI patients and none in UA group.

In our study population, around 96% received revascularization, either in the form of primary revascularization (thrombolysis or primary PCI) or elective revascularization (PCI or CABG surgery). In the study done by Veena Nanjappa *et al.*, 83.6% patients had received revascularization. The higher cumulative percentage found in both studies may be related to the fact that both studies were conducted in a tertiary cardiac care hospital.

PCI was done in only 11.9% of patients in Kerala ACS registry and in 7.5% in CREATE registry. About 47.8% underwent PCI in a study by Sadowski *et al.*

About 6 (12 %) patients underwent CABG surgery, of which about half of them had NSTEMI.

## IN HOSPITAL COMPLICATIONS

Among the study cohort, CCF (14%), hypotension (4%) and cardiogenic shock (2%) were the most common complications. They were predominantly present in STEMI group.

**Table 10: Complications in ACS subtypes**

	Overall (%)	UA	NSTEMI	STEMI
CCF/LVF	7 (13.9)	1	2	4
Hypotension	2 (4)	-	-	2
Cardiogenic shock	1 (2)	-	-	1
Free wall rupture	-	-	-	-
CHB	3 (5.3)	-	-	3
Ventricular tachycardia	1 (2)	-	-	1
AKI	4 (8)	1	1	2
PV bleeding	-	-	-	-
CIN	1 (2)	-	-	1
Intracranial bleeding	-	-	-	-
IN-Hospital death	2 (4)	-	-	2

CHB was observed in 3 (6%) and ventricular tachycardia in 1 (2%) patients. They were present only in STEMI group.

Acute kidney injury was the most common extracardiac complication. It was mostly secondary to cardiogenic shock or contrast-induced nephropathy.

In CADILLAC trial, female gender was an independent predictor of MACE and bleeding complications.

## Mortality

In the study population, 2 (4%) patients died during hospital stay. Most of them were elderly; most of them presented with STEMI, had delayed presentation and had higher Killip's class and TIMI risk scores. Out of 2 patients, 1 died due to cardiogenic shock and 1 patient died due to ventricular tachycardia.

Eleven deaths (8.3%) were noted; 8 (6%) in hospital and 3 (2.3%) in the follow-up period in study done by Veena Nanjappa *et al.* All of them belonged to STEMI group.

In Kerala, ACS registry had in-hospital mortality with 8.2% in STEMI group. In AMI-FLORENCE registry the in-hospital mortality for women was 16%.

## CONCLUSIONS

1. The incidence of CAD increases with age in females with more adverse outcomes in elderly females
2. There is a significant delay in seeking treatment after symptoms onset due to various medical and social reasons causing a delay in delivering guideline-directed treatment and consequently more complications
3. Although the majority of the females have typical symptoms of ischemia, percentages of females having atypical symptoms are also significant, and this may cause delay in seeking treatment, appropriate diagnosis, and treatment
4. Traditional risk factors such as diabetes mellitus, hypertension, dyslipidemia, obesity and physical inactivity, and family history of CAD were most common in study population. Tobacco abuse is less significant risk factor in Indian females than in the western population
5. Risk scoring systems such as Killip's Class and TIMI score were fairly accurate in female patients in predicting adverse outcomes and complications
6. Single vessel disease was the most common coronary angiographic finding in study population. Nearly one-fourth of the patients had triple vessel disease. UA was more commonly associated with normal coronaries as compared to NSTEMI and STEMI
7. Only one-third of the patients received primary revascularization from the eligible population, and about two-thirds of whole study cohort received elective revascularization. This signifies that there is treatment bias toward female population
8. Patient characteristics such as elderly age, diagnosis of STEMI, delayed presentation, and higher Killip's class and TIMI risk scores were associated with significant morbidity and mortality

## Limitations

The limitations of our study include the following

1. This being a single center prospective and observational study with a limited time period, the results cannot be extrapolated in a larger population
2. Sample size is small and further studies including a larger sample size are recommended
3. There was no direct comparison between males

and females in their clinical profiles, treatment, and outcomes to ascertain gender bias in clinical presentation and management

4. As there was no follow-up, so short-term and long-term mortality and morbidity and adherence to treatment were uncertain
5. As ours was a tertiary cardiac care center, the majority of patients were referred from peripheral hospitals causing difficulty in interpreting some clinical data

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# A Clinical Study of Nasal Bone Fractures: A Retrospective Study

Anchal Gupta<sup>1</sup>, Vikrant Mahajan<sup>2</sup>, Padam Singh Jamwal<sup>3</sup>

<sup>1</sup>Senior Resident, Department of Otorhinolaryngology and Head and Neck Surgery, SMGS Hospital, Government Medical College, Jammu, Jammu and Kashmir, India, <sup>2</sup>Senior Resident, Department of Radiodiagnosis, Government Medical College, Jammu, Jammu and Kashmir, India, <sup>3</sup>Professor, Department of Otorhinolaryngology and Head and Neck Surgery, SMGS Hospital, Government Medical College, Jammu, Jammu and Kashmir, India

## Abstract

**Background:** As the most prominent position organ is the face, nose is the most affected location in this trauma and it is possible to compare the nasal trauma etiology separately with that of the facial trauma.

**Materials and Methods:** This hospital-based retrospective study was conducted in the Department of ENT, SMGS Hospital, Jammu, from August 2016 to September 2019. The records of patients with nasal fracture diagnosis were retrospectively evaluated. The diagnosis was based on the clinical history, physical examination, and nasal bones radiography. Clinical assessment of patient included inspection of the face, paying attention to the presence of any swelling, and/or deviation of the nasal axis. Then, nasal cavity is examined with anterior rhinoscopy for septal hematoma and/or fracture, and presence and/or location of epistaxis. Moreover, the nasal dorsum is palpated to detect any sign of crepitation. The presence of crepitation, radiologic findings, swelling, septal hematoma/fracture, and causes of trauma was all documented.

**Results:** The mean age was  $23 \pm 3$  years. The male-to-female ratio was 2.12:1. The frequently affected age group was 21–30 years constituting 44% of total cases. The most common clinical finding was nasal crepitation seen in 100 (80%) patients, followed by epistaxis (76.8%), swelling of dorsum (70.4%), laceration of skin (32%), and septal hematoma (9.6%). The most common cause was aggression seen in 40 (32%) patients followed by road traffic accidents (28.8%). The correlation between nasal crepitis, swelling of nasal dorsum, and septal hematoma was found statistically significant ( $P < 0.05$ ).

**Conclusion:** Men in the 2<sup>nd</sup> and 3<sup>rd</sup> decades are more affected by nasal bone fractures (NBFs). X-ray nasal bones along with findings such as nasal crepitations, swelling of nasal dorsum, and septal hematoma are strongly suggestive of NBFs.

**Key words:** Crepitation, Nasal bone fractures, Trauma

## INTRODUCTION

The nasal fractures are one of the most frequent services performed by the otorhinolaryngologist.<sup>[1]</sup> Like other facial traumas, they affect mostly the male sex and the mostly affected age is between 20 and 30 years of age.<sup>[2,3]</sup>

Nasal bone fracture (NBF) is the most common type of facial fracture and the third most common fracture

of the human skeleton.<sup>[4,5]</sup> Interpersonal violence and motor vehicle crashes are the main causes, and alcohol consumption is often another factor.<sup>[6]</sup>

Identifying NBFs are dependent on a thorough history and physical examination.<sup>[7]</sup> Patients usually present with some combination of epistaxis, edema, laceration, instability, crepitation, ecchymosis, and deformity; however, these physical findings may not always be present and are often fading.<sup>[8]</sup> Untreated NBFs, delayed time to treatment, traumatic edema, and occult septal injury may cause functional and cosmetic defects. Therefore, timely accurate diagnosis and appropriate intervention are important steps for the management of NBFs.<sup>[7]</sup>

There is no uniform protocol for this condition manipulation. There are several approaches reported

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**Corresponding Author:** Dr. Anchal Gupta, Department of Otorhinolaryngology and Head and Neck Surgery, SMGS Hospital, Government Medical College, Jammu, Jammu and Kashmir, India.



such as manual reduction, manual approach associated to forceps, the one uniquely performed with forceps, the carrying out of associated septoplasty, and even rhinoseptoplasty. The nasal bones manipulation may be practiced without anesthesia, with local anesthesia, and general anesthesia.<sup>[4]</sup>

The objective of this study is to verify the age, sex, and the most frequent causes of the nasal fractures treated in a tertiary hospital.

## MATERIALS AND METHODS

This hospital-based retrospective study was conducted in the Department of ENT, SMGS Hospital, Jammu, from August 2016 to August 2019. The records of patients with nasal fracture diagnosis were retrospectively evaluated.

The diagnosis was based on clinical history, physical examination, and nasal bones radiography.

Clinical assessment of patient included inspection of the face, paying attention to the presence of any swelling, and/or deviation of the nasal axis.

Then, nasal cavity is examined with anterior rhinoscopy for septal hematoma and/or fracture, and presence and/or location of epistaxis. Moreover, the nasal dorsum is palpated to detect any sign of crepitation. The presence of crepitation, radiologic findings, swelling, deviation of the nasal axis, septal hematoma/fracture, and causes of trauma was all documented.

## RESULTS AND OBSERVATION

A total of 125 patients were included in our study. The observation and results are as follows:

### Age and Sex Distribution

The youngest patient was 9 years old and oldest was 66 years old. The mean age was  $23 \pm 3$  years. Age-wise distribution is shown in Figure 1. There were 85 males and 40 females. The male-to-female ratio was 2.12:1. The frequently affected age group was 21–30 years constituting 44% of total cases followed by 11–20 years (24%).

### Clinical Findings

The most common clinical finding was nasal crepitation seen in 100 (80%) patients, followed by epistaxis (76.8%), swelling of dorsum (70.4%), laceration of skin (32%), and septal hematoma (9.6%). Figure 2 shows the distribution of clinical findings in patients with NBFs.

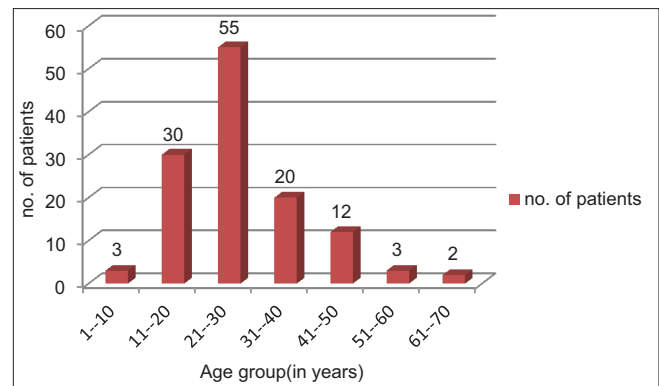


Figure 1: Age-wise distribution of patients

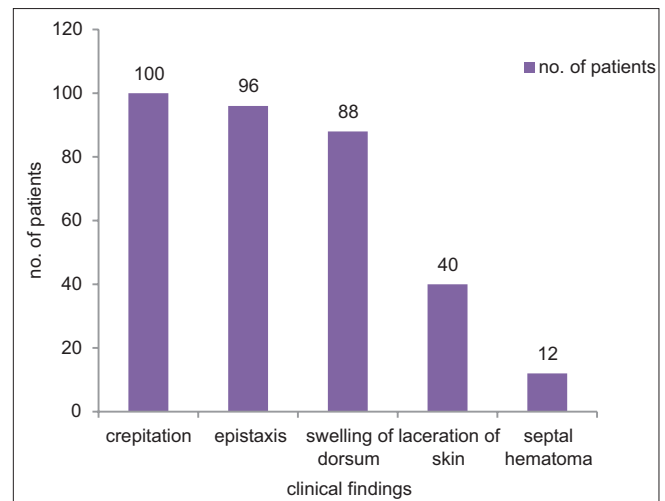


Figure 2: Distribution of clinical findings in patients with nasal bone fractures

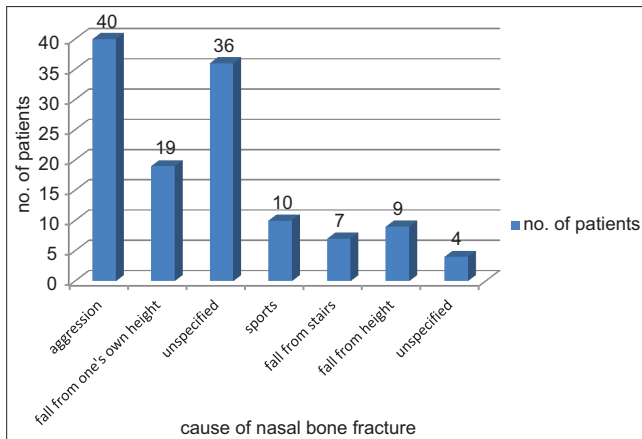
### Distribution of Patients According to the Cause of NBFs

Out of 125 cases of NBFs in the present study, the most common cause was aggression seen in 40 (32%) patients followed by road traffic accidents (28.8%), fall from one's own height (15.2%), sports injury (8%), fall from height (7.2%), fall from stairs (5.6%), and unspecified causes in 3.2% [Figure 3].

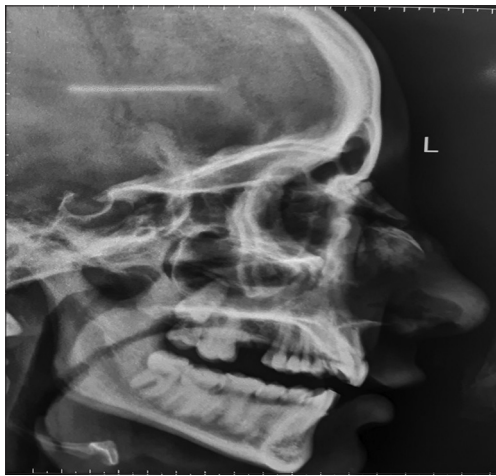
### Accordance between Clinical and Radiological Findings of NBF

When we analyzed the correlation between positive clinical and radiological findings, crepitation was correlated with radiological findings in 98/100 cases (98%), epistaxis in 50/96 (52.08%), swelling of nasal dorsum in 75/88 (85.22%), laceration of skin in 22/40 (55%), and septal hematoma in 8/12 (75%).

The correlation between nasal crepitus, swelling of nasal dorsum, and septal hematoma was found statistically significant ( $P < 0.05$ ) [Figure 4].



**Figure 3: Distribution of patients according to the cause of nasal bone fracture**



**Figure 4: X-ray showing nasal bone fracture**

## DISCUSSION

As the most prominent position organ is the face, it is the most affected location in this trauma and it is possible to compare the nasal trauma etiology separately with that of the facial trauma. Diagnosis of NBF is primarily clinical. Highly suspicious signs of nasal fracture are crepitation, mucosal lacerations, septal fracture and/or dislocation, obvious concavity, and depressions of the nasal bone.<sup>[9]</sup>

The male sex, as verified in other studies, was widely the most affected (80.2%). An information similar to that found by Bakardjiev and Pechalova<sup>[10]</sup> who found a ratio of four men per one woman with facial trauma, and Wulkan *et al.*<sup>[2]</sup> whose work analyzed 164 patients and 78% were men. The three most common causes of nasal fracture in our study were physical aggression, fall from their own height, and motorcycle accident.

In a casuistry of 9543 cases of facial trauma, the most frequent etiologies were respectively accident during daily

life activities, sports, aggression, and car crashes<sup>[11]</sup> Rocchi<sup>[12]</sup> observed that the most frequent facial trauma cause in the age range from 11 to 19 was the motorcycle accident (41% of the cases). In our study, in an analog age range, the most prominent cause was physical aggression (36%).

In our study, the peak age of NBFs was the 2<sup>nd</sup> and 3<sup>rd</sup> decades. In this age group, resultant fractures were frequently associated with bumping and violence, respectively. This result is in agreement with studies in literature.<sup>[13,14]</sup> Radiographic assessment (plain X-ray) of nasal fracture is highly controversial for clinical decisions in the emergency department. Besides, the anatomy of the nose with cartilaginous and bony structures can cause confusion for the management of this injury. For instance, plain X-ray is usually not useful for the diagnosis of NBF in the pediatric population whose nasal bones are not ossified.<sup>[15]</sup> There are some more limitations of X-ray imaging. It is not capable of detecting cartilaginous fracture, and there are several situations with false-positive results such as soft tissue swelling, previous fracture, the presence of suture lines, developmental defects, and vascular marking. Nevertheless, some studies suggest that radiography of the nose should be obtained for showing fractures and for medicolegal purposes.<sup>[10]</sup>

## CONCLUSION

On the basis of the present study, it can be concluded that males aged between 21 and 39 years and violence are the most common characteristics found in our service. Motorcycle accidents also play an important role in this affection. Furthermore, crepitation of nasal bone, swelling of nasal dorsum, and septal hematoma showed significant correlation with X-ray finding of NBF.

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# Advances in Protein Characterization by High-resolution Mass Spectrometry

Asha Mishra

Assistant Professor, Department of Zoology, Hira Lal Ram Niwas PG College, Khalilabad, Uttar Pradesh, India

## Abstract

High-resolution mass spectrometry has become an indispensable tool for a variety of biological research areas, including protein chemistry. The coupling of electrospray ionization to the MS has revolutionized the approaches for the identification of new proteins. Some examples of these applications include the identification of proteins involved in the virulence of pathogenic bacterial strains. MS played an important role in advancing protein folding studies, identification of new biomarkers for the detection of diseases in early stages. A recent development in MS technique called fast photochemical oxidation of proteins significantly advanced the protein structural analysis.

**Key words:** High-resolution mass spectrometry, Virulence, Protein analysis

## INTRODUCTION

Mass spectrometry (MS) has become an indispensable tool for biological and analytical chemistry research. It is a powerful analytical tool with high sensitivity and high mass accuracy. Mass spectrometers measure the mass/charge ratio of ions, whether positive or negative. It is presented as a mass spectrum which is a plot of the intensity of the ions as a function of mass/charge ratio of the ions. These spectra are used to determine the elemental or isotopic pattern of a sample, the masses of particles and of molecules, and to elucidate the chemical identity or structure of molecules and other chemical compounds. In a typical MS procedure, a solid, liquid, or gaseous sample is ionized by ion source, ions are sorted based on their mass and charge by the mass analyzer and then detected by a detector, and the results are displayed in a chart.

The first mass spectrometer was built by Sir Joseph John Thomson at the Cavendish Laboratories in Cambridge, UK, in the early 20<sup>th</sup> century. From 1897, the work carried

out by Thomson *et al.* receives seven Nobel prizes in physics and chemistry. Sir J.J. Thomson is regarded as the “grandfather of the MS.” In the 1940s, the applications of MS started spreading away from mostly academic work into more practical fields such as nuclear isotope enrichment and the analysis of the components of petroleum. The world’s first commercial instrument became available in 1948. The coupling of gas and liquid chromatography to the MS was the major breakthrough. This allowed, for the 1<sup>st</sup> time, the analysis of mixtures of analytes without laborious and time-consuming separation of its components. High-resolution MS (HRMS) and their few applications in protein analysis are discussed below.

## HRMS

HRMS allows detection of analytes to the nearest 0.001 atomic mass unit.<sup>[1]</sup> One of the most popular HRMS has Orbitrap as an ion trap. Ions are electrostatically trapped in an orbit around a central, spindle-shaped electrode. The electrode confines the ions so that they both orbit around the central electrode and oscillate back and forth along the central electrode’s long axis. This oscillation generates an image current in the detector plates which is recorded by the instrument. This ion current is converted to mass spectrum by Fourier transform of the frequency signal. Because of their high sensitivity and high mass accuracy, Orbitrap-based mass spectrometers are used in proteomics, metabolomics, environmental science, and food safety

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**Corresponding Author:** Asha Mishra, Department of Zoology, Hira Lal Ram Niwas PG College, Khalilabad, Sant Kabir Nagar, Uttar Pradesh, India.

analysis.<sup>[2]</sup> In this review, I will focus on the role of MS in protein-related studies.

## MS IN PROTEIN-FOLDING STUDIES

HRMS has been used widely to understand the protein folding.<sup>[3]</sup> Eyles and Kaltashov have published a very thorough article on methods to study protein dynamics and protein folding by MS.<sup>[4]</sup> It was useful in determining the folding pathways of methylenetetrahydrofolate reductase oligomers.<sup>[5]</sup> Another classic paper describing the use of MS methods to study the protein architecture and dynamics was published in protein science.<sup>[6]</sup> Near amino acid resolution step-by-step protein folding was elucidated by hydrogen exchange and MS.<sup>[7]</sup> A recent useful review highlights the role of MS in understanding protein folding by hydrogen–deuterium exchange and fragment separation.<sup>[8]</sup>

## MS IN CANCER BIOMARKER DISCOVERY

A biomarker is a measurable indicator of severity or the presence of a phenomenon such as a disease, infection, or environmental exposure. The use of biomarkers in basic and clinical research as well as in clinical practice has become so commonplace that their presence as primary endpoints in clinical trials is now accepted almost without question. MS played an important role in the discovery of a large number of cancer biomarkers. A recent review article on the advances in the MS-based cancer biomarker discovery summarizes the advances in this field.<sup>[9]</sup> Some notable examples for cancer biomarkers include biomarker for liver cancer detection in early stages, pancreatic cancer, and genitourinary cancer.<sup>[10-12]</sup>

## MS IN THE STUDY OF BACTERIAL VIRULENCE

The study of the bacterial virulence is of immense importance to understand host–pathogen interaction and finding ways to treat multidrug-resistant virulence strains. In recent years, MS has played an important role in understanding the role of virulence proteins in pathogenic bacteria. MS has played a very important role in elucidating the role of these key proteins and identified new proteins involved in virulence in *Listeria monocytogenes*, *Mycobacterium tuberculosis*, and *Streptococcus pneumoniae*.<sup>[13-16]</sup> The catalytic role of urease, converting urea into carbon dioxide and ammonia, has been well studied and shown to protect this bacterium in the low pH environment of the stomach lumen. Mass spectrometric studies on the *Helicobacter pylori* urease revealed the non-catalytical role of this enzyme in quenching oxidant and improved the understanding of

virulence factor.<sup>[17]</sup> A recent review by Perez-Llarena and Bou details the role of MS-based proteomics on the study of bacterial virulence and antibacterial resistance.<sup>[18]</sup>

## MS AND FAST PHOTOCHEMICAL OXIDATION OF PROTEINS (FPOP)

FPOP is an emerging MS-based technique for the high-resolution characterization of protein structure. It offers an ultrafast method for free radical generation using an ultraviolet laser to generate high concentrations of hydroxyl radicals by photolyzing hydrogen peroxide. These free radicals react with protein, buffers, and other components in a sample mixture on roughly a microsecond time scale. The hydroxyl radical is very reactive, and they have broad reactivity. Hence, the ligands, buffers, and excipient present in the sample will all react with hydroxyl radicals. The recent development in this field (JASMS paper, Analytical Biochemistry paper, and Analytical Chemistry paper) offers exciting opportunities to the researchers in probing the structural characterization of proteins and various applications of this technology in the diverse biological research fields.<sup>[19-21]</sup> For example, the conformation of biosimilar adalimumab was compared in phosphate and citrate buffers, using FPOP and HRMS, and adalimumab was found to have different conformations in these buffers. The protective role of polysorbate-80 in aggregate formation for this monoclonal antibody was also shown utilizing FPOP and HRMS.<sup>[22]</sup>

## CONCLUSION

The MS-based proteomics has seen a tremendous application in characterization of protein higher-order structure, the study of the role of key proteins responsible for bacterial pathogenesis and their importance in developing the disease and searching for new means to control the bacterial infectious diseases. The clinical research field has significantly advanced after the MS-based discovery of biomarkers that can accurately indicate the onset of cancer in the early stages and the outcome of treatment.

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