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# Pressor Response to Laryngeal Mask Airway Insertion versus Endotracheal Intubation in Standard Anesthetic Practice

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## Abstract

**Background:** Laryngeal mask airways (LMAs) are being used increasingly nowadays as an alternate option to endotracheal intubation, as it is less invasive and causes less discomfort in the post-operative period. In a few patients, the pressor response associated with laryngoscopy and tracheal intubation may be harmful. The LMA avoids the need for laryngoscopy and allows positive pressure ventilation of the lungs in appropriate patients. In this study pressor responses to LMA insertion versus endotracheal intubation in a standard anesthetic practice were observed and analyzed.

**Aim of the Study:** The aim of the study was to compare the pressor responses to LMA insertion versus endotracheal intubation in standard anesthetic practice.

**Materials and Methods:** A total of 60 patients undergoing general anesthesia for various surgical procedures were divided into 2 groups. Group - I ventilated with endotracheal intubation and Group - II with laryngeal airway mask. During pre-induction, post-induction, and at 1, 3, and 5 min, the following post-induction hemodynamic parameters were noted such as (1) heart rate (HR), (2) blood pressure - systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure using NIBP at different intervals such as (a) before induction, (b) after induction, (c) at laryngoscopy and endotracheal intubation or insertion of the laryngeal mask, (d) 1 min after endotracheal intubation or insertion of the laryngeal mask, (e) 3 min after endotracheal intubation or insertion of the laryngeal mask, and (f) 5 min after endotracheal intubation or insertion of the laryngeal mask, (3) oxygen saturation, and (4) adverse events, if encountered. All the observed parameters were presented in a tabular form, and appropriate statistical methods were applied to obtain the results.

**Observations and Results:** Among 60 patients 16/30 (53.3%) in Group - I and 14/30 in Group - II (46.6%) were aged 21–30 years in Group II. The mean age and standard deviation in Group - I was  $28.40 \pm 9.16$  and in Group - II it was  $30.73 \pm 7.26$ . In Group I there were 16/30 (53.4%) females and in Group - II there were 10/30 (33.4%) females. Similarly, males were 14/30 (46.4%) in Group - I and 20/30 (66.6%) in Group - II. Mean SBP was higher in group ETT (Group - I) as compared to group LMA (Group - II) at intubation, 1<sup>st</sup> min, and 3<sup>rd</sup> min after intubation or LMA insertion. There was significant increase in DBP in Group - I at ETT intubation or insertion of LMA in Group - II, at 1 and 3 min after intubation or insertion of LMA. Mean SBP was higher in group ETT as compared to group LMA at intubation, 1 min, and 3 min after intubation or LMA insertion.

**Conclusions:** Pressor response to LMA insertion is much less than that of laryngoscopy and endotracheal intubation. Duration and magnitude of the pressor response are transient during LMA insertion. LMA may be useful in airway management during anesthesia in situations where marked pressor response would be deleterious, for example, patients with hypertension and coronary artery disease. However, large-scale studies are required to confidently ascertain the findings of present study.

**Key words:** Airway, Anesthesia, Hemodynamic, Intubation, Laryngoscopy

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## INTRODUCTION

The development of laryngeal mask airway (LMA) began in 1982, at Royal London Hospital. Using laryngoscope to expose the larynx and complete endotracheal intubation is now a routine part of delivering a general anesthetic. In general, intubation is indicated for patients who are

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at risk of aspiration and for those undergoing a surgical procedure.<sup>[1-3]</sup> Following laryngoscopy and tracheal intubation during induction of anesthesia, transient hypertension, tachycardia, and arrhythmias are frequently associated. In healthy patients, such hemodynamic changes are of little consequence but they are more serious and hazardous with hypertensive patients and in ischemic heart disease.<sup>[3,4]</sup> Stimulation of the oropharyngolaryngeal mucosal structures may be playing an important role in the hemodynamic response generated with tracheal intubation. In susceptible patients especial with systemic hypertension, coronary heart disease, cerebrovascular disease, and intracranial aneurysm, such these transient changes may result in potentially deleterious effects such as left ventricular failure, arrhythmias, myocardial ischemia, cerebral hemorrhage, and rupture of cerebral aneurysm.<sup>[5-8]</sup> Various non-laryngoscopic intubation devices and methods have provided conflicting evidence of an attenuated hemodynamic response. In general, techniques that avoid or minimize oropharyngolaryngeal stimulation might attenuate the hemodynamic stress response.<sup>[9,10]</sup> One among them is the LMA which has been proved to be a popular addition to the range of equipment available for airway management. The LMA is intermediate in design and occupies a niche between oropharyngeal airway and endotracheal tube. It has the advantages of an endotracheal tube while avoiding its fundamental disadvantages since the vocal cords need to be neither visualized nor forced on.<sup>[11]</sup> However, it has its own limitations and contraindications especially in patients who are at risk of aspiration, with low airway compliance and in bleeding diathesis. To blunt these hemodynamic changes many methods are used such as minimizing the duration of laryngoscopy, the use of intravenous narcotics, lidocaine, vasodilators, and beta-blocking agents, but most of these have produced variable results. Bennet *et al.*<sup>[12]</sup> studied cardiovascular changes with the LMA for cardiac surgery and showed that cardiovascular stability can be achieved when the LMA is used, without the need for pharmacological techniques to control the circulation in patients with ischemic heart disease. Montazari *et al.*<sup>[13]</sup> compared hemodynamic changes after insertion of LMA, facemask, and endotracheal intubation. Aldemir *et al.*<sup>[14]</sup> studied which is responsible for the hemodynamic response due to laryngoscopy and endotracheal intubation- catecholamine, vasopressin, or angiotensin. Blood pressure, heart rate (HR), plasma epinephrine, norepinephrine, and vasopressin concentrations increased slightly in response to laryngoscopy and intubation, all returning to or below baseline 5 min later with no change in angiotensin-converting enzyme activity in normotensive patients. Tasyuz *et al.*<sup>[15]</sup> studied the effects of esmolol on hemodynamic responses to laryngoscopy and intubation in diabetic versus non-diabetic patients. They proposed that esmolol might be used effectively to

control the hemodynamic responses to laryngoscopy and intubation in diabetic patients. They also determined that esmolol causes no difference in the blood glucose levels. Jamil *et al.*<sup>[16]</sup> studied the use of LMA in children and its comparison with endotracheal intubation and concluded that the LMA is a suitable alternative to endotracheal intubation for positive pressure ventilation. The present study is a comparative one to study the hemodynamic stress response to laryngoscopic tracheal intubation and LMA insertion in patients.

### Institute of Study

This study was conducted at Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, Telangana.

### Period of Study

This study was from October 2007 to September 2009.

### Type of Study

This was a prospective randomized comparative study.

### Objectives of the Study

The objectives are to study and compare cardiovascular responses to endotracheal intubation with the insertion of LMA by measuring parameters such as: Measured parameters: (1) Pulse rate, (2) systolic blood pressure (SBP), (3) diastolic blood pressure (DBP), and (4) electrocardiogram and derived parameters such as: Mean arterial pressure (MAP).

## MATERIALS AND METHODS

A total of 60 adult patients undergoing elective surgery under general anesthesia in ASA Grade I and mallampati Grade I were included in the study. An ethical committee clearance was obtained from the Institutional Ethical Committee and its approved written, and informed consent was obtained from all the patients for the performance of anesthesia as well as the conduct of the study.

### Inclusion Criteria

1. Patients belonging to either sex were included
2. Patients aged between 18 and 50 years were included
3. Patients belonging to ASA physical status I were included
4. Patients with airway assessment-mallampati Grade (modified) I were included.

### Exclusion Criteria

Patients with:

1. History of respiratory problems
2. History of angina, palpitations, and syncopal attacks
3. Treatment with beta-blockers or calcium channel blockers
4. Regurgitation prone conditions

5. Pregnant patients
6. More than one attempt to intubate or insertion of LMA
7. Duration of endotracheal intubation or LMA insertion more than 30 sec were excluded from the study.

A total of 60 patients were randomly divided into two groups ( $n = 30$ ) in each group by a computer-assisted randomization technique: Group-I: Endotracheal tube group (ETT) and Group-II: LMA group (LMA). Patients undergoing various procedures such as excision of fibroadenoma of breast, dilatation and curettage, upper limb orthopedic surgeries, and excision of swellings over upper extremity were selected for the study. All patients were assessed clinically preoperatively and investigated to rule out systemic diseases. The investigations carried out before were hemogram, urine analysis, blood urea, serum creatinine, electrocardiogram, and X-ray chest. All patients received Tab. Alprazolam 0.25 mg on the night before surgery orally. All patients kept nil orally 12 h before surgery.

#### **Venous Cannulation and Monitors**

Intravenous cannulation with 18G cannula was done. The intravenous infusion was started with Ringer's lactate solution. Non-invasive blood pressure monitor and pulse-oximetry probe were connected to the patients before induction of anesthesia.

#### **Premedication**

Injection glycopyrrolate 0.01 mg/kg, injection fentanyl 1 µg/kg, and injection midazolam 0.05 mg/kg were given intravenously 10 min before induction of anesthesia.

#### **Anesthetic Technique**

All the patients were preoxygenated for 6 min. Induction of anesthesia was done with injection thiopentone sodium (3–5 mg/kg body weight). Intubation was facilitated by using injection succinylcholine 1.5 mg/kg. Patients were ventilated with 100% oxygen for 1 min. At the end of 1 min, patients were ventilated with 100% oxygen for brief period, and intubation with the aid of Macintosh laryngoscope or insertion of LMA was carried out. Endotracheal tube or LMA of appropriate size was used. Time taken for intubation or insertion of LMA did not exceed 20 s. Anesthesia was maintained with intermittent positive pressure ventilation with nitrous oxide (3 L/min) oxygen (2 L/min) and halothane (0.5–1%). Further top-up doses of Vecuronium were given when required. Surgery was not allowed to commence until the study was completed, i.e., for 5 min after intubation/LMA insertion. At the end of surgery, residual neuromuscular block was reversed with a mixture of glycopyrrolate and neostigmine.

#### **Observed Parameters**

1. HR
2. Blood pressure -SBP, DBP, and MAP using NIBP at different intervals such as:
  - a. Before induction
  - b. After induction
  - c. At laryngoscopy and endotracheal intubation or insertion of the laryngeal mask
  - d. 1 min after endotracheal intubation or insertion of the laryngeal mask
  - e. 3 min after endotracheal intubation or insertion of the laryngeal mask
  - f. 5 min after endotracheal intubation or insertion of the laryngeal mask
3. Oxygen saturation
4. Adverse events, if encountered.

All the observed parameters were presented in a tabular form, and appropriate statistical methods were applied to obtain the results.

#### **Statistical Analysis**

##### *Randomization*

The sample was taken at random from a population when each member of the population has an equal chance of being chosen. The purpose is to produce groups that are as nearly similar as possible before the experimental procedure.

##### *Mean*

The mean of a collection of numbers is their arithmetic average, computed by adding them up and dividing by their number.

##### *Standard deviation (SD)*

It is a statistical measure of spread or variability. The SD is the root mean square deviation of the values from their arithmetic mean.

##### *T-test*

*t*-test or student *t* test gives an indication of separateness of two sets of measurements and is thus used to check whether two sets of measurements are essentially different with the null hypothesis that means of the two sets of measurements are equal. *P*-value: It indicates the probability of error and a value  $<0.05$  is considered statistically significant.

## **OBSERVATIONS AND RESULTS**

In this prospective randomized comparative study, 60 patients were randomly divided into two groups ( $n = 30$ ) in each group, by a computer-assisted randomization technique. Group I was consisted of patients undergoing

surgeries under general anesthesia by endotracheal intubation (ETT) and Group II consisted of patients undergoing surgeries under general anesthesia by LMA group (LMA). The surgeries included various procedures such as excision of fibroadenoma of breast, dilatation and curettage, upper limb orthopedic surgeries, and excision of swellings over upper extremity were selected for the study. Patients belonging to the age group of 21–30 years were 16/30 (53.3%) in Group I and 14/30 (46.6%) in Group II. Patients belonging to the age group of 31–40 years were 07/30 (23.0%) in Group I and 09/30 (30.6%) in Group II. In the age group of 41–50 years they were 7/30 in both the groups [Table 1 and Figure 1].

The mean age and SD in Group-I was  $28.40 \pm 9.16$  and in Group-II it was  $30.73 \pm 7.26$ . *P* value was 0.143 (*P* value was  $>0.05$  hence not significant). Patients of both the groups were identical, and there was no statistically significant difference between them [Table 2].

The gender distribution among the two groups was compared and found that in Group I there were 16/30 (53.4%) females and in Group - II there were 10/30 (33.4%) females. Similarly, males were 14/30 (46.4%) in Group - I and 20/30 (66.6%) in Group - II [Table 3 and Figure 2].

It was observed that the weight of the patients in both the groups was similar with a mean weight of  $59.73 \pm 7.39$  kg in Group - I and  $56.53 \pm 9.40$  kg in Group - II. Statistically, there was no significance as *P* value was 0.241 ( $P > 0.05$ : Not significant) [Table 4 and Figure 3].

The mean SBP values in both the groups were comparable at the pre-induction and post-induction phases ( $P > 0.05$ ). Whereas there was significant increase in SBP at ETT intubation or insertion of LMA, at 1<sup>st</sup> min and 3<sup>rd</sup> min after intubation or insertion of LMA. Mean SBP was higher in group ETT (Group-I) as compared to group LMA (Group - II) at intubation, 1<sup>st</sup> min, and 3<sup>rd</sup> min after intubation or LMA insertion. Mean SBP values were comparable in both the groups 5 min after ETT intubation or insertion of LMA with *P* value at 0.587 ( $P > 0.05$ ) [Table 5 and Figure 4].

The mean DBP values in both the groups were comparable at pre-induction and after induction ( $P > 0.05$ ). There was significant increase in DBP in Group - I at ETT intubation or insertion of LMA in Group - II, at 1 min and 3 min after intubation or insertion of LMA. Mean SBP was higher in group ETT as compared to group LMA at intubation, 1min, and 3 min after intubation or LMA insertion. Mean DBP values were comparable in both the groups 5 min after ETT intubation or insertion of LMA with *P* value at 0.51 ( $P > 0.05$ ) [Table 6 and Figure 5].

**Table 1: Age distribution of patients in the study (n=60)**

Age distribution years	Group - I (ETT) n=30 (%)	Group - II (LMA) n=30 (%)
21–30	16 (53.3)	14 (46.6)
31–40	7 (23.0)	9 (30.6)
41–50	7 (23.6)	7 (23.8)

**Table 2: Mean age of the patients (n=60)**

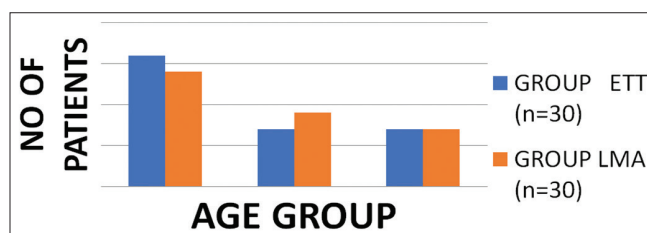
Groups	Mean age in years	<i>P</i> value	Result
I - ETT (n=30)	$28.40 \pm 9.16$	0.143	Not significant
II - LMA (n=30)	$30.73 \pm 7.26$		

**Table 3: Gender distribution of patients in the study (n=60)**

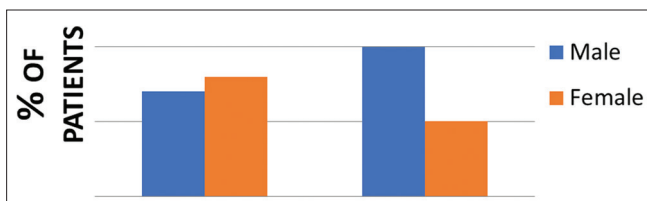
Gender	Group - I (ETT) n=30 (%)	Group - II (LMA) n=30 (%)
Male	14 (46.4)	20 (66.6)
Female	16 (53.4)	10 (33.4)

**Table 4: Weight distribution of patients in the study (n=60)**

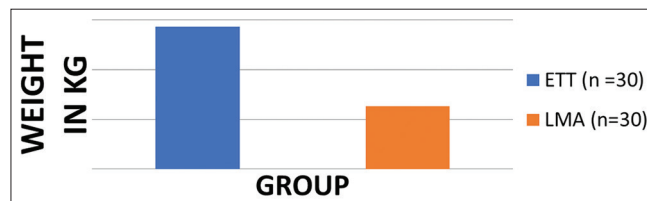
Group	Mean weight (KG)	<i>P</i> value	Result
ETT (n=30)	59.73 (7.39)	0.241	Not significant
LMA (n=30)	56.53 (9.40)		



**Figure 1: Age distribution of patients in the study (n=60)**



**Figure 2: Gender distribution of patients in the study**



**Figure 3: Weight distribution of patients in the study (n=60)**



The MAP values in both the groups were comparable at pre-induction and after induction ( $P > 0.05$ ). There was significant increase in MAP at ETT intubation or insertion of LMA, at 1 min and 3 min after intubation or insertion of LMA. Mean MAP was higher in group ETT as compared to group LMA at intubation, 1<sup>st</sup> min, and 3<sup>rd</sup> min after intubation or LMA insertion. Mean MAP values were comparable in both the groups 5 min after ETT intubation or insertion of LMA with  $P$  value at 0.177 ( $P > 0.05$ ) [Table 7 and Figure 6].

The mean HR values in both the groups were comparable at pre-induction, and after induction ( $P > 0.05$ ). There was significant increased in HR in Group - I at ETT intubation or insertion of LMA in Group - II at 1 min and 3 min after intubation or insertion of LMA. Mean HR was higher in Group - I ETT as compared to Group - II LMA at intubation, 1 min, and 3 min after intubation or LMA insertion. Mean HR values were comparable in both the groups 5 min after ETT intubation or insertion of LMA with  $P$  value at 0.144 ( $P > 0.05$ ) [Table 8 and Figure 7].

## DISCUSSION

Laryngoscopy results in stimulation of pharyngeal wall mucosa and cause marked hemodynamic changes. Endotracheal tube passes through glottis and causes a continuous stimulus and provocation of hemodynamic response. The pressor response to tracheal intubation may be harmful to patients with ischemic heart disease, hypertension, or cerebrovascular disease. Attempts are made to attenuate this response with a variety of pharmacological maneuvers and recently role of fiber-optic laryngoscopy was also investigated. In 1983, Brain A.I.J. described LMA. It does not pass through glottis; rather it sits above the glottis. Moreover, insertion of LMA avoids laryngoscopy. Stimulation of mechanoreceptors in the pharyngeal wall, epiglottis and vocal cords are thought to be the cause for the hemodynamic response. The receptors are abundant over arytenoid cartilage, vocal cords, epiglottis, and hypopharynx. Transitory rises in HR and blood pressure in the perioperative period are a matter of concern in patients with hypertension or coronary artery disease. Hemodynamic instability makes hypertensive patients prone to myocardial ischemia in the perioperative period.

**Table 5: Comparison of mean SBP at various time intervals (n=60)**

Time interval	Group ETT (n=30)	Group LMA (n=30)	t value	P value	Significance
Pre-induction	116.33±12.12	111.60±9.66	1.672	0.120	Not significant
After induction	102.07±10.01	100.60±10.29	0.559	0.578	Not significant
At intubation or insertion of LMA	136.07±9.98	115.73±10.07	7.854	0.000	Significant
Post-intubation/LMA					
1 min	131.47±8.52	112.53±8.48	8.624	0.000	Significant
3 min	120.47±8.34	108.40±7.69	5.824	0.000	Significant
5 min	110.73±8.61	107.67±6.33	0.527	0.587	Not significant

SBP: Systolic blood pressure

**Table 6: Comparison of mean DBP at various time intervals in both groups of the study (n=60)**

Time interval	Group ETT (n=30)	Group LMA (n=30)	t value	P value	Significance
Pre-induction	80.60±8.21	79.67±6.13	0.499	0.620	Not significant
After induction	76.93±(8.98)	77.57 ±(7.66)	2.94	0.770	Not significant
At intubation or insertion of LMA	93.60±(7.87)	78.27±(7.55)	7.701	0.000	Significant
Post-intubation/LMA					
1 min	93.60±7.87	78.27±7.55	7833	0.000	Significant
3 min	85.20±6.78	75.93±6.20	5.524	0.000	Significant
5 min	77.87±8.50	74.27±5.09	1.991	0.051	Not significant

DBP: Diastolic blood pressure

**Table 7: Comparison of mean of mean blood pressures at various time intervals in Groups I and II (n=60)**

Time interval	Group ETT (n=30)	Group LMA (n=30)	t value	P value	Significance
Pre-induction	92.51±9.22	90.31±6.58	0.990	0.326	Not significant
After induction	85.31±7.72	85.24±7.04	0.018	0.986	Not significant
At intubation or insertion of LMA	107.76±7.91	90.76±6.55	9.071	0.000	Significant
Post-intubation/LMA					
1 min	105.87±7.33	89.33±6.79	9.076	0.000	Significant
3 min	96.96±6.14	86.76±5.62	6.658	0.000	Significant
5 min	88.82±7.91	86.07±4.58	1.592	0.177	Not significant

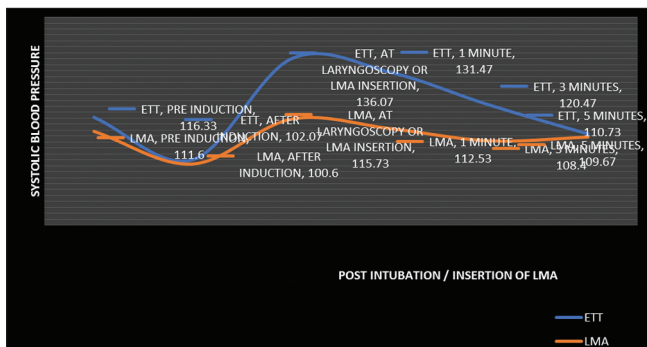


Figure 4: Line diagram showing comparison of systolic blood pressure at different intervals in Groups I and II patients (n=60)

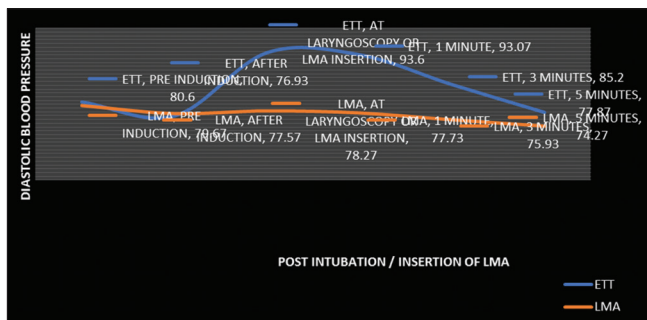


Figure 5: Line diagram showing comparison of diastolic blood pressure at different intervals in both groups of the study (n=60)

There is a significant association between perioperative myocardial ischemia and post-operative ischemic cardiac events such as unstable angina, non-fatal myocardial infarction, and cardiac death.

### Patient Demographics

#### Age-wise distribution of the cases

The mean age in Group - I (ETT) patients was  $28.40 \pm 9.16$  years, whereas the mean age in Group - II (LMA) patients was  $30.73 \pm 7.26$  years. Thus, both the groups were statistically comparable ( $P > 0.05$ ). The mean age in Group - I (ETT) patients was  $34.72 \pm 9.20$  years whereas the mean age in Group - II (LMA) patients was  $35.60 \pm 6.93$  years. In a similar study carried out by Bukhari *et al.*, [Table 9].<sup>[17]</sup> It was observed that both the groups consisted of patients of similar age groups.

#### Sex-wise distribution of cases

There were more male patients (66.6%) in Group - II (LMA) as compared to Group - I (ETT), (46.4%), similarly, there were more female patients in Group - I (ETT), (53.4%) as compared to Group - II (LMA) (33.4%). There were more female patients in ETT (64.0%) as well as in LMA group (84.0%) in the study carried out by Bukhari *et al.* [Table 10].<sup>[17]</sup>

#### Weight wise distribution of cases

The mean weight in Group - I (ETT) patients was  $59.73 \pm 7.39$  kg; whereas the mean weight in Group - II (LMA)

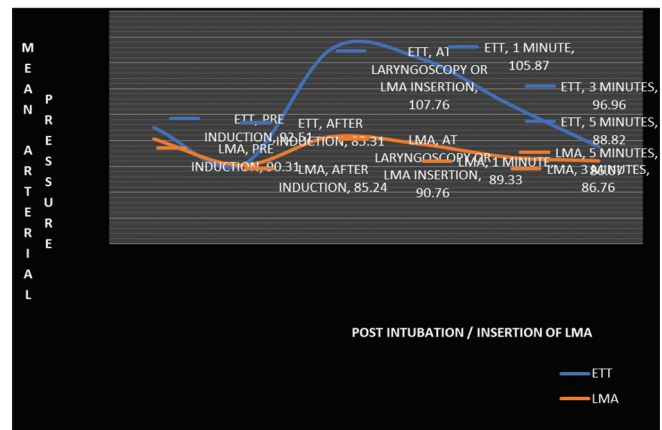


Figure 6: Line diagram showing a comparison of mean arterial pressures at different intervals in both the study groups (n=60)

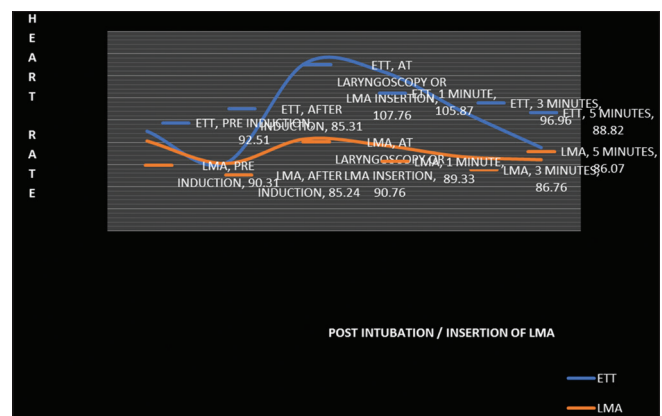


Figure 7: Line diagram showing a comparison of mean heart rates at different intervals in Groups I and II of the study (n=60)

patients was  $56.53 \pm 9.40$  kg. Thus, both the groups were statistically comparable ( $P > 0.05$ ) [Table 11]. It was observed that in the study by Bukhari *et al.*<sup>[17]</sup> also both the groups consisted of patients with similar weight  $58.08 \pm 11.07$  and  $57.60 \pm 6.64$ , respectively.

#### Changes in HR

The pre-induction mean HR in Group - I (ETT) was  $80.47 \pm 9.30$  beats/min, whereas in Group - II (LMA) it was  $82.20 \pm 7.56$  beats/min. Thus, the baseline mean HR in both the groups was statistically comparable ( $P = 0.432$ ). There was a statistically significant ( $P = 0.034$ ) rise in mean heart after induction in both the groups. The rise in HR after induction can be attributed to compensatory tachycardia in response to thiopentone sodium-induced hypotension. At the time of ETT intubation or LMA insertion, there was an increase in mean HR values in both the groups. This rise was marked in Group - I (ETT), ( $116.43 \pm 3.94$  beats/min) as compared to Group-II (LMA) ( $107.80 \pm 8.18$  beats/min). This rise was statistically significant as  $P$  value was 0.000 ( $P$  significant at  $<0.05$ ). The mean HR values in Group - I (ETT) at 1 min, 3 min, and 5 min after ETT intubation were  $107.80 \pm 7.33$ ,  $109.53 \pm 17.47$ , and  $96.4 \pm$



**Table 8: Comparison of mean HRs at various time intervals in both the study groups (n=60)**

Time interval	Group ETT (n=30)	Group LMA (n=30)	t value	P value	Significance
Pre-induction	80.47±9.30	82.20±7.56	-7.92	0.432	Not significant
After induction	85.27±11.44	87.13±6.24	-7.85	0.436	Not significant
At intubation or insertion of LMA	116.43±3.94	107.80±8.18	5.209	0.001	Significant
Post-intubation/LMA					
1 min	107.80±9.27	98.00±11.79	3.579	0.001	Significant
3 min	109.53±17.47	97.80±11.50	3.073	0.003	Significant
5 min	96.40±13.04	92.00±9.71	1.482	0.144	Not significant

**Table 9: A comparative study of age distribution between present study and Bukhari *et al.* study**

Group	Bukhari <i>et al.</i> <sup>[17]</sup>	Present study
ETT	34.72±9.20	28.40±9.16
LMA	35.60±6.93	30.73±7.26

**Table 10: Comparative study of gender distribution among the patients of the study Groups I and II**

Group	Bukhari <i>et al.</i> <sup>[17]</sup> (%)	Present study (%)
ETT	Male: 36 Female: 64.0	Male: 46.4 Female: 53.4
LMA	Male: 16 Female: 84	Male: 66.6 Female: 33.4

**Table 11: Comparative study of weight distribution in the patients of Groups I and II in the study**

Group	Bukhari <i>et al.</i> <sup>[17]</sup> Mean weight (kg)	Present study Mean weight (kg)
ETT	58.08±11.07	59.73±7.39
LMA	57.60±6.64	56.53±9.40

13.04 beats/min, respectively. Whereas mean HR values at 1, 3, and 5 min after LMA insertion in Group - II (LMA) were  $98.00 \pm 11.79$ ,  $97.80 \pm 11.50$ , and  $92.00 \pm 9.71$  beats/min, respectively. Thus, mean HR values in Group - I (ETT) were significantly higher as compared to those of Group - II (LMA) at 1 min ( $P = 0.000$ ) and 3 min ( $P = 0.003$ ) after ETT intubation or LMA insertion. At 5 min, the mean HR values were statistically comparable in both the groups ( $P = 0.144$ ). Further, it was observed that the mean HR values increased markedly at ETT insertion in group ETT, whereas the same values increased marginally in group LMA. The mean HR values did not return to pre-induction levels even after 5 min after ETT intubation or LMA insertion in both the groups. The results pertaining to changes in HR in the present study are in accordance with those of a similar study conducted by Bukhari *et al.*<sup>[17]</sup> who observed a significant increase in HR in both the groups immediately after ETT intubation as well as LMA insertion. They further noticed that mean HR remained elevated up to 3 min after ETT intubation or LMA insertion ( $P < 0.01$ ). However, the

increase in HR was found to be more in Group - I (ETT) at 1 min after intubation ( $121.16 \pm 15.68$  beats/min) as compared to Group - II (LMA) ( $110.24 \pm 13.07$  beats/min). The results of the present study are also in accordance with those of Joad *et al.*<sup>[18]</sup> who observed a significant increase in HR in both the groups immediately after ETT intubation as well as LMA insertion. They further noticed that mean HR remained elevated up to 5 min after ETT intubation or LMA insertion ( $P < 0.01$ ). However, the increase in HR was found to be more in group ETT at 1 min and 3 min after intubation ( $111.24 \pm 13.06$  and  $111.04 \pm 12.06$  beats/min) as compared to group LMA ( $103.88 \pm 11.67$  and  $92.12 \pm 12.6$  beats/min). Further group LMA had a significantly lower HR than group ETT (repeated measure ANOVA:  $P < 0.005$ ) [Table 12].

### Changes in SBP

The pre-induction mean SBP in Group - I (ETT) was  $116.33 \pm 12.12$  mmHg, whereas in Group - II (LMA) it was  $111.60 \pm 9.66$  mmHg. Thus, the baseline mean SBP in both the groups was statistically comparable ( $P = 0.100$ ). There was a statistically significant ( $P = 0.001$ ) fall in mean SBP after induction in both the groups. The fall in SBP after thiopentone induction may be attributed to decreased systemic vascular resistance. At the time of ETT intubation or LMA insertion, there was an increase in mean SBP values in both the groups. This rise was marked in Group - I (ETT) ( $136.07 \pm 9.98$  mmHg) as compared to Group - II (LMA) ( $115.75 \pm 10.07$  mmHg). This rise was statically significant ( $0.000$ ). The mean SBP values in Group - I (ETT) at 1 min, 3 min, and 5 min after ETT intubation were  $131.47 \pm 8.52$ ,  $120.7 \pm 8.34$ , and  $110.73 \pm 8.61$  mm Hg, respectively. Whereas mean SBP values at 1, 3, and 5 min after LMA insertion in group LMA were  $112.53 \pm 8.48$ ,  $108.40 \pm 7.69$ , and  $109.67 \pm 6.33$  mmHg, respectively. Thus, mean SBP values in Group - I ETT were significantly higher as compared to those of Group - II LMA at 1 min ( $P = 0.000$ ) and 3 min after ETT intubation or LMA insertion. At 5 min, the mean SBP values were statistically comparable in both the groups ( $P = 0.587$ ) further it was observed that the mean SBP values increased markedly at ETT insertion in Group - I (ETT), whereas the same values increased marginally in group LMA. The mean SBP values returned to pre-induction levels after

3 min in Group - I (ETT) as compared to after 1 min in Group - II (LMA). The results pertaining to changes in SBP in the present study are in accordance with those of a similar study conducted by Bukhari *et al.*<sup>[17]</sup> who observed a significant increase in SBP in Group - I (ETT) at 1 and 2 min after insertion as compared to group LMA ( $P < 0.01$ ). The results of the present study are also in accordance with those of Joad *et al.*<sup>[18]</sup> who observed a significant increase in SBP in group ETT at 1 min, 2 min, and 3 min after insertion as compared to group LMA ( $P < 0.01$ ) [Table 13].

### Changes in DBP

The pre-induction mean DBP in Group - I (ETT) was  $80.60 \pm 8.21$  mmHg whereas in Group - II (LMA), it was  $79.67 \pm 6.13$  mmHg. Thus, the baseline mean DBP in both the groups was statistically comparable ( $P = 0.620$ ). There was a statistically significant ( $P = 0.001$ ) fall in Mean DBP after induction in both the groups. At the time of ETT intubation or LMA insertion, there was an increase in mean DBP values in both the groups. This rise was marked in Group - I (ETT) ( $93.60 \pm 7.87$  mmHg) as compared to Group-II (LMA) ( $78.27 \pm 7.55$  mmHg). This rise was statically significant in Group-I (ETT) (0.000) but not in Group-II (LMA) ( $P = 0.120$ ). The mean DBP values in Group - I (ETT) at 1 min, 3 min, and 5 min after ETT intubation were  $93.07 \pm 7.53$ ,  $85.20 \pm 6.78$ , and  $77.87 \pm 8.50$  mmHg, respectively. Whereas mean DBP values at

1, 3, and 5 min after LMA insertion in Group - II (LMA) were  $77.73 \pm 7.53$ ,  $75.93 \pm 6.20$ , and  $79.27 \pm 5.09$  mmHg, respectively. Thus, mean DBP values in Group - I (ETT) were significantly higher as compared to those of Group - II (LMA) at 1 min ( $P = 0.000$ ) and 3 min ( $P = 0.000$ ) after ETT intubation or LMA insertion. At 5 min, the mean DBP values were statistically comparable in both the groups ( $P = 0.051$ ) further it was observed that the mean DBP values increased markedly at ETT insertion in Group - I (ETT), whereas the same values increased slightly in Group - II (LMA). The mean DBP values returned to pre-induction levels at 5 min in both the groups. The results pertaining to changes in DBP in the present study are in accordance with those of a similar study conducted by Bukhari *et al.*<sup>[17]</sup> who observed a significant increase in DBP in group ETT at 1 and 2 min after insertion as compared to Group - II (LMA) ( $P < 0.01$ ). The results of the present study are also in accordance with those of Joad *et al.*<sup>[18]</sup> who observed a significant increase in DBP in Group - I (ETT) at 1 min, 2 min, and 3 min after insertion as compared to Group - II (LMA) ( $P < 0.01$ ), [Table 14].

### Changes in mean arterial blood pressure

The pre-induction mean MAP in Group - I (ETT) was  $92.51 \pm 9.22$  mmHg, whereas in Group - II (LMA) it was  $90.31 \pm 6.58$  mmHg. Thus, the baseline mean DBP in both the groups was statistically comparable ( $P = 0.620$ ).

**Table 12: Comparative study of HR between the study group and another two studies**

Time interval	Bukhari <i>et al.</i> <sup>[17]</sup>		Joad <i>et al.</i> <sup>[18]</sup>		Present study	
	ETT	LMA	ETT	LMA	ETT	LMA
Pre-induction	84.68±11.21	84.88±6.96	81.12±13.3	81.18±13.05	80.4±9.30	82.20±7.56
After induction	98.08±12.01	105.4±11.27	91.44±1.95	91.64±2.61	85.27±11.44	87.13±6.24
At intubation/insertion of LMA	**	**	**	**	116.43±3.94	107.80±8.18
Post-intubation/LMA						
1 min	121.16±15.68	110.24±13.07	111.24±13.06	103.88±11.67	107.80±7.33	98.00±11.79
2 min	102.02±11.85	102.62±12.71	111.32±12.64	98.88±11.13	**	**
3 min	86.24±12.11	90.62±9.86	111.04±12.06	92.12±12.6	109.53±17.4	97.80±11.50
4 min	**	**	108.84±11.46	88.88±12.73	**	**
5 min	**	**	90.64±11.22	85.64±11.19	96.4±13.04	92.00±9.71

\*\*Not observed

**Table 13: Comparative study of systolic blood pressure (SBP) between the present study and other studies**

Time interval	Bukhari <i>et al.</i> <sup>[17]</sup>		Joad <i>et al.</i> <sup>[18]</sup>		Present study	
	ETT	LMA	ETT	LMA	ETT	LMA
Pre-induction	128.02±16.91	133.32±11.38	120.40±14.73	119.36±14.87	116.3±12.12	111.60±9.66
After induction	108.68±14.24	102.92±6.76	106.32±12.43	105.76±12.21	102.07±10.01	100.60±10.2
At ETT intubation/insertion of LMA	**	**	**	**	136.07±9.98	115.75±10.0
Post-intubation/LMA						
1 min	157.44±28.17	111.32±14.93	144.72±13.01	130.94±10.59	131.47±8.52	112.53±8.48
2 min	132.64±11.85	110.08±10.93	145.92±11.66	130.02±10.69	**	**
3 min	119.64±17.11	114.08±8.46	144.40±11.31	126.56±10.70	120.47±8.34	108.40±7.69
4 min	**	**	133.68±13.01	124.00±10.40	**	**
5 min	**	**	126.68±14.00	120.36±9.58	110.73±8.6	109.67±6.73

\*\*Not observed

**Table 14: Comparative study of DBP between the present study and another two studies**

Time interval	Bukhari <i>et al.</i> <sup>[17]</sup>		Joad <i>et al.</i> <sup>[18]</sup>		Present study	
	ETT	LMA	ETT	LMA	ETT	LMA
Pre-induction	80.92±8.21	83.36±6.93	78.68±7.57	79.08±7.47	80.60±8.21	79.67±6.13
After induction	67.44±6.94	66.04±5.97	76.98±7.43	77.04±7.68	76.93±8.98	77.57±7.66
At ETT intubation/insertion of LMA	**	**	**	**	93.60±7.87	78.27±7.57
Post-intubation/LMA						
1 min	103.48±15.35	74.06±9.87	86.96±5.59	82.52±7.32	93.07±7.53	77.73±7.53
2 min	86.88±14.09	77.82±6.57	86.96±5.19	81.48±7.41	**	**
3 min	78.12±11.97	75.76±7.21	84.32±5.73	80.06±7.25	85.20±6.78	75.93±6.20
4 min	**	**	81.48±6.56	79.58±7.27	**	**
5 min	**	**	78.92±7.43	79.56±7.32	77.87±8.50	79.27±5.09

\*\*Not observed. DBP: Diastolic blood pressures

**Table 15: Comparative study of MAP of the present study and other two studies**

Time interval	Bukhari <i>et al.</i> <sup>[17]</sup>		Present study	
	ETT	LMA	ETT	LMA
Pre-induction	96±10.9	100±8.6	92.51±9.22	90.31±6.58
After induction	80±9.6	78±6.3	85.3±7.72	85.24±7.04
At ETT intubation/insertion of LMA	**	**	107.76±7.91	90.76±6.55
Post-induction intubation/LMA				
1 min	120±20.2	86±11.6	105.87±7.33	89.33±6.79
2 min	102±13.3	88±7.2	**	**
3 min	92±12.9	88±7.62	96.96±6.14	86.76±5.62
4 min	**	**	88.82±7.9	86.07±4.58
5 min				

\*\*Not observed. MAP: Mean arterial pressures

There was a statistically significant ( $P = 0.001$ ) fall in the mean MAP after induction in both the groups. At the time of ETT intubation or LMA insertion, there was an increase in mean MAP values in both the groups. This rise was marked in group ETT ( $107.76 \pm 7.91$  mmHg) as compared to group LMA ( $90.76 \pm 6.55$  mmHg). This rise was statically significant in Group - I (ETT) ( $P=0.000$ ) as well as in Group - II (LMA) ( $P=0.031$ ). The mean MAP values in Group - I (ETT) at 1 min, 3 min, and 5 min after ETT intubation were  $105.87 \pm 7.33$ ,  $96.96 \pm 6.14$ , and  $88.82 \pm 7.97$  mmHg, respectively, whereas mean MAP values at 1, 3, and 5 min after LMA insertion in Group - II (LMA) were  $89.33 \pm 6.79$ ,  $86.78 \pm 5.62$ , and  $86.07 \pm 4.58$  mmHg, respectively. Thus, mean MAP values in Group - I (ETT) were significantly higher as compared to those of Group - II (LMA) at 1 min ( $P = 0.000$ ) and 3 min ( $P = 0.000$ ) after ETT intubation or LMA insertion. At 5 min, the mean MAP values were statistically comparable in both the groups ( $P = 0.117$ ). Further, it was observed that the mean MAP values increased markedly at ETT insertion in group ETT, whereas the same values increased marginally in group LMA. The mean MAP values returned to pre-induction levels after 3 min in group ETT as compared to within 1 min in group ETT. The results pertaining to changes in MAP in the present study are in accordance with those of a similar study conducted by Bukhari *et al.*<sup>[17]</sup> who observed a significant increase in mean

arterial blood pressure in group ETT at 1 and 2 min after insertion as compared to group LMA ( $P < 0.01$ ) [Table 15].

There was no evidence of desaturation in patients belonging to any of the groups in the present study as well as in a study carried by Bukhari *et al.*<sup>[17]</sup> and Joad *et al.*<sup>[18]</sup>

In the present study, no other complications were observed except, sinus tachycardia (HR >110 bpm), the incidence of which was higher in group ETT (70%) as compared to group LMA (53.3%). In addition to the comparative study above review of literature also showed a similar study by Braude *et al.* who concluded that significant differences between the two groups were evident in arterial DBP immediately after insertion and again 2 min later. They opined that use of the laryngeal mask may, therefore, offer some limited advantages over tracheal intubation in the anesthetic management of patients where the avoidance of the pressor response is of particular concern.

A study by Braude *et al.*<sup>[19]</sup> and Kiran *et al.*<sup>[20]</sup> in 2015, observed that the hemodynamic response to laryngeal mask insertion is transient. No untoward incidents with airway management by LMA occurred in their study. Khalid *et al.*<sup>[21]</sup> concluded that the attenuated response of the LMA was desirable as the time taken to insert an LMA was significantly shorter and insertion was easier as compared

to laryngoscopy and ETT insertion. These factors might be contributory to the higher hemodynamic changes seen with laryngoscopy and ETT insertion. In a randomized clinical trial by Khan *et al.*<sup>[22]</sup> found that LMA removal was found to be accompanied with lesser pressor responses as compared to endotracheal tube extubation in controlled hypertensive patients. Malti *et al.*<sup>[23]</sup> concluded from their study that LMA is advantageous in penetrating eye injuries, glaucoma, and strabismus in whom elevation of intraocular pressure is likely to be detrimental. They found the rise in intra-ocular pressure was minimal with LMA insertion. Sara *et al.*<sup>[24]</sup> in a prospective randomized clinical trial observed that with LMA the advantage of promoting smaller hemodynamic response during its management and lower incidence of sore throat and dysphagia in the 1<sup>st</sup> h after surgery.

## CONCLUSIONS

The pressor response to LMA insertion is much less than that of laryngoscopy and endotracheal intubation. Duration and magnitude of the pressor response are transient during LMA insertion. LMA may be useful in airway management during anesthesia in situations where marked pressor response would be deleterious, for example, patients with hypertension and coronary artery disease. However, large-scale studies are required to confidently ascertain the findings of present study.

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# A Randomized Double-blind Control Study Comparing the Efficacy of Palonosetron Versus a Combination of Dexamethasone with Palonosetron in Preventing Post-operative Nausea and Vomiting in Patients Undergoing Laparoscopic Cholecystectomy

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## Abstract

**Introduction:** Post-operative nausea and vomiting (PONV) is distressing symptoms occurring after anesthesia and surgery with incidence of about 20–30% during the first 24 post-operative hours. In patient undergoing laparoscopic cholecystectomy (LC), the incidence is as high as 63–72%.

**Objective:** The objective of this study was to compare the efficacy of “palonosetron” versus a combination of “dexamethasone and palonosetron” in preventing PONV in patients undergoing LC.

**Materials and Methods:** A total of 84 patients were randomized into two groups. Group I received palonosetron (0.075 mg) and Group II received a combination of palonosetron (0.075 mg) and dexamethasone (8 mg). Incidence of PONV was measured using visual analog score from the time of arrival to recovery until discharge at specified intervals. The absence of nausea and vomiting was considered as complete response (CR). Requirement of rescue antiemetic (metoclopramide) in each group was noted.

**Results:** At 0–2 h, CR of 85.7% in Group II and 66.7% in Group I was observed ( $P = 0.040$ ). During 2–24 h, CR in Group II in comparison to Group I (88.1% vs. 69%,  $P = 0.033$ ) was more. During 0–24 h, CR of 85.7% of patients in Group II and 66.7% of patients in Group I ( $P = 0.040$ ) was observed. Between 24 h till discharge, 100% in Group II and 97.6% in Group I showed CR ( $P = 0.314$ ). Requirement for rescue antiemetic was higher in Group I ( $P = 0.026$ ).

**Conclusion:** A combination of palonosetron and dexamethasone significantly reduced the incidence of PONV during the first 24 h. After 24 h, both groups showed similar efficacy.

**Key words:** Complete response, Dexamethasone, Palonosetron, Post-operative nausea and Vomiting

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## INTRODUCTION

Post-operative nausea and vomiting (PONV) is the most common distressing symptoms with incidence around 20–30% occurring in the first 24 post-operative hours.<sup>[1,2]</sup> The incidence can be as high as 70–80% in high-risk patients.<sup>[3]</sup> The incidence of PONV after general anesthesia

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is also determined by various other factors such as patient sex, habits such as smoking, presence of motion sickness, or previous PONV and also surgical factors such as type of surgery (laparoscopic surgeries, strabismus, middle ear surgeries, stomach, duodenum, and gallbladder surgeries<sup>[1,4,5]</sup> are at high risk of PONV), duration of surgery (high incidence if duration is more than 3 h), and use of opioids and nitrous oxide.<sup>[1,4]</sup> A simplified scoring system was developed by Apfel *et al.* [Figure 1] to predict the incidence of PONV in undergoing surgery under general anesthesia. The incidence of PONV may vary from 10% when no risk factors are present to as high as 80% when all four risk factors are present.

Emetic episodes can predispose to aspiration of gastric contents, wound dehiscence, bleeding, rise in intracranial pressure, fluid and electrolyte imbalance, and psychological distress.<sup>[6,7]</sup> PONV may also delay discharge from post-anesthesia care unit (PACU) and is the leading cause of unexpected hospital admissions after planned ambulatory surgery.<sup>[1]</sup> After planned ambulatory surgery. The incidence of PONV in patient undergoing laparoscopic cholecystectomy (LC) is around 63–72%.<sup>[8,9]</sup> The use of prophylactic antiemetic in these patients is justified.

Vomiting center, which is located in the lateral reticular formation of the medulla oblongata in close proximity to the nucleus of the solitary tract in the brain stem, has access to the motor pathways that are responsible for the visceral and somatic output involved in vomiting. Main sensors of somatic stimuli are located in the gut and chemoreceptor trigger zone in the area postrema. Other stimuli are those from oropharynx, mediastinum, peritoneum, and genitalia as well as afferents from the central nervous system.<sup>[10,11]</sup> Five neurotransmitter systems appear to play important roles in mediating the emetic response [Figure 2].

Five neurotransmitter systems appear to play important roles in mediating the emetic response. Various pharmacological agents used in preventions and treatment of PONV such as antihistamines, butyrophenones and dopamine receptor antagonists. Of these 5-hydroxytryptamine-3 receptor antagonist have been chosen as first line of therapy because of their fewer side effect profile.<sup>[12]</sup>

Palonosetron is a second generation 5-HT<sub>3</sub> antagonist that has recently been approved for prophylaxis against PONV. It has a higher receptor affinity due to its binding to receptor in an allosteric positively cooperative manner and so has a much longer half-life (36–40 h) than other 5-HT<sub>3</sub> antagonists.<sup>[13]</sup> Palonosetron has been evaluated for prophylaxis against PONV in two placebo-controlled trials.<sup>[14,15]</sup> Based on these trials, the minimum effective dose of palonosetron in the setting of PONV is 0.075 mg.

Dexamethasone is a corticosteroid whose prophylactic antiemetic effect has been documented in laparoscopic surgery, and its efficacy reported to be equal as 5-HT<sub>3</sub> antagonists.<sup>[16,17]</sup> When combined with dexamethasone, the efficacy of palonosetron was much improved for both early and delayed chemotherapy-induced nausea and vomiting (CINV).<sup>[18]</sup>

On the basis of promising results shown in combination therapy of palonosetron with dexamethasone in CINV, combination of palonosetron and dexamethasone may studied as a choice for prophylaxis in patients at high risk for PONV. Therefore, the present study was designed to compare palonosetron versus palonosetron and dexamethasone combination for the prevention of PONV in patients undergoing LC.

## MATERIALS AND METHODS

The present study was a randomized control trial conducted between July 2013 and July 2014 at Apollo Hospital, Chennai, after getting informed consent from the patient and also ethical committee approval. 84 patients of American Society of Anesthesiologists (ASA) physical status I and II and aged between 25 and 60 years were included in the study and randomly divided into two Groups I and II based on computer randomization.

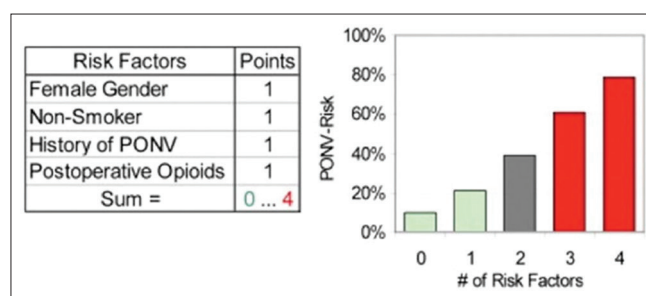


Figure 1: Apfel score

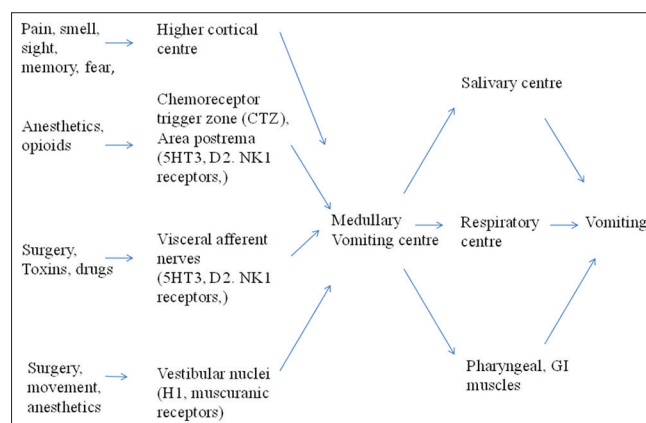


Figure 2: Pathophysiology of vomiting

Patients who are allergic to study drug, prolonged surgery more than 3 h, patient who received antiemetic 24 h before surgery, history of motion sickness or PONV, history of bronchial asthma, pregnant patient, and conversion from laparoscopy to laparotomy were excluded from the study. Before day of surgery, all patients were explained about visual analog scale for nausea and pain. All patients were premedicated with tablet pantoprazole 40 mg on the night before surgery and 8 h fasting before surgery was observed.

The study drug palonosetron is available as palonosetron hydrochloride 0.075 mg in 1.5 ml ampoule. Group I - patient received 0.075 mg of palonosetron i.v diluted to 4 ml with 0.9% sodium chloride solution. Group II - patient received 0.075 mg of palonosetron and dexamethasone 8 mg i.v diluted to 4 ml with 0.9% sodium chloride solution. Drug solution was prepared in identical syringes by a person not involved in the study.

After performing a thorough machine check and attaching all ASA standard monitors, patients were pretreated with the study drugs. Anesthesia was induced by injection propofol 2 mg/kg i.v, injection fentanyl 2 mcg/kg i.v, and vecuronium 0.1 mg/kg i.v. After endotracheal intubation, anesthesia was maintained by desflurane 6% with air in oxygen ( $\text{FiO}_2$  0.4). After induction, nasogastric tube was inserted and suction was applied to empty the stomach of air and other contents. Ventilation was mechanically controlled and adjusted to maintain end-tidal  $\text{CO}_2$  (end-tidal carbon dioxide [ $\text{ETCO}_2$ ]) at 35–40 mmHg throughout the surgery as measured by anesthesia gas analyzer. Intraoperatively, heart rate (HR), non-invasive blood pressure (NIBP), saturation using pulse oximeter ( $\text{SPO}_2$ ), and  $\text{ETCO}_2$  were noted every 10 min until the end of surgery. The total duration of surgery (from incision to application of bandage) and anesthesia (from induction to discontinuation of the inhaled anesthetic agent) was noted. Total duration of  $\text{CO}_2$  insufflations was also noted.

Before tracheal extubation, the nasogastric tube was suctioned again and then removed. At the end of anesthesia, glycopyrrolate 10 mcg/kg i.v and neostigmine 50 mcg/kg i.v were administered for reversal of residual neuromuscular blockade and trachea extubated once the patient satisfied the extubation criteria. Before skin closure, the surgeon was asked to inject 0.25% bupivacaine (5 ml) at the fascial level of each surgical portal. In addition, all patients received injection diclofenac 75 mg by infusion for post-operative analgesia 30 min before end of the procedure. Postoperatively, all patients were observed for PONV from time of arrival to recovery room till 36 h or until discharge, whichever is longer. All episodes of PONV during the post-operative period were recorded by a blinded observer at the time intervals of 0–2 h, 2–24 h,

and from 24–36 h or until discharge. Nausea was assessed using VAS scale. A score of  $>5$  was considered severe, 5 = moderate and  $<5$  minimal, and 0 = nil. Rescue antiemetic metoclopramide 10 mg i.v was given for moderate and severe nausea, vomiting episode, or at patients request and repeated if necessary. Complete response (CR) was defined as no nausea and vomiting with no administration of rescue antiemetic medication during the 24 h observation period and will be the primary efficacy end point.

## RESULTS

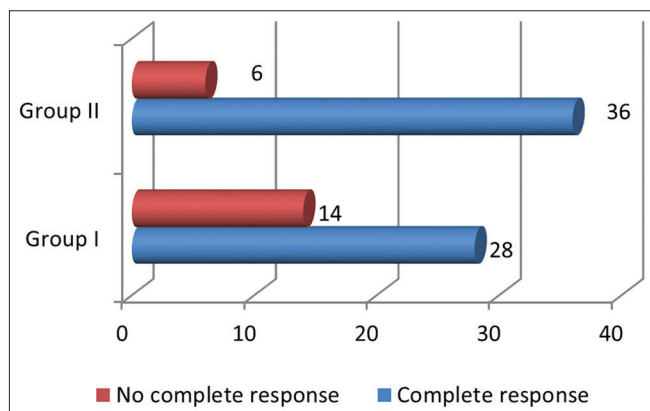
The statistical analysis was carried out using Statistical Package for the Social Sciences V11.0. All the continuous variables were assessed for the normality using Shapiro–Wilk's test. All normally distributed variables are expressed as mean  $\pm$  standard deviation. Median (interquartile range) comparisons of all the normally distributed continuous variables were done by independent sample *t*-test or ANOVA based on number of groups. Comparison of all the non-normally distributed continuous variables was done by Mann–Whitney *U*-test or Kruskal–Wallis test based on number of groups. All categorical variables were expressed as either percentage or proportions. Comparisons of categorical variables were done by Chi-square test or Fischer's exact test based on number of observation.  $P < 0.05$  was considered as statistically significant. Data entry and validation were done on MS Excel spreadsheet. The sample size has been calculated on the basis of a previous study, which shows the incidence of PONV in patients undergoing LC who have not received any antiemetic prophylaxis as 70%.<sup>[8,9]</sup> Presuming that after palonosetron prophylaxis, there would be 30% reduction in incidence,<sup>[15]</sup> power analysis with  $\alpha = 0.05$  and  $\beta = 0.90$  showed that we need to enroll 38 patients in each group. To minimize the effect of data loss, 42 patients were recruited in each group.

The mean age of patients in Group I was  $42.43 \pm 7.96$  years and in Group II was  $43.29 \pm 7.09$  years. The mean weight of patients in Group I and II was  $71.12 \pm 6.60$  kg and  $70.36 \pm 2.48$  kg. The mean height of patient was  $163.34 \pm 6.50$  cm in Group I and  $163.29 \pm 5.47$  cm in Group II. Group I consisted of 27 females and 15 males and Group II consisted of 30 females and 12 males. Distribution of ASA I:II patients was 27:15 in Group I and 31:11 in Group II. Both the groups were well matched with respect to age, weight, height, sex ratio, and ASA grades ( $P > 0.05$ ) [Table 1]. The mean baseline HR of Group I was  $76.84 \pm 4.43$  and in Group II was  $75.34 \pm 4.15$ , the mean systolic blood pressure in Group I was  $130.29 \pm 9.51$  and in Group II was  $129 \pm 8.86$ , the mean diastolic blood pressure (DBP) in Group I was  $78.67 \pm 4.80$  and in Group II was  $78.74 \pm 4.45$ , and the mean oxygen saturation ( $\text{SPO}_2$ ) in Group I was 99.88

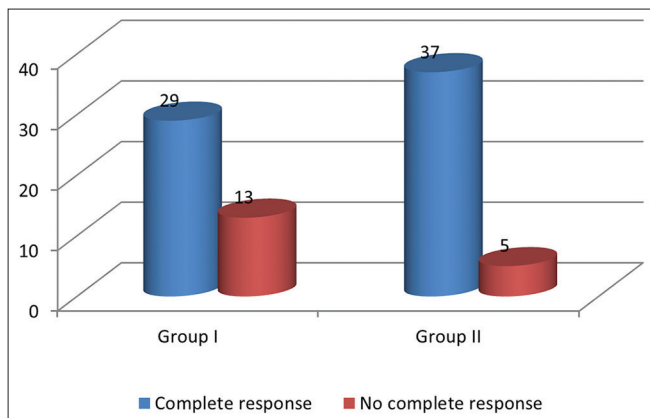


$\pm 0.33$  and in Group II was  $99.88 \pm 0.33$ . Both the groups were well matched with respect to mean HR, BSP, DBP, and  $\text{SPO}_2$ . The mean duration of surgery in Group I was  $59.05 \pm 6.91$  and in Group II was  $60.02 \pm 6.99$ , the mean duration of anesthesia in Group I was  $80.40 \pm 7.15$  and in Group II was  $79.43 \pm 7.50$ , and mean duration of  $\text{CO}_2$  insufflations in Group I was  $47.52 \pm 6.66$  and Group II was  $47.86 \pm 6.29$ . Both the groups were comparable with regard to mean duration of  $\text{CO}_2$  insufflations, surgery, and anesthesia. Both the groups were comparable with regard to intraoperative vital parameters such as HR, blood pressure, and saturation over time interval ( $P > 0.05$ ).

All the patients were observed for 2 h (0–2 h) in the PACU. During their stay in PACU, HR, NIBP, and pain scale were monitored every 30 min and  $\text{SPO}_2$  was monitored continuously. All episodes of PONV were also assessed at 30 min interval. We used the total incidence of nausea and vomiting to present PONV. After 2 h, patients were shifted to the ward and from 2 h until discharge episodes of PONV were recorded at 2, 4, 8, 12, 24 h, and until discharge.



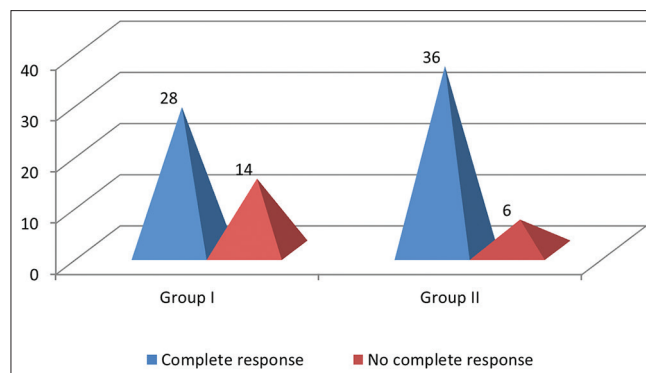
**Graph 1: Incidence of complete response, nausea, vomiting, and post-operative nausea and vomiting during 0–2 h: Values are expressed as  $n$  (%)**



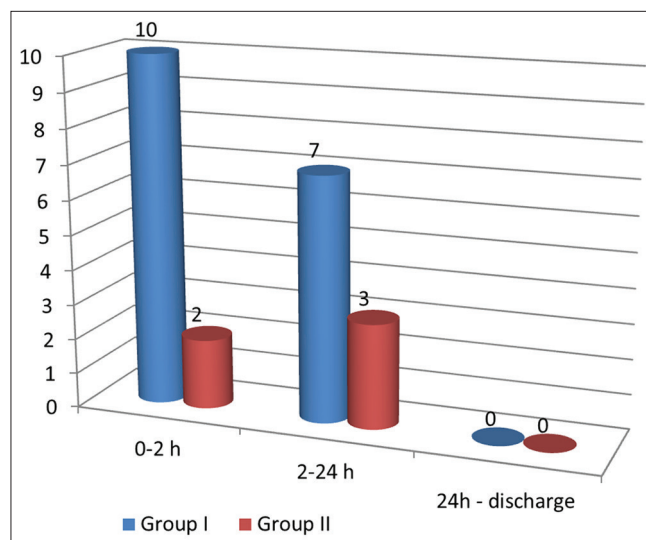
**Graph 2: Incidence of complete response, nausea, vomiting, and post-operative nausea and vomiting during 2–24 h: Values expressed as  $n$  (%)**

During the first 2 h postoperatively, 36 patients (85.7%) in Group II did not complain of nausea compared to 28 patients (66.7%) in Group I ( $p$  value 0.228) [Table 2] and 37 patients (88.1%) in Group I and 40 patients (95.2%) in Group II did not experience vomiting ( $P = 0.433$ ), and the difference was not statistically significant. However, CR was observed in 85.7% of patients in Group II as compared to 66.7% of patients in Group I, and the difference was statistically significant ( $P = 0.040$ ) [Graph 1 and Table 5].

During 2–24 post-operative hours, 88.1% of patients in Group II were nausea free, whereas 69% of patients did not experience nausea in Group I ( $P = 0.205$ ) [Table 3] and 39 patients (92.9%) in Group II did not experience vomiting compared with 37 (88.1%) patients in Group I ( $P = 0.713$ ). The results were not statistically significant. During 2–24 h time period, significantly more patients showed CR in Group II in comparison to Group I (88.1% vs. 69%  $P = 0.033$ ) [Graph 2].



**Graph 3: Incidence of complete response, nausea, vomiting, and post-operative nausea and vomiting during 0–24 h: Values expressed as  $n$  (%)**



**Graph 4: Requirement of rescue antiemetic. Values expressed as  $n$  (%)**

**Table 1: Demographic data (mean±SD) unless specified**

Data	Group I (n=42)	Group II (n=42)	P value (between groups)
Age (years)	42.43±7.96	43.29±7.09	0.604
Weight (kg)	71.12±6.60	70.36±2.48	0.486
Height (cm)	163.34±6.50	163.29±5.47	0.971
M: F	15:27	12:30	0.641 (Fischer's exact test)
ASA I: II	27: 15	31:11:00	0.479 (Fischer's exact test)

SD: Standard deviation, ASA: American Society of Anesthesiologists

**Table 2: Incidence of CR, nausea, vomiting, and PONV during 0–<2 h: Values are expressed as n (%)**

Data	Group I n=42 (%)	Group II n=42 (%)	P value (between groups)
CR	28 (66.7)	36 (85.7)	0.040 (Fischer's exact test)
No CR	14 (33.3)	6 (14.3)	

PONV: Post-operative nausea and vomiting,  $P < 0.05$  statistically significant difference between the groups, CR: Complete response

**Table 3: Incidence of CR, nausea, vomiting, and PONV during 2–24 h: Values expressed as n (%)**

Data	Group I n=42 (%)	Group II n=42 (%)	P value (between groups)
CR	29 (69)	37 (88.1)	0.033 (Fischer's exact test)
CR	29 (69)	37 (88.1)	
No CR	13 (31)	5 (11.9)	

PONV: Post-operative nausea and vomiting,  $P < 0.05$  statistically significant difference between the groups, CR: Complete response

During 0–24 h, CR was observed in 85.7% of patients in Group II and 66.7% of patients in Group I, and the difference was statistically significant ( $P = 0.040$ ) [Graph 3 and Table 4]. During the time period of 24 h post-surgery and until discharge of patient, CR was observed in all the patients (100%) in Group II, whereas 41 patients (97.6%) showed CR in Group I with no significant difference between the groups. During the entire post-operative hours until discharge of patient, 36 patients (85.7%) showed CR in Group II as compared to 28 patients (66.7%) in Group I, and the difference was statistically significant ( $P = 0.040$ ).

Rescue antiemetic in the form of metoclopramide 10 mg was administered intravenously to patients who experienced moderate or severe nausea or vomiting or at patient request. During 0–2 h, 10 patients in Group I and two patients in Group II required rescue antiemetic therapy and the difference was significant ( $P = 0.026$ ). Between 2 and 24 h, higher numbers of patients in Group I (7) required rescue antiemetic than in Group II (3), and the difference was statistically insignificant [Graph 4]. Between 24 and 48 h, no patient required rescue antiemetic in either of the groups [Table 6].

## DISCUSSION

PONV is a common sequel of general anesthesia. Although PONV is almost always self-limiting and non-fatal, it can cause significant morbidity, including dehydration, electrolyte imbalance, suture tension and dehiscence, venous hypertension and bleeding, esophageal rupture, and life-threatening airway compromise. Each vomiting episode delays discharge from the recovery room by about 20 min.

Patients undergoing LC are at a particularly high risk for the development of PONV, and an incidence of 63–72% is reported when no prophylactic antiemetic is provided. The 5-HT<sub>3</sub> receptor antagonists are considered the first-line therapy because of their efficacy and safety. However, their absolute efficacy is disappointing and they have relatively short elimination half-life of < 12 h. Dexamethasone a corticosteroid has emerged as potentially useful prophylaxis for PONV when used as a single agent. Addition of dexamethasone as a part of multimodal approach to 5-HT<sub>3</sub> antagonists has been shown to decrease PONV symptoms compared with the use of 5-HT<sub>3</sub> antagonists alone after LC. Palonosetron, a second generation 5-HT<sub>3</sub> receptor antagonist, is an established antiemetic drug for CIN, and combination therapy using palonosetron and dexamethasone has been found to be safe and more effective than palonosetron alone.

In view of the promising results for combination of dexamethasone with palonosetron in CIN, in the present study, we have compared the efficacy of palonosetron with palonosetron and dexamethasone combination for the prevention of PONV in patients undergoing LC. 84 ASA I and II patients scheduled for LC were randomly divided into two groups. Group I patients received 0.075 mg palonosetron only and Group II patients received 0.075 mg palonosetron and dexamethasone 8 mg. In the present study, both the groups were well matched with respect to demographic data, baseline parameters, duration of anesthesia, surgery and CO<sub>2</sub> insufflations, and intraoperative hemodynamics.

Significantly more number of patients had CR in palonosetron-dexamethasone combination group (Group II) compared to only palonosetron group (Group I) between 0 and 24 h. Between 0 and 24 h, 85.7% of patients showed CR in Group II as compared to 66.7% in Group I ( $P = 0.040$ ). CR was observed in 97.6% of patients in Group I and 100% of patients in Group II between 24 h and discharge, with no significant difference between the groups. Significantly more number of patients required rescue antiemetic in Group I than Group II between 0 and 2 h period.

In the present study, 14 (33.3%) patients treated with 0.075 mg palonosetron (Group I) experienced nausea

**Table 4: Incidence of CR, nausea, vomiting, and PONV during 0–24 h: Values expressed as n (%)**

Data	Group I n=42 (%)	Group II n=42 (%)	P value (between groups)
CR	28 (66.7)	36 (85.7)	0.040
Number CR	14 (33.3)	6 (14.3)	

PONV: Post-operative nausea and vomiting,  $P < 0.05$  no statistically significant difference between the groups, CR: Complete response

**Table 5: Incidence of CR, nausea, vomiting, and PONV during 0 h–discharge: Values expressed as n (%)**

Data	Group I n=42 (%)	Group II n=42 (%)	P value (between groups)
CR	28 (66.7)	36 (85.7)	0.040
Nausea	14 (33.3)	6 (14.3)	

PONV: Post-operative nausea and vomiting,  $P < 0.05$  statistically significant difference between the groups, CR: Complete response

**Table 6: Requirement of rescue antiemetic. Values expressed as n (%)**

Time interval	Group I n=42 (%)	Group II n=42 (%)	P value (between groups)
0–2 h	10 (23.8)	2 (4.8)	0.026 (Fischer's exact test)
2–24 h	7 (16.7)	3 (7.1)	0.178
24 h–discharge	0	0	0

$P < 0.05$  statistically significant difference between groups in 0–2 h

during 0–24 h time interval. Kovac *et al.*<sup>[14]</sup> have also reported nausea in 50%. Of patients who had two or more risk factors for PONV and were pretreated with palonosetron 0.075 mg. In that study, 70% of patients in the placebo group experienced nausea between 0 and 24 h.

In the present study, 23.81% of patients in Group I experienced vomiting during 0–24 h and 0–48 h which is similar to that reported by Kovac *et al.*<sup>[14]</sup> between 0–24 h (40%) and 0–72 h (44%) and Candiotti *et al.*<sup>[15]</sup> (0–24 h - 33% and 0–72 h - 36%). None of the patients in the present study vomited between 24 h and till discharge, whereas Kovac *et al.*<sup>[14]</sup> and Candiotti *et al.*<sup>[15]</sup> reported emetic episodes in 4% and 9% of patients, respectively, between 24 and 72 h. The difference in the emetic episodes after 24 h between our studies and these two previous studies could be because of the use of opioids for post-operative analgesia in these studies. In our study, the patients did not receive post-operative opioids for analgesia.

In the present study between 0 and 24 h post-operative time interval, CR rate was 66.7% in patients who received palonosetron 0.075 mg. In the previous studies by Kovac *et al.*<sup>[14]</sup> and Candiotti *et al.*<sup>[15]</sup> the CR rate was 56% and 43% at 0–24 h time interval. For the 24–till discharge interval after surgery, the CR rate in our study was 97.6% which is similar to that reported by Bhattacharjee *et al.*<sup>[19]</sup> (90%) but higher than

that reported by Kovac *et al.*<sup>[14]</sup> (70%) and Candiotti *et al.*<sup>[15]</sup> (49%). The lower CR rates in these studies could be because of the patient population chosen that had two or more risk factors for PONV, use of opioids for post-operative pain and including day care patients by Candiotti *et al.*<sup>[15]</sup>

During the secondary time interval of 0–2 h, 2–24 h, and 0–till discharge, the CR rate in our study was 66.7%, 69%, and 66.7% in Group I which is consistent with that reported by Kovac *et al.*<sup>[14]</sup> between 0 and 6 h (61%), 6 and 72 h (56%), and 0 and 72 h (52%) but higher than that reported by Candiotti *et al.*<sup>[15]</sup> (0–6 h = 49%, 6–72 h = 45%, and 0–72 h = 39%). To the best of our knowledge, no previous study has been carried out to compare the efficacy of palonosetron versus a combination of dexamethasone and palonosetron for the prevention of PONV. However, combination of palonosetron-dexamethasone has been found to be better than palonosetron alone for CINV. Palonosetron 0.25 mg and dexamethasone 8 mg produced high early CR rates (84%) falling to 59% for late CINV.<sup>[18]</sup>

The incidence of vomiting was lower in Group II as compared to Group I between 0 and 2 h and 2 and 24 h, but results were not statistically significant. No patient in either of the groups vomited between 24 h and discharge. A CR rate was significantly higher in Group 2 at all-time intervals except during 24 h–till discharge when the CR rate was statistically insignificant.

In the present study, only 1 patient (2.4%) in Group I experienced mild nausea between 24 h and till discharge. During 24 h–till discharge, the incidence of CR was high in both groups (97.6% in Group I and 100% in Group 2). The higher CR rate in both the groups after 24 h in our study may be because of the longer acting drugs used. Palonosetron itself has a half-life of 36–40 h and dexamethasone is also found to be better for late PONV. Moreover, we avoided opioids for post-operative analgesia.

In the present study, significantly higher number of patients required rescue antiemetic in Group I as compared to Group II between 0 and 2 h. Between 2 and 24 h, the number of patients requiring rescue antiemetic was high in Group I when compared with Group II, but results were not statistically significant to conclude that Group II had less requirement of antiemetic. No patient required rescue antiemetic between 24 h and till discharge in both the groups. It is probable that the action of dexamethasone has not started by the time surgery was completed. Perhaps that may be the reason that requirement of rescue antiemetic was comparable between the groups during 0–2 h.

In the present study, all these factors were well balanced among the groups. Fentanyl was used in the dose of 2 µg/kg for all the patients. Patients with a history of



motion sickness or previous PONV and menstruating females were excluded from the study because they are considered high risk for PONV. Therefore, the difference in the rates of patients experiencing PONV among the groups can be attributed exclusively to the study drugs.

In the present study, palonosetron was used in the dose of 0.075 mg which has been found to be the minimum effective dose in various studies.<sup>[14,15]</sup> A wide dose range of dexamethasone has been used in the prophylaxis of PONV after various types of surgeries. The dose most often used is 8–10 mgs.<sup>[20-22]</sup> Therefore, dexamethasone 8 mg was administered for the prevention of PONV in our study.

The timing of prophylactic antiemetic administration is important. We administered the drugs at the beginning of the procedure. It is recommended that palonosetron should be administered 30 min before prophylaxis for CINV and immediately before induction of anesthesia for the prevention of PONV.<sup>[23]</sup> It has been confirmed recently that dexamethasone is more effective when given at the induction of anesthesia.<sup>[24]</sup> Therefore, we administered palonosetron and palonosetron dexamethasone combination before induction of anesthesia.

## CONCLUSION

The use of a combination therapy of palonosetron and dexamethasone than palonosetron alone for LC procedures has distinct advantage in the first 24 h. Hence, it is recommended to use a combination of palonosetron and dexamethasone. Whenever palonosetron is used it is necessary to follow-up the patient for a period of at least 36 h for side effect. The ideal time to use palonosetron to prevent PONV is at the time of induction. The use of palonosetron intraoperative reduces the need for rescue antiemetics in succeeding 24 h period, thereby providing a cost benefit to patients.

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# Study of Serum Calcium Level in Pre- and Postmenopausal Women of Jamshedpur, Jharkhand

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## Abstract

**Background:** Today, one of the most rapidly emerging global health problems in the postmenopausal women is osteoporosis. In postmenopausal women, two major causes of bone loss are estrogen deficiency and age-related process. The objective of this study was to evaluate calcium status in premenopausal and postmenopausal women.

**Materials and Methods:** This cross-sectional study was carried out in 42 premenopausal and 58 postmenopausal women at the Department of Physiology, M G M Medical College, Jamshedpur. Serum calcium level of each subject was determined.

**Results:** Mean serum calcium was significantly decreased in postmenopausal women compared to premenopausal women.

**Conclusion:** Serum calcium level was significantly deficient in postmenopausal women than in premenopausal women.

**Key words:** Osteoporosis, Postmenopausal, Serum calcium

## INTRODUCTION

Calcium ion is an essential structural component of the skeleton. There is growing evidence for the importance of nutrition in the maintenance of bones and joints health. Nutrition imbalance with endocrine abnormalities may be involved in osteoporosis.<sup>[1]</sup> Extracellular calcium ion concentration is determined by the interaction of calcium absorption from the intestine, renal excretion of calcium, and bone uptake and release of calcium, each of which is regulated by parathyroid hormone and Vitamin D and calcitonin.<sup>[2]</sup> Bone mineralization and rate of bone turnover are controlled by a number of hormones in the body. Parathyroid hormone causes bone resorption and helps to maintain blood calcium level. Estrogen exerts a major effect in women on bone remodeling by inhibiting interleukin-6 production that reduces bone resorption

and also controls the timing of osteoclast apoptosis. Estrogen deficiency, therefore, results in a longer life span of osteoclasts.<sup>[3]</sup> In female, at the age of 40–50 years, the monthly menstrual cycle becomes irregular, ovulation fails to occur during many cycles, and ultimately, there is cessation of the cycle which is called menopause. The female sex hormone diminishes to almost nil. In woman, the two major causes of bone loss are estrogens deficiency after menopause and age-related process.<sup>[4]</sup> Calcium is obtained from the diet through dairy as well as from non-dairy sources. The bioavailability of calcium from dairy sources is much higher than non-dairy sources. Several studies have reported that Indian diet does not meet the recommended dietary allowance of 600 mg/day of calcium for adult women, which has been recommended by Indian council of medical research.<sup>[5]</sup> Milk and milk product are expensive commoditize, and amount purchased by the lower socioeconomic classes are likely to be meager.<sup>[6]</sup> Further, unequal distribution of milk and milk product between male and female is another factor for worsening the situation. The difference in calcium intake between sexes is high in lower socioeconomic classes. Indian diets are predominantly vegetarian, and the contribution of dairy products to the overall calcium intake is minimal in the lower socioeconomic classes. Phytate and oxalate

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in fiber rich Indian diet also retard the absorption of calcium.<sup>[7,8]</sup>

Government supplementation program provides pregnant and lactating mother with 500 mg/day of calcium through a serving of 165 g of micronutrient of fortified food per day; however, there is no national program for supplementation of calcium for promotion of bone health.<sup>[9]</sup>

### Aim and Objective

This study was carried out to estimate calcium level in premenopausal and postmenopausal women to evaluate the need of calcium supplementations in the study population.

## MATERIALS AND METHODS

This cross-sectional study was conducted in women of age 40–75 years at the Department of Physiology, M.G.M Medical College, Jamshedpur, after permission from ethical committee. The period of study was July 2017–July 2018. Data source subjects were selected from the Outpatient Department of M.G.M Medical College and Hospital, Jamshedpur. Women having hypertension, diabetes mellitus, history of hormones replacement therapy, and fracture were excluded from the study. Informed consent from each subject was taken. 3–5 ml of venous blood was drawn aseptically from antecubital vein of each subject. The blood sample was collected clean plain labeled tube and transferred to laboratory for the estimation of calcium ion. Serum calcium was measured by colorimetry method using calcium (Arsenazo III) reagent.

## RESULTS

A total of 100 patients from obstetrics and gynaecology, medicine, and orthopaedic outpatient department were enrolled in the study. Of 100, 42 were premenopausal and 48 were postmenopausal women. Mean serum calcium was significantly decreased in postmenopausal compared to that premenopausal women. The graph also shows significant decrease in calcium level in postmenopausal as compared to premenopausal. Dietary intake of calcium was not good in 70% of the patient, because most of the patients are from low or middle socioeconomic group [Tables 1 and 2]. Comparison of serum calcium level in post and premenopausal women [Figure 1].

## DICUSSION

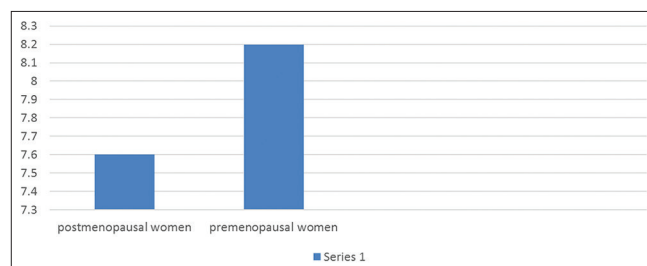
Calcium status was evaluated in premenopausal and postmenopausal women in the present study. Postmenopausal women had significantly lower serum calcium levels than in premenopausal women. Declining

**Table 1: Mean calcium level in patients based on age group**

Age group (year)	Number of patient	Mean calcium level (mg/dL)
40–45	24	8.3
46–50	18	8.2
51–55	20	8.1
56–60	12	8.1
61–65	11	7.5
66–70	10	7.5
71–75	05	7.1

**Table 2: Mean calcium level of both groups**

Patient group	Number of patient	Mean calcium level	S.D
Premenopausal	42	8.2±5.7	6.40
postmenopausal	58	7.6±7.1	6.85



**Figure 1: Serum calcium**

ovarian function before menopause is accompanied by the reduction in bone mass and altered calcium metabolism.<sup>[10]</sup> Estrogen deficiency may induce calcium loss due to decreased intestinal calcium absorption and decreased renal calcium conservation.<sup>[11]</sup>

The intake of calcium ions among our study participant assesses using a questionnaire was low as determined by Indian council of medical research, for postmenopausal women, with 74.5% of women having low dietary intake of calcium ion, this was in accordance with similar studies done in Tamil Nadu and Andhra Pradesh among different population group.<sup>[12]</sup>

Besides osteoporosis, studies have shown that low dietary calcium intake may be associated with hypertension that can be corrected with calcium supplementation.<sup>[13,14]</sup> The majority of women (70%) in our study as well as other study conducted in India had poor intake of calcium in their diet and are, therefore, at risk for these conditions. Although calcium supplementation in elderly postmenopausal women has proven benefits for bone density, there is no national program for supplementation of calcium for promotion of bone health.

Multiple studies have shown that poor dietary calcium intake along with low physical activity is the two major

risk determinant for osteoporosis and fracture.<sup>[15-17]</sup> In this study, 70% of postmenopausal women had both of these risk factors together. Health education on the importance of calcium intake in diet and knowledge on calcium-rich dietary sources would go a long way in improving the current scenario as those with poor knowledge, and low socioeconomic status was 4–5 time higher risk for consuming low calcium in their diet when compare to other.

## CONCLUSION

On the basis of the result of the present study, it is concluded that serum calcium level was significantly decreased in postmenopausal women than in premenopausal women. It can be recommended that calcium supplementation can be given as a prophylaxis to prevent the long-term bone loss and to decrease the risk of fracture and osteoporosis in postmenopausal.

Women health education regarding calcium-rich diet must be given to postmenopausal women, especially those from low socioeconomic status. However, further studies are needed to evaluate the levels of calcium in postmenopausal.

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# External versus Endoscopic Dacryocystorhinostomy for Acquired Nasolacrimal Duct Obstruction: A Comparative Study

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## Abstract

**Purpose:** The purpose of this study was to compare the success rates of endoscopic endonasal dacryocystorhinostomy (DCR) and external DCR in cases of acquired nasolacrimal duct obstruction.

**Design:** This was a prospective randomized clinical study.

**Methods:** A total of 58 consecutive patients were selected for DCR surgery. Among these, 30 patients underwent endonasal DCR and 28 patients underwent external DCR. Surgical success was defined by patients' resolution of symptoms along with a patent lacrimal drainage system. Failure was defined as a lack of symptomatic reduction in epiphora and/or inability to irrigate lacrimal drainage system post-operatively.

**Results:** Mean age of the patients was 38.64 years (34 ± 10.8 years). 81% of the study subjects were female and 19% were male. The success rate of endonasal DCR was 93.33% compared to a success rate of 92.85% in cases of external DCR ( $P = 0.898$ ). Complication rate was low in both the groups.

**Conclusion:** Endonasal DCR surgery is an attractive alternative to external DCR surgery with the advantages of a shorter operative time, lack of cosmetic scar, and equivalent success rate.

**Key words:** Endonasal dacryocystorhinostomy, External dacryocystorhinostomy, Nasolacrimal duct obstruction

## INTRODUCTION

Dacryocystorhinostomy (DCR) operation is the standard procedure to treat nasolacrimal duct obstruction. The surgery creates a lacrimal drainage pathway into the nasal cavity. Although external DCR is regarded as "gold standard,"<sup>[1]</sup> endoscopic DCR is rapidly evolving as an effective alternative. While external DCR involves a standardized technique, endonasal DCR can be carried out in several ways - with or without the endoscope, with the help of various types of instruments such as rongeur,<sup>[2]</sup>

drill,<sup>[3]</sup> chisel, and various types of lasers.<sup>[4]</sup> The purpose of our study was to compare the success rate of external DCR and endonasal DCR over a 6-month follow-up period.

## MATERIALS AND METHODS

In this prospective study, 58 eyes of 58 patients were randomized to external DCR and endonasal DCR. External DCR was done in 28 eyes, while 30 patients were subjected to endonasal DCR. Preoperatively, a detailed ophthalmic and ENT examination was done to rule out any other coexisting nasal pathology. Nasolacrimal duct obstruction was confirmed preoperatively by syringing. People with a history of past failed DCR, cases with suspicion of sac malignancy, canicular, or common canicular obstruction and those with bony deformity of lacrimal fossa (post-traumatic), were excluded from the study. In external DCR, the area around lacrimal sac was infiltrated with local anesthetic (2% xylocaine

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with 1:100,000 adrenaline). Following exposure, anterior and posterior flaps of lacrimal sac were sutured to the nasal mucosa. In endonasal DCR, nasal packing was done with a gauge soaked in 4% xylocaine with 1:100,000 adrenaline. A standard rigid endoscope was used to identify the anterior end of the middle turbinate. A rectangular mucosal flap (10 mm × 10 mm) was incised anterior and superior to the uncinate process. Then, a bony ostium was made over the lacrimal fossa using hammer and chisel. An opening was made in the lacrimal sac. The openings were packed with gelatin foam. Postoperatively, the patients were put on oral antibiotics and nonsteroidal anti-inflammatory drugs. All the patients were followed for a 6-month period - at 1<sup>st</sup> week, 2<sup>nd</sup> week, 3<sup>rd</sup> week, 6<sup>th</sup> week, 3<sup>rd</sup> month, and 6<sup>th</sup> month. Patency was tested during the follow-up visits by syringing.

## RESULTS

Of 58 patients, 11 (18.96%) were male and 47 (81.03%) were female [Table 1 and Figure 1]. In this prospective study, a total of 58 eyes of 58 patients were included in the study. 30 eyes underwent endoscopic DCR and 28 eyes underwent external DCR. Mean age of the patients was 38.64 years ( $34 \pm 10.8$  years). 81% of the study population was female and 19% was male. The right eye was found to be involved in 65% of the cases. Most of the patients presented with persistent watering, followed by mucopurulent regurgitation, mucocele, and lacrimal fistula [Table 2 and Figure 2].

Patient data were analyzed using independent samples *t*-test. At the end of 6-month follow-up period, 28 of

30 patients in the endonasal DCR group had a successful outcome (93.33%) compared to 26 of 22 patients in the external DCR group (92.85%). The difference was not statistically significant ( $P = 0.898$ ). The mean duration of endonasal DCR was 45 min ( $\pm 5.67$  min) compared to 75 min ( $\pm 7.76$  min) in cases of external DCR, which was statistically significant ( $P = 0.001$ ). Two of the patients of external DCR had post-operative bleeding from nose on the 1<sup>st</sup> post-operative day which resolved with nasal packing for 48 h. During the 6-month follow-up, one patient of external DCR group had hypertrophic scar and two had ostium closure [Table 3 and Figure 3a]. In the endonasal

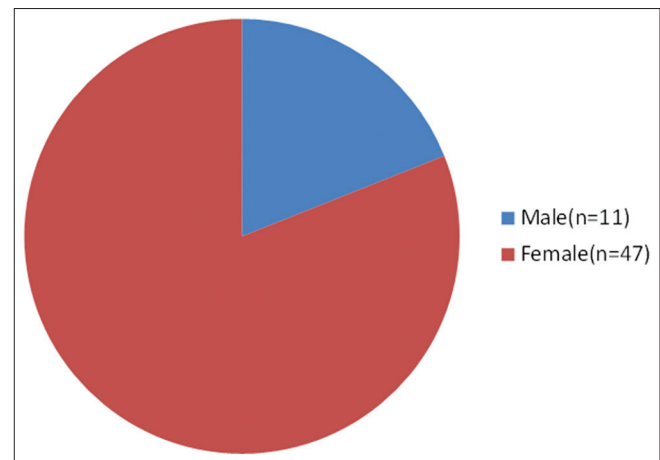


Figure 1: Sex distribution of the patients

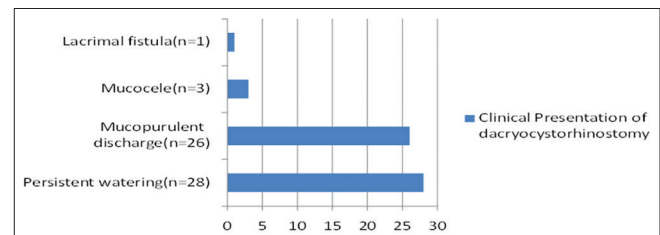


Figure 2: Clinical presentation of the patients suffering from dacryocystorhinostomy

Table 1: Sex distribution of the patient

Male	Female
11	47

Table 2: Clinical presentation of dacryocystorhinostomy

Persistent watering (%)	28 (48.28)
Mucopurulent discharge (%)	26 (44.23)
Mucocele (%)	3 (05.17)
Lacrimal fistula (%)	1 (1.72)

Table 3: Complication of external versus endonasal DCR

External DCR group (%)	
1. Ostium closure - 2 (7.14)	
2. Hypertrophic scar - 1 (3.57)	
Endonasal DCR group (%)	
1. Nasal synechia - 2 (6.67)	
2. Granulation of ostium - 2 (6.67)	

DCR: Dacryocystorhinostomy

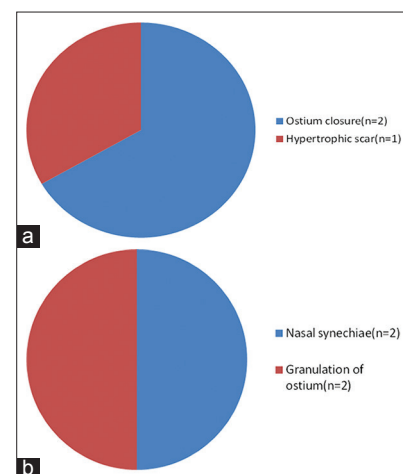


Figure 3: (a) Complication of external dacryocystorhinostomy (DCR). (b) Complication of endonasal DCR

DCR group, two patients had synechiae and two had granulation of the ostium [Table 3 and Figure 3b].

cutaneous scar provide better patient satisfaction making endonasal DCR an attractive alternative to external DCR.

## DISCUSSION

Several studies have compared external DCR with endonasal DCR showing variable success rate ranging from 63% to 97%.<sup>[5-10]</sup> Khan *et al.*<sup>[11]</sup> showed that success rate was 73.3% with endoscopic approach compared to 80% with external approach. Tsirbas *et al.*,<sup>[12]</sup> in his study, had compared external DCR to mechanical endonasal DCR during a follow-up period of around 1 year. Both had similar success rates (93.5% in mechanical endonasal DCR and 95.8% in external DCR.  $P = 0.06$ ). In our study, the mean duration of endonasal DCR was 45 min compared to 75 min in cases of external DCR. This was similar to the study by Hartikainen *et al.*<sup>[13]</sup> where the average duration of endonasal DCR and external DCR was 38 min and 78 min, respectively. Endoscopic DCR offers the advantage of the absence of skin incision, thus preserving the pump mechanism of orbicularis oculi muscle.<sup>[14]</sup> Besides, there is less of intraoperative bleeding. Furthermore, one can identify and/or treat any nasal or paranasal sinus pathology at the same time.<sup>[15]</sup> Patient satisfaction is better in endonasal DCR due to faster rehabilitation. However, the drawbacks include high cost of the instruments, steep learning curve for the surgeons, and inadequate exposure of the lacrimal system, especially in cases of suspected malignancy. External DCR, on the other hand, offers advantage of adequate exposure of the surgical area and ability to obtain lacrimal sac biopsy.

## CONCLUSION

Although external DCR is still considered the “gold standard,” endoscopic DCR is a rapidly evolving procedure with comparable success rates. Besides, the shorter operating time, less intraoperative bleeding, and lack of

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# A Clinical Profile and Diagnostic Management of First-time Seizures in Children Aged 1–12 Years - A Tertiary Hospital-based Study in Kerala

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## Abstract

**Background:** First-time seizures in children present a complex situation in the family that may have profound emotional, social, and vocational consequences. The seizures are unlikely to recur if the first seizure is provoked an acute disturbance of brain function (acute symptomatic or provoked); however, if it is unprovoked meta-analyses suggest that 30–50% will recur. Among the second unprovoked seizures, 70–80% will recur, justifying the diagnosis of epilepsy (a tendency for recurrent seizures). Seizures can be either generalized or focal. Types of seizures such as absence or complex partial seizures typically occur several times before the person or family become concerned.

**Aim of the Study:** The study aimed to study the prevalence and clinico-demographic profile of children with first-time seizures and its diagnosis in a tertiary care hospital of Kerala.

**Materials and Methods:** A thorough clinical history taking was done to include the information of age (from 1 year to 12 years), gender, type of seizure, loss of consciousness, with or without status epilepticus, associated symptoms (fever, headache, vomiting, and altered sensorium), developmental history, and family history of seizure or epilepsy. Preliminary investigations such as complete blood count, blood glucose, serum electrolytes, cerebrospinal fluid (CSF) analysis, Malaria parasite test, Chest X-ray, Montoux test, and neuroimaging including computed tomography scan head or cranial magnetic resonance imaging, electroencephalography (EEG), and other tests were undertaken depending the urgency, availability, and necessity being taken into account. Initial treatment given, recurrence of seizures, time taken for disappearance of total seizures, and status at the time of discharge were recorded and analyzed. Classification of seizures including generalized tonic-clonic (GTC), absence, myoclonic, focal, and other seizures types was based on the Commission on Epidemiology and Prognosis, 2010 International League against Epilepsy.

**Results and Observations:** A total of 218 children with first - time seizures included 112 (51.37%) children were male and 106 (48.62%) were females. The male to female ratio was 1.05:1. The overall mean age was  $5.28 \pm 1.18$  years. 94/218 (43.11%) children were of 1–4 years, 65/218 (29.81%) of 5–8 years, and 59 (27.06%) of 9–12 years. Loss of consciousness observed in 49/218 (22.47%) children, status epilepticus history among 27/218 (12.38%), associated symptoms in 86/218 (39.44%) children, and development history in 34/218 (15.59%) children, and family history of seizure or epilepsy in 55/218 (25.22%) children. Generalised convulsions in 118/218 children (54.12%) and focal seizures in 100/218 (45.87%) was observed. Among 218 children, 151 (69.26%) had GTC seizures, 46 (21.10%) had tonic seizures, 17 (07.79%) had myoclonic type, and 4 (01.83%) had other types.

**Conclusions:** First - time seizures in children have the reasons for physical, mental, and financial stress for the parents. Both the genders are equally affected. Generalized seizures were the far most common type of all seizures. Central nervous system infections, febrile convulsions, seizure disorders, head injuries, and space-occupying lesions were the main etiological factors in that order. Investigations to rule out metabolic diseases are equally important in the diagnosis. CSF analysis, neuroimaging, and EEG are accepted as investigative procedures by the parents for early diagnosis and remain essential. A continuation of the study is required to detect and follow-up children with recurrences.

**Key words:** Childhood fits, Epilepsy, Febrile seizures, Neuroimaging, Seizures, Status epilepticus

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## INTRODUCTION

Seizures are defined as a transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. Seizures are an important cause for hospital admissions in children from developing countries with increased prevalence

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in younger children.<sup>[1,2]</sup> Review of literature shows that 4–10% of children experience seizures before 16 years of age, whereas 1/5<sup>th</sup> of total children with unprovoked seizures may develop epilepsy.<sup>[3]</sup> Prevalence of epilepsy in Kerala according to a study shows a crude point prevalence ratio of 4.9 cases per 1000 people and an age-adjusted prevalence ratio of 4.7 cases per 1000 population.<sup>[4]</sup> The common causes of seizures in children are: Neonatal seizures (infections, birth asphyxia, and metabolic causes), febrile convulsions, meningitis, viral encephalitis, neurocysticercosis, cerebral malaria, and epilepsy (symptomatic, cryptogenic, and idiopathic).<sup>[5–10]</sup> Between 6 months and 5 years of age, febrile seizures account for 2–5% of all seizures in children experiencing the first episode. Infections remain the major cause of seizures in developing nations.<sup>[3,11]</sup> Epilepsy is defined by International League Against Epilepsy (ILAE; 1993) as a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause.<sup>[12]</sup> According to the World Health Organization, of the 50 million people with epilepsy worldwide, 80% reside in developing countries.<sup>[13]</sup> Epilepsy was estimated to account for 0.5% of the global burden of disease, accounting for 7,307,975 disability-adjusted life years in 2005.<sup>[14]</sup> Seizures account for about 1% of all emergency department visits, and about 2% of visits of children's hospital emergency department visits.<sup>[14]</sup> In most of the studies, febrile seizures were reported to be the most common type seen in the pediatric population and account for the majority of seizures seen in children younger than 5 years of age.<sup>[15,16]</sup> Central nervous system (CNS) infections are the main cause of seizures and acquired epilepsy in the developing world.<sup>[6,11]</sup> Classification of seizures, including generalized tonic-clonic (GTC), absence, myoclonic, focal, and other seizures types was based on the Commission on Epidemiology and Prognosis, 2010 ILAE.<sup>[17]</sup> According to the ILAE, status epilepticus is a single epileptic seizure which lasts >30 min or a series of epileptic seizures in which function is not retrieved between ictal events for >30 min.<sup>[18]</sup> ILAE in 1993 defined febrile seizure as an epileptic seizure which occurs in childhood postneonatal age, associated with fever not caused CNS infection, with no history of seizures during neonatal period or previous unprovoked seizure, and not fulfilling criteria for other acute symptomatic seizure. Furthermore, febrile seizures were divided into simple and complex febrile seizures. A simple febrile seizure occurs not >15 min and is generalized initially, and occurs 1 time during a 24-h interval. In contrast, a complex febrile seizure occurs for >15 min can has focal features at any time, or there is recurrence within a 24-h interval.<sup>[19]</sup> Etiologies of seizures such as meningitis and encephalitis were analyzed on the basis of clinical presentation and laboratory investigation and verified with a standard reference. Moreover, the cases

were classified into three age groups: 6 months–5 years, 6 months–10 years, and 11 months–18 years. Items such as age, sex, seizure type, related symptoms, family history of seizure or epilepsy, neurodevelopmental history, lab test results, neuroimaging findings, electroencephalography (EEG), hospital stay duration, medical diagnosis, and final outcome were analogized among children of different age groups. Analysis of data was made using descriptive statistics and hypothesis testing. Even though neuroimaging is not necessary for well-appearing children after a first, unprovoked nonfebrile seizure, it plays an important role in the etiological diagnosis of seizures neuroimaging helps in identifying the focal seizure or persistent seizure activity, focal neurologic deficit, neurocutaneous disorder, signs of elevated intracranial pressure, VP shunting, trauma, or traveling to cysticercosis endemic countries.<sup>[12–14]</sup> According to the ILAE, status epilepticus is a single epileptic seizure which lasts >30 min or a series of epileptic seizures in which function is not retrieved between ictal events for >30 min.<sup>[16]</sup> ILAE in 1993 defined febrile seizure as an epileptic seizure which occurs in childhood postneonatal age, associated with fever not caused by CNS infection, with no history of seizures during neonatal period or previous unprovoked seizures and not fulfilling criteria for other acute symptomatic seizure. Furthermore, febrile seizures were divided into simple and complex febrile seizures. A simple febrile seizure occurs not >15 min and is generalized initially, and occurs 1 time during a 24-h interval. In contrast, a complex febrile seizure occurs for >15 min can has focal features at any time, or there is recurrence within a 24-h interval.<sup>[17]</sup>

### Type of Study

This was a prospective, cross-sectional analytical study.

### Institute of Study

This study was conducted at Kannur Medical College Hospital, Anjarakandy, Kannur, Kerala, India.

### Period of Study

This study was from February 2016 to January 2018.

## MATERIALS AND METHODS

A prospective, clinical and demographic study of first - time seizures was conducted in a tertiary teaching hospital in Kerala including 218 consecutive children attending the department of paediatrics. An Ethical Committee Clearance was obtained from the Institutional Ethical Committee, and committee approved consent form was used for the study.

### Inclusion Criteria

1. Children of both genders above the age of 1 year and below 12 years were included.

- Children attending with first - time seizures alone were included.
- Children with a history of fever were included.
- Children with a history of head injury were included.
- Children with acute symptoms and signs of seizures with altered sensorium were included in the pediatric intensive care unit were included.

### Exclusion Criteria

- Children <1 year and >12 years were excluded.
- Children with the previous history of seizures or treatment of seizures were excluded.
- Children with severe head injuries requiring surgical interventions were excluded.
- Children with head injuries but associated with other body injuries were excluded.

A thorough clinical history taking was done to include the information of age (from 1 year to 12 years), gender, type of seizure, loss of consciousness, with or without status epilepticus, associated symptoms (fever, headache, vomiting, and altered sensorium), developmental history, and family history of seizure or epilepsy. Preliminary investigations such as complete blood count, blood glucose, serum electrolytes, cerebrospinal fluid (CSF) analysis, Malaria parasite test, Chest X-ray, Montoux test, and neuroimaging including computed tomography (CT) scan head or cranial magnetic resonance imaging (MRI), EEG, and other tests were undertaken depending the urgency, availability, and necessity being taken into account. Classification of seizures, including GTC, absence, myoclonic, focal, and other seizures types was based on the Commission on Epidemiology and Prognosis, 2010 ILAE.<sup>[19]</sup> Etiologies of seizures such as meningitis and encephalitis were analyzed on the basis of clinical presentation and laboratory investigation and verified with standard reference. The children were classified into three age groups: 1 year–4 years, 5–8 years, and 9–12 years. Items such as age, sex, seizure type, related symptoms, family history of seizure or epilepsy, neurodevelopmental history, lab test results, neuroimaging findings, EEG, hospital stay duration, medical diagnosis, and final outcome were analogized among children of different age groups. Analysis of data was made using descriptive statistics and hypothesis testing. The Chi-square test and Fisher test were used to examine the association between different variables and strength of the relationship.  $P < 0.05$  was considered as statistically significant.

## RESULTS AND OBSERVATIONS

A total of 218 consecutive children attending the department of paediatrics with first - time seizures with different causes were included in this study. Among

them, 112 (51.37%) children were male and 106 (48.62%) were females. The male to female ratio was 1.05:1. The overall mean age was  $5.28 \pm 1.18$  years; in males, the mean was  $5.76 \pm 1.52$  and  $5.13 \pm 1.47$  in females. The youngest child was 1 year 1 month old, and the eldest child was 12 years old. 94/218 (43.11%) children belonged to the age group of 1–4 years, 65/218 (29.81%) belonged to the age group of 5–8 years, and 59 (27.06%) belonged to the age group of 9–12 years [Table 1].

Generalized convulsions were observed in 118/218 children (54.12%) and focal seizures in 100/218 (45.87%). Among 218 children, 151 (69.26%) had GTC seizures (GTCS), 46 (21.10%) had tonic seizures, 17 (7.79%) had myoclonic type, and 4 (1.83%) had other types [Table 2].

Clinical history of children in this study showed loss of consciousness in 49/218 (22.47%) children, status epilepticus history in the family among 27/218 (12.38%) children, associated symptoms in 86/218 (39.44%) children, and development history in 34/218 (15.59%) children, and family history of seizure or epilepsy in 55/218 (25.22%) children. Their distribution among the gender was tabulated in Table 3.

Preliminary laboratory investigations showed abnormal complete blood counts in 61/218 (27.98%) children, abnormal blood glucose levels in 30/218 (13.76%) children, abnormal serum electrolytes values in 44/218 (20.18%) children, abnormal CSF analysis results in 138/218 (63.30%) children, positive Malaria parasite test in 59/218 (27.06%) children, abnormal Chest X-ray was seen in 91/218 (41.74%) children, positive Montoux test in 46/218 (21.10%) children, abnormal neuroimaging including CT scan head, or cranial MRI was seen in 111/218 (50.91%) children. Abnormal neuroradiology findings were gliosis in 46 - (21.10%), dysmyelination in

**Table 1: Age incidence (n - 218)**

Age groups	Male - 112 (%)	Female - 106 (%)	Percentage
1–4 years - 94	48 (22.01)	46 (21.10)	43.11
5–8 years - 65	34 (15.59)	31 (14.22)	29.81
9–12 years - 59	30 (13.76)	29 (13.30)	27.06

**Table 2: Type of seizures (n - 218)**

Type of seizures (%)	Male - 112 (%)	Female - 106 (%)	Percentage
Generalized - 118 (54.12)	67 (30.73)	52 (23.85)	54.12
Focal - 100 (45.87)	46 (21.10)	54 (24.77)	45.87
GTCS - 151 (69.26)	78 (35.77)	73 (33.48)	69.26
Tonic - 46 (21.10)	22 (10.09)	24 (11.00)	21.10
Myoclonic - 17 - (7.79)	8 (3.66)	9 (4.12)	7.79
Others - 4 - (1.83)	3 (0.137)	1 (0.45)	1.83

GTCS: Generalized tonic-clonic seizures

**Table 3: The history of seizures in the study (n - 218)**

History details	Male - 112	Female - 106	Percentage
Loss of consciousness - 49	27	22	22.47
Status epilepticus - 27	16	11	12.38
Associated symptoms (fever, headache, vomiting, and altered sensorium) - 86	45	41	39.44
Developmental history - 34	16	18	15.59
Family history of seizure or epilepsy - 55	30	25	25.22

22 - (10.09%), hemorrhage in 20 (9.17%), brain atrophy in 8 - (3.66%), dysgenesis in 6 - (2.75%), infarction in 5 - (2.29%), and encephalomalacia in 4 (1.83%) children, abnormal EEG in 67/218 (30.73%) children [Table 4]. The abnormal recordings in EEG noted in this study were temporal shortwave discharges in 34 (15.59%), centrotemporal spikes in 19 (8.71%), occipital spikes/spike-waves in 17 (7.78%), generalized slowing in 17 (7.78%), focal slowing in 9 - (4.12%), frontal sharp wave discharge in 5 (2.29%), central epileptic discharge in 4 (1.83%), and generalized high spikes in 2 (0.91%) children [Table 4].

The diagnosis in the present study was based on the investigation, clinical symptomatology, and history from the parents. It was observed that CNS infections were diagnosed in 58/218 (26.60%) of the children, febrile convulsions were observed in 45/218 (20.64%) of the children, seizure disorder in 35/218 (16.05%), head injuries in 27/218 (12.38%), space-occupying lesions of the brain were noted in 25 (11.46%) of the children, metabolic disorders such as diabetes mellitus was seen 18/218 (8.25%) children, and hypertensive encephalopathy in 12/218 (4.58%). Their incidences in different age groups and gender-wise distribution were tabulated in Table 5. CNS infections were the most common etiology observed in 58/218 (26.60%) children; 32/218 (14.67%) in males and 26/218 (11.92%) in females; 27/218 (12.38%) in 1–4 years group, 19/218 (8.71%) in 5–8 years group, and 12/218 (5.50%) in 9–12 years group. Febrile convulsions were seen in 45 (20.64%) of the children; 24/218 (11.00%) male children and 22/218 (10.09%) female children; among these 24/218 (11.00%) in 1–4 years age group, 13/218 (5.96%) in 5–8 years group, and 8/218 (3.66%) in 9–12 years age group. Seizure disorders were observed in 35/218 (16.05%) children; males were 17/218 (7.79%) and females were 18/218 (8.25%). Among these, 14/218 (6.42%) were in 1–4 years group, 9/218 (4.12%) were in 5–8 years group, and 12/218 (5.50%) were in 9–12 years group. Head injuries were seen in 27/218 (12.38%) children; 13/218 (5.96%) male and 14/218 (6.42%) female children. Among these, 11/218 (5.04%) were in 1–4 years group, 8/218 (3.66%) were in 5–8 years group, and 8/218 (3.66%) were in 9–12 years group. Space-occupying lesions were observed in

25/218 (11.46%) children; males were 12/218 (5.50%) and females were 13/218 (5.96%). Among these, 9/218 (4.12%) were in 1–4 years group, 12/218 (5.50%) were in 5–8 years group, and 8/218 (3.66%) were in 9–12 years group. Metabolic disorders were observed in 18/218 (8.25%) children; males were 9/218 (4.12%) and females were 9/218 (4.12%). Among these, 7/218 (3.21%) were in 1–4 years group, 4/218 (1.83%) were in 5–8 years group, and 7/218 (3.21%) were in 9–12 years group. Hypertensive encephalopathy was observed in 10/218 (4.58%) children; males were 6/218 (2.75%) and females were 4/218 (1.83%). Among these, 2/218 (0.91%) were in 1–4 years group, 4/218 (1.83%) were in 5–8 years group, and 4/218 (1.83%) were in 9–12 years group [Table 5].

Among the CNS infections (58/112) in this study, there were 19/218 (7.33%) children with Viral Infections (encephalitis), 17/218 (7.79%) with Pyogenic meningitis, 14/218 (6.40%) with tuberculosis meningitis, and 8/218 (3.66%) with cerebral malaria. Children with febrile convulsions with pyrexia of unknown origin were 45/218 (20.64%). Among the head injury children, extradural hematoma was 13/218 (5.96%), subdural hematoma was 7/218 (3.21%), and transient concussion was 7/218 (3.21%). Among the seizure disorders idiopathic were 21/218 (9.63%), cerebral palsy were 07/218 (3.21%), Sturge-Weber syndrome were 2/218 (0.91%), tuberous sclerosis were 2/218 (0.91%), dravet syndrome, infantile spasm, vein of galen malformation, Rasmussen's encephalitis, and others were one each (0.45%). Among the space-occupying lesions, inflammatory granuloma was seen in 11/218 (5.04%), gliomas in 9/218 (4.12%), and meningioma in 5/218 (2.29%) children. Metabolic disorders included diabetes mellitus 7/218 (3.21%), 5 (2.29%) were with hyponatremia, 3 (2.29%) were hypocalcemia, and 3 (2.29%) with acute liver failure were 3/218 (1.37%) each. There were 10 children with hypertensive encephalopathy - 10/218 (4.58%); among them, hypertensive crisis was in 5 (2.29%) and antihypertensive withdrawal in 5 (2.29%) [Table 6].

## DISCUSSION

In the present tertiary hospital - based study, 218 consecutive children with first - time seizures were either admitted directly to the pediatric ICU or OPD were included depending on their symptoms. There were 112 males and



**Table 4: Abnormal laboratory investigation (n - 218)**

Lab investigations	Male - 112	Female - 106	Percentage
Complete blood counts - 61/218 - (27.98%)			
Neutropenia - 22	12	10	10.09
Lymphocytosis - 39	22	17	17.88
Blood glucose levels - 30/218 - (13.76%)			
Hypoglycemia - 21	12	9	9.63
Hyperglycemia - 9	5	4	4.12
Serum electrolytes - 44/150 - (20.18%)			
Hypernatremia - 11 - (%)	6	5	5.04
Hypokalemia - 19 - (8.71%) hyponatremia - 14 - (%)	7 (8)	12 (6)	8.71 (6.42)
CSF analysis - 138/218 - (63.30%)			
White blood cells - 31 - (14.22%)	20	11	14.22
RBCs - 17 - (7.79%)	10	7	7.79
Low chloride levels - 15 - (6.88%)	9	6	6.88
Bacteria positive - 63 - (28.89%) high proteins - 55 - (25.22%)	39 (35)	24 (20)	28.89 (25.22)
Malaria parasite test - 166/218 - (76.14%)			
Positive - 59 - (27.06%)	38	21	27.06
Negative - 107 - (49.08%)	77	30	49.08
Montoux test - 175/218 - (80.27%)			
Positive - 46 - (21.10%)	24	22	21.10
Negative - 129 - (59.17%)	67	62	59.17
Chest X-ray - 91/218 - (41.74%)			
Pneumonitis - 20 - (09.17%)	13	7	9.17
Pleural effusion - 12 - (5.50%)	8	4	5.50
Consolidation - 10 - (4.58%)	5	5	4.58
Kohn's focus - 31 - (14.22%)	19	12	14.22
Emphysema - 18 - (8.25%)	8	10	8.25
Neuroimaging - 111/218 - (50.91%)			
Gliosis - 46 - (21.10%)	25	21	21.10
Dysmyelination - 22 - (10.09%)	11	11	10.09
Hemorrhage - 20 - (09.17%)	9	11	9.17
Atrophy - 08 - (03.66%)	5	3	3.66
Dysgenesis - 06 - (2.75%)	3	3	2.75
Infarction - 05 - (2.29%)	2	3	2.29
Encephalomalacia - 4 (1.83%)	2	2	1.83
EEG - 107/218 - (49.08%)			
Temporal short wave discharges - 34 - (15.59%)	24	10	15.59
Centrotemporal spikes - 19 - (08.71%)	12	7	8.71
Occipital spikes/spike - waves - 17 - (7.78%)	8	9	7.79
Generalized slowing - 17 - (7.78%)	12	5	7.79
Focal slowing - 9 - (4.12%)	4	5	4.12
Frontal sharp wave discharge - 05 - (02.29%)	3	2	2.29
Central epileptic discharge - 4 - (1.83%)	2	2	1.83
Generalized high spikes - 2 (0.91%)	1	1	0.91

**Table 5: The incidence of different etiologies of seizures in the study (n - 218)**

Etiology	Male - 112	Female - 106	1-4 years	5-8 years	9-12 years
Central nervous system infections - 58/218 (26.60%)	32	26	27	19	12
Febrile convulsions - 45/218 (20.64%)	23	22	24	13	08
Seizure disorder - 35/218 (16.05%)	17	18	14	9	12
Head injuries - 27/218 (12.84%)	13	14	11	8	8
Space occupying lesions - 25/218 (12.38%)	12	13	9	8	8
Metabolic disorders - 18/218 (08.25%)	9	9	7	4	7
Hypertensive encephalopathy - 10/218 (5.50%)	6	4	2	4	4

106 females with a ratio of 1.05:1 which reflects a higher national female population ratio in Kerala. Worldwide literature showed a ratio of 1.35:1.<sup>[19,20]</sup> The overall mean age was  $5.28 \pm 1.18$  years, 94/218 (43.11%) children belonged to the age group of 1-4 years, 65/218 (29.81%) belonged to the age group of 5-8 years, and 59 (27.06%)

belonged to the age group of 9-12 years. The incidence of first - time seizures was more common before 4 years in this study. The incidence of seizures was found decreasing with the increasing age of children. This may be due to more susceptibility and high incidence of febrile seizures as well these children are more prone to CNS infections and

**Table 6: The final diagnosis in the study group (n - 218)**

Etiology	Final diagnosis	Male	Female
Central nervous system infections - 58/218 (26.60%)	Viral Infections (encephalitis) - 19	10	9
	Pyogenic meningitis - 17	9	8
	Tuberculous meningitis - 14	7	7
	Cerebral malaria - 8	4	4
Febrile convulsions - 45/218 (20.64%)	PUO - 45	24	21
Head injuries - 27/218 (12.38%)	Extradural Hematoma - 13	7	6
	Subdural hematoma - 7	4	3
	Transient concussion - 7	3	4
	Idiopathic - 21	12	9
Seizure disorder - 35/218 (16.05%)	Cerebral palsy - 7	3	4
	Sturge-Weber syndrome - 2	2	0
	Tuberous sclerosis - 2	1	1
	Drave syndrome - 1	0	1
	Infantile spasm - 1	0	1
	Vein of Galen malformation - 1	1	0
	Rasmussen's encephalitis - 1	0	1
	Others - 1	1	0
	Inflammatory granuloma - 11	6	5
	Glioma - 9	5	4
Metabolic disorders - 18/218 (8.25%)	Meningioma - 5	3	2
	Diabetes Mellitus - 7	4	3
	Hyponatremia - 5	3	2
	Hypocalcemia - 3	1	2
	Acute liver failure - 3	2	1
Hypertensive encephalopathy - 10/218 (5.50%)	Hypertensive crisis - 5	2	3
	Antihypertensive withdrawal - 5		2

PUO: Pyrexia of unknown origin

metabolic derangements.<sup>[19,21]</sup> Generalized convulsions were observed in 118/218 children (54.12%) and focal seizures in 100/218 (45.87%). Among 218 children 151 (69.26%) had GTCS, 46 (21.10%) had tonic seizures, 17 (7.79%) had myoclonic type, and 4 (1.83%) had other types [Table 2]. These findings were similar to other studies.<sup>[19,20,22]</sup> Children without seizures were reported in a few studies<sup>[11]</sup> which were higher. In the present study, there was no child without seizures as the sample was from admitted patients with first - time seizures. 27% of children in this study presented with status epilepticus. Certain studies showed an incidence of 10.9% and 7.3%.<sup>[23]</sup> Of status epilepticus which was low compared to our study which could be explained by the fact that in this study the CNS infections accounted for 58/218 (26.60%) of the study sample. The incidence of recurrence of seizures was negligible 10/218 (04.58%) in this study compared to other studies which recorded recurrence especially among the children with inflammatory granuloma with 18.23% or withdrawal (20%) seizures.<sup>[6]</sup> Some studies reported 19% of patients with recurrence (most were epilepsy followed by febrile seizures), while others reported higher recurrence (29–44%) with increasing age.<sup>[24]</sup> Etiological analysis of the showed CNS infections to be the most common cause of first - time seizure, followed by seizure disorders, head injury, and SOL and metabolic causes; least being hypertensive encephalopathy. In a study by Hirtz *et al.*<sup>[22]</sup> febrile seizures were most common cause followed by trauma, seizure disorder, and CNS infections.

Among CNS infections, the most common cause of seizures in this study was viral encephalitis followed by pyogenic meningitis, tuberculosis meningitis, and cerebral malaria. Cerebral malaria was common in countries of tropical nature as evidenced by certain study.<sup>[25]</sup> 8.25% of the children had metabolic disturbances producing first - time seizures in this study. Similar studies by Huang *et al.*<sup>[9]</sup> reported 11% of cases with metabolic etiology for seizures only 3 years of age. Chen *et al.*<sup>[19]</sup> reported that only 3/319 as a metabolic etiology for seizures suggesting investigations to find the metabolic cause of seizures was unnecessary. However, the incidence of hypoglycemia, hypocalcemia, and hyponatremia is commonly encountered in a tropical country like India. Hence, the metabolic investigations should be undertaken. Neuroimaging studies were done in all the patients in this study, and 111/218 (50.91%) imaging studies showed abnormal reports. Gaillard *et al.* quoted in their study that not all MRI abnormalities cause seizures and not all seizures originate from identified structural cerebral abnormalities.<sup>[26]</sup> They also opined that it is necessary to establish with clinical and neurophysiologic data whether a given lesion is likely to cause the seizures. In the research field, MRI allows us to better understand the pathophysiology of epilepsy.<sup>[27]</sup> Mishra *et al.* observed from their study. In the present study, neuroradiology was useful in diagnosis in first - time seizures in children in nearly 50% of the sample. MRI investigation will detect most common lesions causing neocortical epilepsy,

which are: Low-grade tumors, malformations of cortical development, post-traumatic and post-ischemic lesions, inflammatory infectious scars, cavernous malformations, and arteriovenous malformations.<sup>[28]</sup> In patients with malformations of cortical development multimodal imaging techniques can be useful for localizing suspected lesions. Among the multimodal imaging, interictal fluorodeoxyglucose positron emission tomography (PET), ictal single-photon emission CT (SPECT), ictal/interictal subtraction of SPECT scans, PET/MRI coregistration, multiplanar reconstruction, and curvilinear reformatting represent non-invasive methods to evaluate patients with focal seizures.<sup>[27]</sup> Review of EEG abnormalities in the present study showed that most of the abnormalities were in the form of focal discharges confined to a specific brain lobe in 55/107 (70.09%) children. Focal slowing was reported in 20/107 (18.69%) children, whereas generalized non-specific slowing was observed in 19/107 (17.75%) children. These results are similar to the study by McHugh and Delanty<sup>[29]</sup> and Seneviratne *et al.*<sup>[30]</sup> Among these, there were classical centrotemporal spikes suggestive of benign epilepsy of childhood with centrotemporal spikes.

## CONCLUSION

First - time seizures in children have the reasons of physical, mental, and financial stress for the parents. Both the genders are equally affected. Generalized seizures were the far most common type of all seizures. CNS infections, febrile convulsions, seizure disorders, head injuries, and space-occupying lesions were the main etiological factors in that order. Investigations to rule out metabolic diseases are equally important in the diagnosis. CSF analysis, neuroimaging, and EEG are accepted as investigative procedures by the parents for early diagnosis and remains essential. A continuation of the study is required to detect and follow-up children with recurrences.

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# Conjunctival Autotransplant in Pterygium Excision Using a Novel Technique: A Follow-up Study of 100 Cases

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## Abstract

The study was conducted in District Hospital Baramulla from January 1, 2015, to December 31, 2016. It was a post-operative interventional study. In this study, 100 eyes of 100 patients with primary nasal pterygium were operated, 65 males and 35 females. Simple excision under local anesthesia was performed followed by closure of bare sclera by sutureless and glue-free conjunctival autograft with adhesion enforced by mild cautery application between free edges. Follow-up period was 6 months. Recurrence occurred in 1 patient (1%), other complications include conjunctival chemosis in 11 (11%) patients, partial graft displacement in 2 (2%) patients, graft retraction from nasal side 3 (3%) patients, total graft displacement in 1 (1%) patient, overriding of graft on cornea (2%) patients, and granuloma in donor site in 1 (1%) patient.

**Key words:** Complications, Conjunctival autograft, Glue free, Pterygium, Recurrence, Suture free

## DEFINITION

Pterygium is a common ocular surface lesion originating in the limbal conjunctiva within the palpebral fissure with progressive involvement of the cornea. The lesion occurs more frequently at the nasal limbus than the temporal with a characteristic wing-like appearance.

## ETIOLOGY

The etiology is unknown. An increased incidence is noted in latitudes nearer the equator and individuals with a history of increased UV exposure.

Risk factors include UV radiation, dry climate, and outdoor lifestyle.

## PATHOPHYSIOLOGY

The pathophysiology of pterygium is characterized by elastotic degeneration of collagen and fibrovascular proliferation with an overlying covering of epithelium. Histopathology of the abnormal collagen in the area of elastotic degeneration shows basophilia with hematoxylin and eosin stain. Destruction of Bowman's layer by fibrovascular growth is typical.

## CURRENT MANAGEMENT TECHNIQUES

The main problems with pterygium surgery are the problems with post-operative recurrence and scarring.

In the bare scleral technique, an exposed area of sclera is left. However, the recurrence rate is very high ranging from 30% to 80%. To reduce recurrence rate, antimetabolites like mitomycin-C have been used intraoperatively and postoperatively. However, mitomycin C is associated with serious complications like scleral thinning with uveal tissue show through. Others include photophobia, secondary glaucoma, sudden onset mature cataracts, corneal melt, iridocyclitis, symblepharon formation, and punctal occlusion.

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Conjunctival autograft remains the gold standard for the treatment of pterygium. These techniques involve the use of sutures or fibrin glue<sup>[1-5]</sup> and are vulnerable to associated complications.

The use of sutures<sup>[2,4-6]</sup> may lead to local complication such as discomfort, scarring, or infection. Fibrin glue<sup>[7-9]</sup> may produce possible hypersensitivity reactions, whereas the risk of viral transmission remains.

We have evolved techniques which are sutureless and glue free.<sup>[6,9-12]</sup>

## SURGICAL TECHNIQUE

Peribulbar anesthesia was given with 2% lignocaine. Body of pterygium was dissected 4 mm from limbus in two layers. Superficial layer included only conjunctiva and deep layer of Tenon's capsule included immediate subjacent and adjacent Tenon's capsule. Pterygium was removed from cornea by avulsion.

Remnants on cornea were scrapped by crescent blade and sclera bed was also cleared of remnants by scraping of bed by crescent blade. Hemorrhages were controlled by direct compression. The defect was measured by Castroviejo caliper in mm.

An oversized graft by 1 mm was taken from superior 12 O'clock position. Saline was injected by 26 G needle and a thin graft<sup>[13]</sup> was fashioned between conjunctiva and Tenon's capsule. Care was taken to include as little Tenon's capsule as possible. The graft was dissected anteriorly to include stem cells in limbus and graft was resected with conjunctival scissors. The graft was placed on bare scleral and positioned so as to maintain the limbus-limbus orientation with epithelial surface up. The edge of the graft and free conjunctival margin (left after excision of pterygium) is apposed with toothed forceps at multiple spots. Moreover, adhesion is enforced by applying mild bipolar cautery at multiple spots. The graft is apposed to scleral bed for a period of 8–10 min and eye is bandaged for 24 h.

The patient was followed on the 1<sup>st</sup> day, 3<sup>rd</sup> day, 1 week, 2 weeks, 3 weeks, 6 weeks, 3 months, and 6 months<sup>[14]</sup> postoperatively. Patients were put on antibiotic steroid (moxifloxacin-dexamethasone) eye drop and lubricant eye drops (1% carboxymethyl cellulose) postoperatively 4 times daily initially, then antibiotic-steroid eye drops were tapered over a period of 4 weeks.

**Table 1: Post operative complications**

1	Hemorrhage subconjunctival/subgraft	9
2	Conjunctival chemosis	11
3	Partial graft displacement	02
4	Graft retraction (from nasal side)	03
5	Total graft displacement	01
6	Overriding of graft on cornea	02
7	Granuloma in donor site	01
8	Graft recurrence <sup>[15]</sup>	01
Total		20 cases

## RESULTS

The study included 100 eyes of 100 patients with primary nasal pterygium only. It was a prospective interventional study, 100 eyes of 100 patients with primary nasal pterygium were included in the study. Of 100 eyes, 60 were left and 40 were right. There were 65 males and 35 females. The following complications took place [Table 1].

The total number of complications exceeds total number of cases as more than one complication was noticed in some cases.

Two cases of partial graft displacement were again taken to theater and episcleral bleeding was induced by 26 G needle and graft was stabilized in position again by blood<sup>[16,17]</sup> only and waiting time of 8–10 min was observed. The graft stayed and procedure was successful.

Two cases of overriding of graft on cornea were taken to theater and excess graft was trimmed off postoperatively. The patient behaved nicely.

In 1 case of granuloma at donor conjunctival site, patient was taken to theater and granuloma was excised.

It was concluded that glue-free and suture-free conjunctival autotransplantation is a cheap technique with excellent results.

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# Pleural Effusion - Video-assisted Thoracoscopic Surgery - Two-Port Technique: Our Experience

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## Abstract

**Introduction:** Video-assisted thoracoscopic surgery (VATS) is a minimally invasive procedure employed as a diagnostic and therapeutic procedure in diseases of the pleura and lung.

**Materials and Methods:** A total of 15 patients who presented with pleural effusion, after a trial of intercostal drainage, underwent VATS.

**Results:** Histopathological examination of tissue in five cases showed granulomatous inflammation, one showed poorly differentiated malignancy, and remaining nine showed empyema with inflammatory pathology. None of the cases required conversion to open surgery. The average period of intercostal drainage tube was 8.4 days, postoperatively. There were no complications such as bronchopleural fistula or hemorrhage.

**Conclusion:** VATS is an effective diagnostic as well as therapeutic tool in cases of pleural effusion, with an acceptable complication profile. The two-port technique modification yields the results comparable to the three-port technique.

**Key words:** Pleural effusion, Vats, Two ports

## INTRODUCTION

### Pleural Effusion

Many benign and malignant pleural space diseases can cause effusion. The amount of pleural fluid is controlled by a balance of oncotic and hydrostatic pressure within the pleural space.

### Empyema

It is the infection of the pleural space, commonly an exudate. It progresses from an auto phase with fluid that is thin and can be drained completely with a chest tube, typically worsening as the fluid becomes turbid and thick and begins to loculate. This debris can compress lung parenchyma.

### Tuberculous Pleuritis

The pleural space is the second most common site of extrapulmonary tuberculosis,<sup>[1]</sup> the first being the lymphatic system. Positive diagnosis relies on direct sampling of pleural fluid and pleural biopsies.

Analysis of fluid will show exudative, lymphocyte predominant picture. Other studies such as ADA (non-specific and non-sensitive) and AFB are not reliable. The most reliable investigation being pleural biopsy.

## MATERIALS AND METHODS

This was a retrospective observational study conducted in General Surgery Department, Unit III of St. Martha's Hospital, Bengaluru, from August 2015 to August 2016. The medical records of the 15 patients, age ranging from 15 to 44, were reviewed to conduct this study [Table 1].

The patients have undergone pre-operative evaluation of pleural effusion in the form of chest radiograph posteroanterior view, ultrasound chest, or computed

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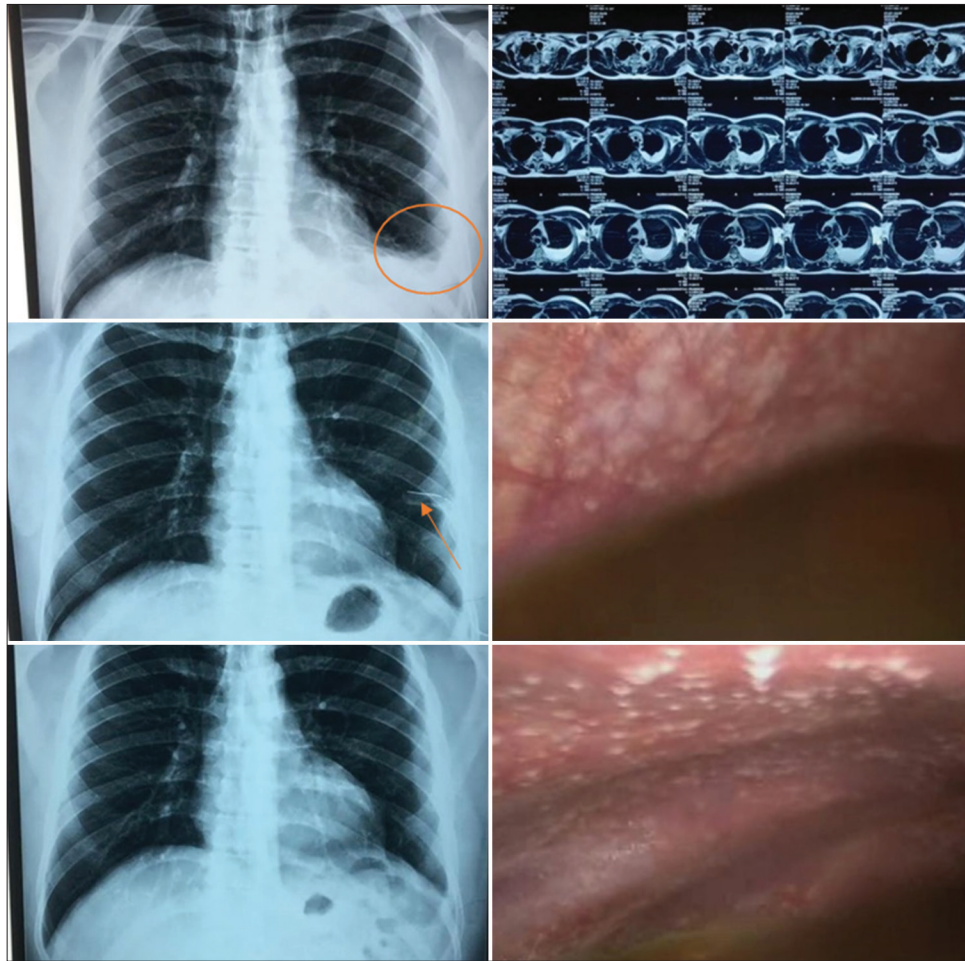
**Table 1: Summary**

Patient, Fluid and Surgery Details	Results
Mean age	33.7 years
Male/Female	15/0
Presenting complaints (%)	
Pleuritic chest pain	7 (46.67)
Fever+cough	6 (40)
Breathlessness	1 (6.7)
Pleural fluid characteristics	
C/S positive	1
Mean lymphocyte %	47
Mean total count	6895/mm <sup>3</sup>
Malignant cytology positive	1
Operative results (%)	
Mean operative time	1.7 h
Conversion	0
Post-operative ventilatory support	0
Post-operative mean ICU stay (%)	1 day
Chest tube duration	8.7 days
Air leak	0
Peri-operative mortality	0

tomography thorax. Thoracocentesis and fluid analysis were done in all the cases which included total and differential leukocyte count, adenosine deaminase, malignant cytology, acid-fast bacilli, and culture + sensitivity. Routine blood investigations done were hemoglobin, total leukocyte count, differential count, erythrocyte sedimentation rate, and renal function test in all patients.

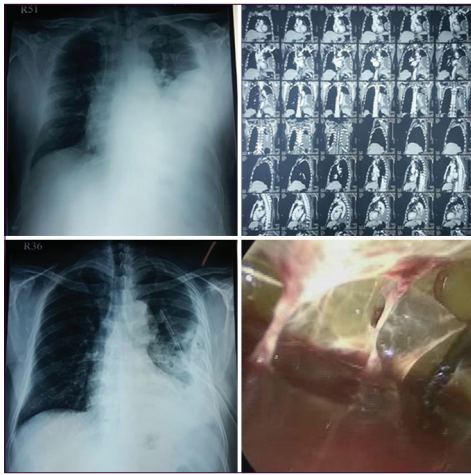
### Video-assisted Thoracoscopic Surgery (VATS)

General anesthesia with selective one-lung ventilation and with double lumen endotracheal tube was employed in all cases. The first port was placed in the previous implantable cardioverter-defibrillator (ICD) site, 5 mm 30-degree scope used. Two-port technique was employed in all the cases, and the second port was placed according to the findings, under vision. After port placement, fluid was collected for analysis, the loculations broken, decortication done if required, and tissue was sampled for biopsy.



**Figure 1: (a-f) Anti-clockwise from top left - (1) Pre-operative chest X-rays (CXR) (blunting of costophrenic angle indicated by circle) posteroanterior (2). Post-operative day 1 CXR (ICD indicated by arrow) (3). POD 14 CXR (4). Pre-operative computed tomography thorax (5 and 6). Intraoperative findings - Nodular lesions on the parietal pleura with effusion 33-year-old male, left-sided pleuritic chest pain**





**Figure 2: (a-d) Anti-clockwise from top left - (1) Pre-operative chest X-rays (CXR) posteroanterior (2). Post-operative day 1 CXR (3). Pre-operative computed tomography Thorax (4). Intraoperative findings - Thick loculations and empyema 67-year-old male, cough, fever, and breathlessness**

Frozen section was done for one case to rule out malignancy - came as granulomatous lesion and was started on ATT. The effusion was evacuated, chest tube placed, and port closed.

All patients were observed in SICU post-operatively, chest X-rays was done on post-operative day 1 for all patients [Figure 1]. 12 patients were discharged with ICD *in situ*. Follow-up period was a minimum of 2 years. Treatment of the underlying cause was initiated once holoprosencephaly (HPE)/fluid analysis helped us arrive at a diagnosis.

## RESULTS

15 patients with pleural effusion who underwent VATS were included in the study, and all patients were males ranging in the age range from 15 to 44, with a mean age of 33. The most common presentations were pleuritic chest pain (46%) on the affected side and fever associated with cough (40%). 53% of the patients were smokers. All the patients underwent thoracentesis and fluid analysis.

All samples had elevated TC, mean TC being 6895/mm<sup>3</sup>, and lymphocyte predominant picture was seen in all patients, with mean percentage being 47%. Pleural fluid cultures yielded no growth in all except one in which the sample yielded *Burkholderia* species and was treated as per sensitivity pattern. The fluid was sent for gene Xpert study which yielded negative in all but one, which showed indeterminate result. Fluid study for malignant cytology was positive in one patient, the HPE was in agreement with it, the patient was diagnosed to have poorly differentiated malignancy, and the patient was further managed by our

oncology team. In view of advanced malignancy, the patient was treated by chemotherapy.

The patients underwent adequate pre-operative evaluation, and the procedure was on an elective basis. The mean operative time was 1.7 h, ranging from 45 min to 3 h. All the patients were shifted out from OT after extubation in a stable condition with ICD *in situ* and were observed in SICU for 1 day [Figure 2]. Incentive spirometry and chest physiotherapy started from POD1, and 12 cases were discharged within 6 days post-operative with ICD *in situ*. The remaining three patient's chest tubes were removed before discharge. Mean duration of ICD was 8.4 days.

The histopathology study revealed empyema with inflammatory etiology in 9 cases, granulomatous inflammation in 5, and poorly differentiated malignancy in 1. Follow-up data showed that all patients had a resolution of symptoms, and none of them underwent resurgery. None of the cases had complications such as sepsis or bronchopleural fistulae.

## DISCUSSION

The human body contains two non-communicating pleural spaces in contrast to other mammals such as horses, which have extensive communications between the right and the left thoracic spaces, effectively rendering them with a single pleural cavity. The anatomy in humans allows for selective one-lung ventilation, affording ample room in the pleural cavity for instrument maneuvering, making it ideal for minimal access surgery.<sup>[2]</sup>

Thoracoscopy was first introduced by Jacobeous, a Swedish internist, in 1910, as a diagnostic procedure for exudative pleuritis, and published his case series in 1921, describing its value in TB and malignant pleural effusions.<sup>[3]</sup>

Around 1990, instruments such as endoscopic stapler and biopsy forceps were introduced, and this has helped to broaden the vistas of thoracic surgery. Thoracoscopy can be diagnostic as well as therapeutic, and pleural effusion being the most common indication. The common indications for thoracoscopic surgery are pleural effusion, infiltrates, pneumothorax, pleural mass/thickening, mediastinal mass, and empyema.<sup>[4]</sup>

## CONCLUSION

VATS is an effective diagnostic as well as therapeutic tool in cases of pleural effusion, with an acceptable complication profile.<sup>[5,6]</sup> The two-port technique modification yields the results comparable to the three-port technique.<sup>[7]</sup>

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# Pathological Spectrum of Gastrointestinal Stromal Tumors - A 1.5-year Experience at Kidwai Cancer Institute

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## Abstract

**Introduction:** Gastrointestinal stromal tumors (GISTs) have an incidence of 10–15 per million per year worldwide. Majority of GISTs are located in the stomach (55.6%) followed by small bowel (31.8%). Some GISTs may be found outside the GIT, and they are referred to as extra-GISTs (EGISTs). The frequency of EGISTs is <1%. Cases of EGISTs have been reported in the retroperitoneum, mesentery, and omentum. GISTs are immunohistochemically positive for KIT (CD117), phenotypically paralleling Cajal cell differentiation and most examples contain KIT or PDGFRA activating mutations.

**Materials and Methods:** A total of 37 cases of spindle cell neoplasm, suspected of GIST and 15 cases of other mesenchymal tumors of the GIT were studied. IHC panel of markers included KIT, DOG1, CD34, SMA, S-100, Desmin, CK, and a proliferation marker Ki67 performed on tumor blocks (Formalin fixed paraffin embedded tissue). KIT-negative cases were subjected to next-generation sequencing.

**Results:** Gastrointestinal stromal tumor was the most common mesenchymal tumor of GIT with stomach being the most common site of involvement and the mean tumor size was 10.7 cms. Metastatic disease was present in 16.2% of cases while recurrences of GISTs were seen in 13.5% of cases. Combination of KIT and DOG1 highly improved the sensitivity of identifying cases of GIST. Of 3 cases which were KIT-negative by IHC, 2 cases showed mutational analysis consistent with GIST, and the other case was negative for both KIT and PDGFRA. Additional IHC for this case showed WT1 and D240 positivity and was diagnosed with malignant mesothelioma.

**Key words:** DOG1, Gastrointestinal stromal tumor, GIST, Immunohistochemical markers, KIT, Mutations in GIST, PDGFRA, Prognosis

## INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors arising in the gastrointestinal tract. Most GISTs were thought to be of smooth muscle origin but have now been found to be distinctive entities based on morphological, immunohistochemical, and ultrastructural studies.<sup>[1]</sup> GISTs are thought to arise

from interstitial cells of Cajal both of which show KIT positivity.<sup>[2]</sup>

According to most studies, GISTs have an incidence of 10–15 per million per year with a median age of presentation in the mid-60s with equal sex distribution. GISTs commonly involve the stomach followed by the small intestine. Other sites of involvement include colorectum, rarely esophagus, and appendix.<sup>[3]</sup> GISTs can also be found in the omentum, mesentery, or the retroperitoneum and are referred to as extra-gastrointestinal tract tumors (EGISTs).<sup>[4]</sup>

The pathogenesis of sporadic GISTs is thought to be driven by Gain-of-function mutations in the genes encoding tyrosine kinase receptors KIT and PDGFRA, both of which are located on chromosome 4q.<sup>[5]</sup> Rarely,

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GISTs can show loss of succinate dehydrogenase expression. They typically lack KIT or PDGFRA mutations, and the majority of them are seen in pediatric age group, and some may be part of Carney's triad.<sup>[6]</sup> GISTs have also been discovered in patients with neurofibromatosis type 1.<sup>[4]</sup>

Morphologically, GISTs are composed of spindle cells in the majority of the cases, epithelioid cells in few cases and rarely a mixed morphology. Immunohistochemically majority of GISTs show KIT positivity with a minority of cases being KIT-negative. Other markers which could be positive include CD34, SMA, and rarely S100 but are mostly negative for desmin.<sup>[7]</sup> Discovered on GIST 1 (DOG1) is a recently discovered sensitive marker for GISTs which also stains a subset of KIT-negative cases.<sup>[8,9]</sup> Mitotic rate and tumor size have been found to be of predictive value in the behavior of GISTs. These parameters have been used to stratify GISTs into low, intermediate, and high-risk categories to predict the clinical behavior of these tumors.<sup>[10]</sup> The treatment of GISTs includes surgery and imatinib therapy. Imatinib is a selective inhibitor of tyrosine kinase receptors especially KIT and PDGFRA which is especially useful in advanced GISTs and high-risk GISTs.<sup>[11]</sup>

## MATERIALS AND METHODS

This hospital-based study was conducted at Kidwai Cancer Institute, Bengaluru. This prospective study included patients diagnosed with GISTs in our institute as well as those cases referred from other hospitals over a period of 1½ years from January 2016 to June 2017. The study protocol was approved by the Institutional Review Board and the Ethical Committee.

### Informed Consent

Patients who voluntarily registered at the hospital were taken for the study for which a panel of immunohistochemical markers, which are done on a routine basis to confirm a diagnosis of GIST, were performed. Informed consent was taken from the patients selected for next-generation sequencing (NGS). Both immunohistochemistry (IHC) and NGS were performed on formalin-fixed paraffin-embedded (FFPE) tissue blocks from the material sent by the clinician for diagnostic purpose.

### Patient Selection

This study was conducted on patients with pathologically confirmed GISTs in the Department of Pathology, Kidwai Cancer Institute, Bengaluru, over a period of 1½ years from January 2016 to June 2017. Furthermore, other stromal tumors of the gastrointestinal tract other than GISTs were studied for comparison.

### Clinical Data

Patient's clinical details including age, gender, site of involvement, and treatment history were collected from medical records of the patients.

### Sample Collection

FFPE tissue blocks including cell blocks made from the material (which included biopsies, resection specimens, and FNA material) sent by the clinician and FFPE tissue blocks received from other institutions were collected, and H and E, as well as IHC slides, were prepared from the same.

### Inclusion Criteria

1. Patients with pathologically confirmed GIST whose paraffin-embedded tissue blocks were available at Kidwai Cancer Institute, Bengaluru.
2. KIT-negative GISTs which were diagnosed on morphology.
3. Patients with other mesenchymal tumors other than GISTs arising from the gastrointestinal tract, retroperitoneum and presenting as intra-abdominal masses, including tumors of myogenic, neurogenic, and fibroblastic origin were studied for comparison.

### Exclusion Criteria

1. Patients with GISTs whose paraffin-embedded tissue blocks were unavailable at Kidwai Cancer Institute, Bengaluru.
2. Patients with other mesenchymal tumors other than GISTs arising from the gastrointestinal tract, retroperitoneum and presenting as intra-abdominal masses whose paraffin-embedded tissue blocks were unavailable at Kidwai Cancer Institute, Bengaluru.
3. Biopsies which lacked adequate material to perform IHC were excluded from the study.

### IHC (n = 52)

A one-step polymer-horseradish peroxidase detection system was used.

### Procedure

Tissue sectioned (3 µ) on poly-L-Lysine slides was deparaffinized, treated with an antigen retrieval solution, blocked with a peroxidase 2% skimmed milk blocking solution and then incubated with the primary antibody. The primary antibody binds to the antigen of interest. This was followed by incubation with the secondary antibody conjugated with horseradish peroxidase polymer and color development using 3,3'-diaminobenzidine substrate. When adequate color development was seen, the slides were washed in water to stop the reaction, counterstained with hematoxylin and covered with a mounting medium.

### Next-generation Sequencing (n = 3)

The cases which were C-kit-negative and DOG1-positive were analyzed for mutational status using NGS to look



for KIT and PDGFRA mutations or any other mutations present.

Genomic DNA was extracted from 10 µm sections obtained from the FFPE blocks. QIA amp DNA FFPE Tissue Kit was used for DNA extraction. Quantitation and QC of extracted DNA were carried out using Nanodrop, Bioanalyzer/Tapestation.

### Procedure

Illumina sequencing by synthesis (SBS) chemistry was used for our cases, and it included 4 basic steps:

1. **Library Preparation:** Libraries were prepared using 250 ng of the genomic DNA. The TruSeq Amplicon Cancer Panel Kit paired with the TruSeq Amplicon Cancer Panel (212 DNA-specific amplicon covering hotspots in 48 genes) was used to construct the libraries. The sequencing library was prepared by random fragmentation of the DNA sample, followed by 5' and 3' adapter ligation. Adapter-ligated fragments were then PCR amplified and gel purified.
2. **Cluster generation:** For cluster generation, the library was loaded into a flow cell where fragments were captured on a lawn of surface-bound oligonucleotides complementary to the library adapters. Each fragment was then amplified into distinct, clonal clusters through bridge amplification.
3. **Sequencing:** Illumina SBS technology utilizes a proprietary reversible terminator-based method that detects single bases as they are incorporated into DNA template strands.
4. **Data analysis:** During data analysis and alignment, the newly identified sequence reads were then aligned to a reference genome.

### Statistical Analysis

The collected data were subjected to statistical analysis using SPSS version 21 and STATA version 13 software. Frequency tables were generated on the parameters studied. Sensitivity and specificity of KIT and DOG1 were calculated based on receiver operating characteristic curve, and Chi-square test was used to correlate Ki67 with the risk of metastasis.

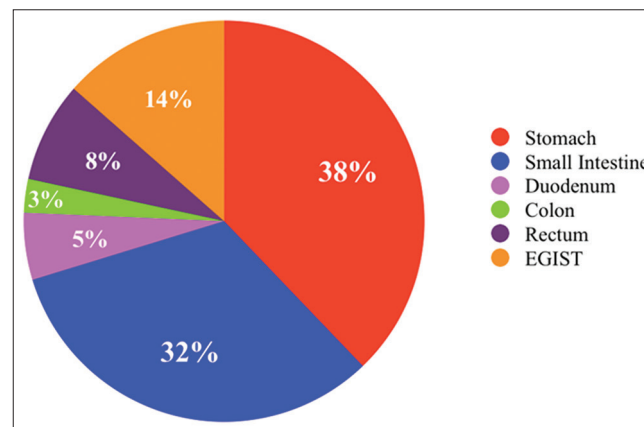
## RESULTS

There were 39 cases of mesenchymal tumors of the GIT after excluding tumors from sites outside the GIT such as retroperitoneum and omentum. Of these cases, there were 32 cases of GISTs (82%), 3 cases of leiomyosarcomas (8%), 2 cases of leiomyoma (5%), 1 case of schwannoma (3%), and 1 case of solitary fibrous tumor (3%).

Of 37 cases of GIST (including EGIST), there were 22 males and 15 females with a male to female ratio equal to 1.5. The age of presentation of GIST ranged from 22 to 72 years with a mean of 52.8 years. The mean age for males was 53.6 years while the mean age for females was 51.6 years in this study. No case of pediatric GIST was encountered in this study. The most common presenting symptom of GIST was pain abdomen which was seen in 17 cases (46%) followed by mass per abdomen in 5 cases (14%). There were 14 cases of GISTs involving the stomach (38%) followed by 12 cases in the small intestine (32%) [Figure 1]. Other sites of involvement included 2 duodenal GISTs, 1 colonic GIST, and 3 rectal GISTs. There were 5 cases of EGISTs which included retroperitoneal, omental, and pelvic GISTs. The size of GISTs ranged from 1.5 to 29 cm with a mean of 10.7 cm. The size distribution of GISTs was as follows - 1 case with size <2 cm (3%), 3 cases with size 2–5 cm (8%), 16 cases with size 5–10 cm (43%), and 17 cases with size >10 cm (46%) [Figure 2]. Of the 37 cases of GISTs, 28 cases had a spindle cell morphology (76%), 6 cases had an epithelioid morphology (16%), and 3 cases had a mixed spindle and epithelioid morphology (8%) [Figures 3-5]. Necrosis was seen in 9 cases (24%) of GIST, all cases had spindle cell morphology, and 77.8% of cases belonged to the high-risk category.

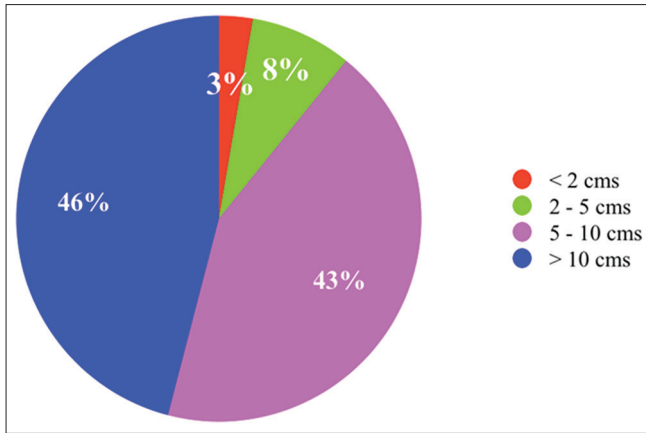
### Expression of Kit and Dog1 in GISTs

In this study, kit was positive in 91.9% of cases, and DOG1 was also positive in 91.9 % of cases [Figures 6 and 7]. Of 37 cases of GIST, 32 cases showed both KIT and DOG1 positivity (82%), 2 cases showed only KIT positivity (8%), 2 cases showed only DOG1 positivity (8%), and 1 case was both kit- and DOG1-negative (3%) [Figure 8]. Both kit and DOG1 when used together identified 36 of 37 cases of GIST (97.3%). IHC for CD34 was available in 30 cases of GISTs, and 18 cases were positive (60%).

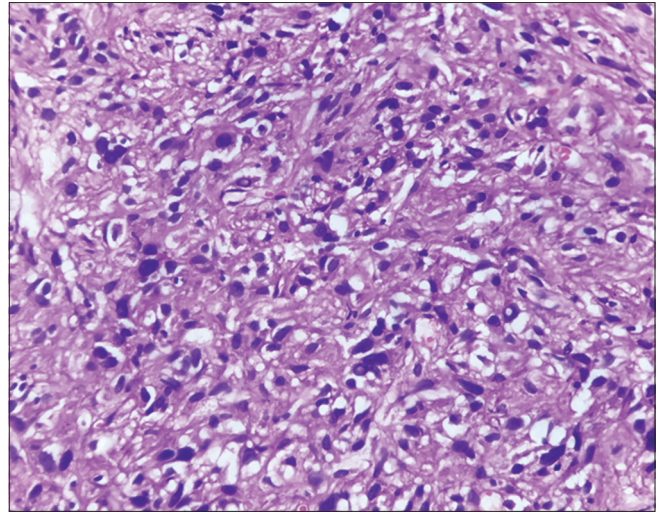


**Figure 1: Distribution of gastrointestinal stromal tumors cases by site**

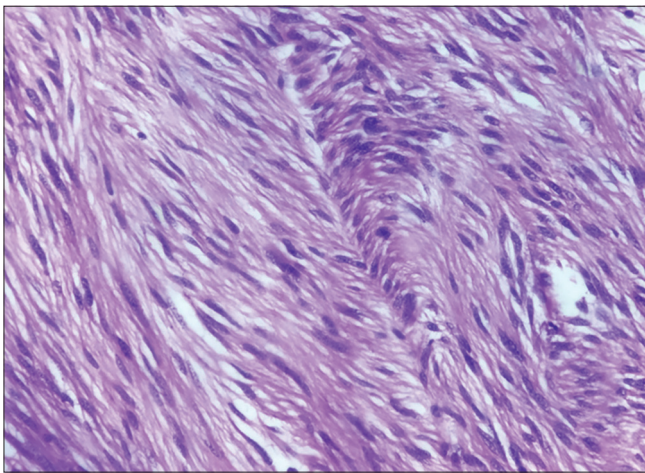




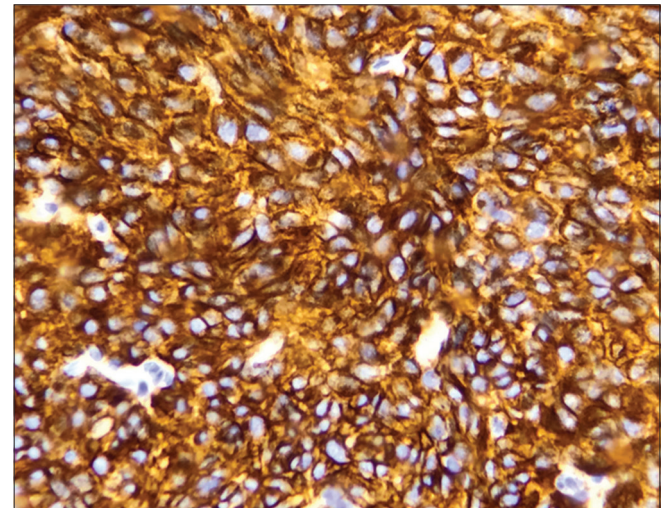
**Figure 2: Distribution of gastrointestinal stromal tumors cases by size**



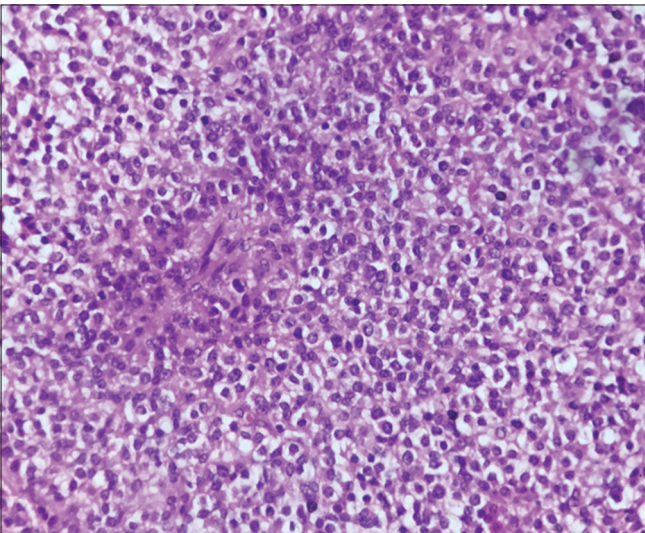
**Figure 5: Gastrointestinal stromal tumors with mixed epithelioid and spindle cell morphology, H and E (x40)**



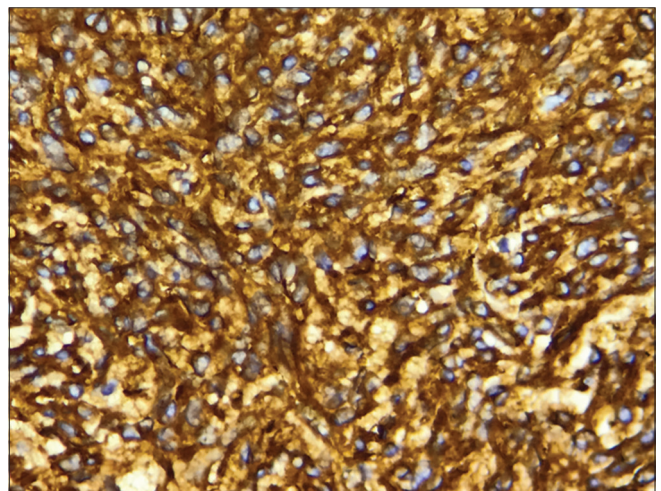
**Figure 3: Gastrointestinal stromal tumors showing spindle cell morphology with nuclear palisading, H and E (x40)**



**Figure 6: KIT IHC - diffuse, strong cytoplasmic, and membranous staining (x40)**



**Figure 4: Epithelioid morphology of gastrointestinal stromal tumors showing vacuolated cytoplasm, H and E (x40)**



**Figure 7: DOG1 IHC - diffuse, strong membranous, and cytoplasmic staining (x40)**

IHC for SMA was available in 30 cases of GISTs and 21 cases were positive (70%). IHC for S100 was available

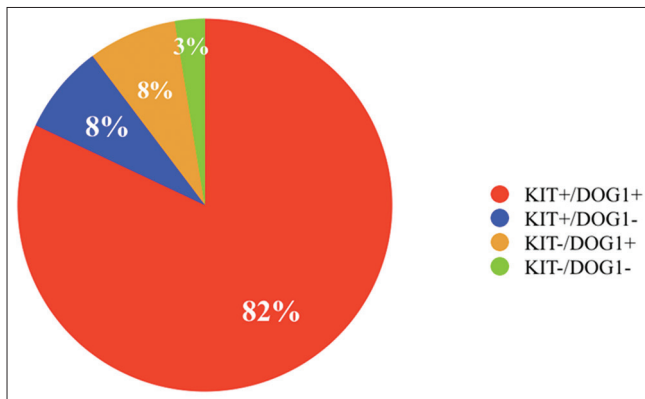


in 27 cases of GISTs, and 1 case was positive (3.7%). IHC for desmin was available in 25 cases of GISTs and 2 cases were positive (8%).

### Mutational Analysis by NGS

There were 3 cases which were KIT-negative and DOG1-positive on IHC with CD34, SMA, S100, and desmin being negative. Mutational analysis was done for these 3 cases of which 2 showed mutations consistent with GIST. The remaining one case was negative for both KIT and PDGFRA and was diagnosed with biphasic malignant mesothelioma after additional IHC markers such as WT1 and D2-40 showed positivity. One case of KIT IHC negative GIST, involving the stomach had KIT point mutations involving exon 17. Other mutations present included NRAS, IDH1, and TP53. The other case involving the retroperitoneum harbored PDGFRA point mutations involving exon 18. Other mutations present included NRAS [Table 1].

Treatment details were available only for 14 of the 37 cases of GIST. 5 cases underwent only surgical resection (36%), 3 cases received only imatinib therapy (21%), 5 cases had both surgical resection and imatinib therapy (36%), and one case did not receive any treatment. One of the 3 cases which received only imatinib therapy showed resistance to imatinib and was started on sunitinib.



**Figure 8: KIT and DOG1 immunophenotypes in gastrointestinal stromal tumors**

### Prognosis

Of the 37 cases, there were 32 cases of primary GISTs of which 6 cases presented with metastatic disease. Remaining 5 cases were recurrent GISTs. Statistical analysis showed an association between epithelioid and mixed morphology and a high rate of recurrence and metastatic disease [Table 2]. Fletcher's criteria were used to prognosticate risk of metastasis in 31 cases of GISTs without metastasis [Table 3].<sup>[10]</sup> There were 26 cases (83.9%) in the high-risk category, and 5 cases (16.1%) were in the intermediate risk category. There were no cases in the low and very low-risk categories. Site wise prognostication for risk of metastasis was used to categorize GISTs of different sites into 8 groups (1, 2, 3a, 3b, 4, 5, 6a, and 6b) [Table 4].<sup>[12]</sup> In this study, all GISTs were encompassed in one of four categories, which were the groups 3a, 3b, 6a, and 6b. There were no cases in the remaining categories. After site wise categorization of the cases 83% gastric GISTs, 67% of small intestinal GISTs, and 100% each of duodenal, and rectal GISTs were in the high-risk group while 17% of gastric GISTs and 33% of small intestinal GISTs were in the medium risk group. There were no cases in the low-risk group. The Ki67 index ranged from 3 to 45%. We found an association between Fletcher's prognostic criteria and Ki67 index for risk of metastasis when the cutoff for Ki67 was taken at 8% [Table 5].

### DISCUSSION

GISTs are the most common mesenchymal tumors of the gastrointestinal tract. The discovery of KIT mutations in GISTs and the available targeted therapy, the tyrosine kinase inhibitor imatinib, has necessitated the need for an accurate diagnosis of GISTs. In this study, 82% of true mesenchymal tumors of the GIT were GISTs followed by leiomyosarcoma and leiomyoma. Rarely, cases of schwannoma and solitary fibrous tumor were diagnosed. This was comparable with other studies by Yamaguchi *et al.*<sup>[13]</sup> and Patnayak *et al.*<sup>[14]</sup> The mean age of presentation in this study was 52.8 years with females presenting at a

**Table 1: Mutational analysis of KIT-negative cases**

Case details	Age (years)	Sex	Morphology	IHC findings	Mutational analysis by NGS	Diagnosis
Retroperitoneal tumor	60	M	Epithelioid	DOG1+KIT - SMA- Desmin - S100-	PDGFRA (p.D842V) NRAS	GIST
Stomach tumor with lung metastasis	35	M	Spindle	DOG1+KIT - SMA- Desmin - S100-	KIT (p.V821A, p.V822A, p.V825A, p.V826A) NRAS (p.Q61K)	GIST
Peritoneal tumor	66	M	Epithelioid	DOG1+WT1+D2-40+KIT - SMA- Desmin - S100-	IDH1 TP53 KIT and PDGFRA negative	MALIGNANT MESOTHELIOMA

slightly earlier age than males. This was comparable with Indian data obtained from studies by Patnayak *et al.*,<sup>[14]</sup> Ravikumar *et al.*,<sup>[15]</sup> and Lakshmaiah *et al.*<sup>[16]</sup> whereas global data had a higher median age of presentation of around 60 years.<sup>[3]</sup> A slight male predominance was observed in this study with a male to female ratio of 1.5:1 which was comparable with other Indian studies by Patnayak *et al.*<sup>[14]</sup> and Rajappa *et al.*<sup>[17]</sup> Global data showed equal distribution between males and females.<sup>[3]</sup>

GISTs have a varied clinical presentation with pain abdomen, GI bleeding, intestinal obstruction, and mass per abdomen being the most common symptoms encountered in both Indian studies and global studies.<sup>[3,15-17]</sup> Pain abdomen followed by mass per abdomen was the most common symptoms encountered in this study. Patients presented with localized GIST in 26 cases (70.3%), metastatic GIST in 6 cases (16.2%), and recurrent GIST in 5 cases (13.5%). This was similar to studies by Sharma.<sup>[18]</sup> A study by Bhargami *et al.*<sup>[19]</sup> had a higher incidence of presentation with metastatic GIST. The sites of metastasis

in this study included liver, omentum, abdominal wall, and lung. Sites of recurrence included abdominal wall, lower abdominal cavity, and a rare case of spermatic cord recurrence in a treated case of small intestinal GIST. Stomach was the most common site of involvement followed by small intestine in this study which was similar to other Indian and global studies.<sup>[3,14,15,17]</sup> Tumor size varied from 1.5 to 29 cm with a mean size of 10.7 cm. Majority of GISTs had a size of more than 10 cm (46%). This was similar to data obtained from both Indian studies and global epidemiological data.<sup>[3,14,15,17]</sup> Spindle cell pattern was the most common histological pattern observed in this study and was present in 28 cases (76%) which was in concordance with studies by Vij *et al.*,<sup>[20]</sup> Kim *et al.*,<sup>[21]</sup> and Lakshmi *et al.*<sup>[22]</sup> Epithelioid pattern was observed in 6 cases (16%) and mixed epithelioid and spindle cell pattern was observed in 3 cases (8%) which in comparison to other studies showed slightly more cases of epithelioid morphology than mixed morphology.<sup>[20-22]</sup> Epithelioid morphology was more commonly seen in EGISTs and small intestinal GISTs accounting for 2 cases each. This study showed that epithelioid and mixed morphology have a higher rate of recurrence and metastatic disease than spindle cell morphology. Secondary changes such as necrosis, hyalinization, and calcification were also noted in GISTs. Necrosis was noted in 9 cases (24%) out of which 7 cases (77.8%) belonged to high-risk category, similar to a study by Kim *et al.*<sup>[21]</sup> IHC is a highly sensitive tool in the diagnosis of GISTs. KIT and recently DOG1 have primarily emerged as diagnostic markers of GIST. KIT positivity on IHC varied from focal-to-diffuse and weak-to-strong cytoplasmic and membranous positivity. In this study, KIT showed a sensitivity of 91.9% and a specificity of 100% [Table 6]. Few studies have shown a slightly higher rate of positivity for KIT while one Indian study has shown a lower positivity rate for KIT [Table 7]. DOG1 positivity on IHC varied from focal to diffuse and weak to strong cytoplasmic and membranous positivity. DOG1 showed a sensitivity of 91.9% and a specificity of 76.9% in this study. Different studies show varying positivity rates for DOG1.

**Table 2: Correlation between morphology and recurrence or metastasis**

Morphology	Spindle (%)	Epithelioid (%)	Mixed (%)	Total (%)
Primary	22 (78.6)	3 (50)	1 (33.3)	26 (70.3)
Recurrent	2 (7.1)	1 (16.7)	2 (66.7)	5 (13.5)
Metastatic	4 (14.3)	2 (33.3)	0 (0)	6 (16.2)
Total	28	6	3	37

P=0.05

**Table 3: Approach for defining risk of aggressive behavior in GISTs - Fletcher's criteria**

Risk	Size (single largest dimension) (cm)	Mitotic count
Very low-risk	<2	<5/50 HPF
Low-risk	2-5	<5/50 HPF
Intermediate risk	<5	6-10/50 HPF
	5-10	<5/50 HPF
High-risk	>5	>5/50 HPF
	>10	Any mitotic rate
	Any size	>10/50 HPF

**Table 4: Prognostication of GISTs of different sites**

Tumor parameters			Percentage of patients with progressive disease during long-term follow-up and characterization of risk for metastasis			
Group	Tumor size (cm)	Mitotic rate (per 50HPF)	Gastric GISTs (%)	Small intestinal GISTs (%)	Duodenal GISTs (%)	Rectal GISTs (%)
1	2	≤5	0	0	0	0
2	2-5	≤5	1.9 (VL)	4.3 (L)	8.3 (L)	8.5 (L)
3a	5-10	≤5	3.6 (L)	24 (M)	34 (H)	57 (H)
3b	>10	≤5	12 (M)	52 (H)		
4	2	>5	0	50 (H)		54 (H)
5	2-5	>5	16 (M)	73 (H)	50 (H)	52 (H)
6a	5-10	>5	55 (H)	85 (H)	86 (H)	71 (H)
6b	>10	>5	86 (H)	90 (H)		

GIST: Gastrointestinal stromal tumors



**Table 5: Correlation between Ki67 and Fletcher's criteria for risk of metastasis in GIST**

Prognostic criteria	Ki67<8 (%)	Ki 67≥8 (%)	Total (%)
High-risk	3 (42.9)	21 (95.5)	24 (82.8)
Intermediate risk	4 (57.1)	1 (4.5)	5 (17.2)
Total	7	22	29

Chi-square test. P=0.007, GIST: Gastrointestinal stromal tumors

**Table 6: Sensitivity and specificity of KIT, DOG1, and KIT+DOG1 combined**

IHC marker	Sensitivity (%)	Specificity (%)	ROC
KIT	91.9	100	0.96
DOG1	91.9	76.9	0.84
KIT+DOG1	97.3	76.9	0.87

ROC: Receiver operating characteristic

**Table 7: Positivity rates of KIT in different studies**

Study	n (%)
Our study	91.9
Bhargami <i>et al.</i> <sup>[15]</sup>	87.6
Miettinen <i>et al.</i> <sup>[32]</sup>	94.9
Liu <i>et al.</i> <sup>[33]</sup>	92.9
Xu <i>et al.</i> <sup>[23]</sup>	93.94

The positivity rates observed in this study was comparable with a study by Xu *et al.* [Table 8].<sup>[23]</sup>

When using IHC for KIT and DOG1 in combination to identify GIST, the sensitivity increased to 97.3% which was comparable with the study by Xu *et al.*<sup>[23]</sup> while the specificity was 76.9%. This indicated the usefulness of combining the two markers in identifying cases of GIST. Other markers which were positive in a subset of GISTs include CD34, SMA, S100, and desmin. CD34 was positive in 60% of cases which was similar to studies by Güler *et al.*,<sup>[24]</sup> Bhargami *et al.*,<sup>[19]</sup> and Vij *et al.*<sup>[20]</sup> SMA was positive in 70% of cases which was higher than studies by Güler *et al.*,<sup>[24]</sup> Kim *et al.*,<sup>[21]</sup> and Vij *et al.*<sup>[20]</sup> S100 was positive in 3.7% of cases which was comparable to the study by Güler *et al.*<sup>[24]</sup> Desmin was positive in 8% of GISTs in this study which was lower than studies by Bhargami *et al.*<sup>[19]</sup> and Ueyama *et al.*<sup>[25]</sup>

This study encountered 3 cases which showed KIT negativity and DOG1 positivity on IHC. Mutational analysis was performed for these three cases to look for KIT, PDGFRA, or other GIST associated mutations. One case of KIT-negative GIST harbored PDGFRA D842V point mutation involving exon 18 which is the most common PDGFRA mutation reported in literature.<sup>[26-28]</sup> The site of involvement was retroperitoneum. This case had an epithelioid morphology which is commonly seen in PDGFRA exon 18 mutations.<sup>[28]</sup> The second case harboring

**Table 8: Positivity rates of DOG1 in different studies**

Study	n (%)
Our study	91.9
West <i>et al.</i> <sup>[6]</sup>	97.8
Miettinen <i>et al.</i> <sup>[32]</sup>	94.8
Liu <i>et al.</i> <sup>[33]</sup>	97.0
Xu <i>et al.</i> <sup>[23]</sup>	90.91

**Table 9: Comparison of the distribution of risk of metastasis using Fletcher's criteria with other studies**

Study	High-risk (%)	Intermediate risk (%)	Low-risk (%)	Very low-risk (%)
Our study	83.9	16.1	0	0
Lakshmi <i>et al.</i> <sup>[13]</sup>	70.4	20.6	8	1
Ravikumar <i>et al.</i> <sup>[14]</sup>	60	20	15	5
Sharma <sup>[18]</sup>	52.9	17.6	29.4	

KIT exon 17 mutations, showed a spindle cell morphology and was located in the stomach. The patient presented with lung metastasis and died within 2 months. The patient did not receive any treatment. KIT exon 17 mutations are rare KIT mutations seen in <1 % of GISTs.<sup>[29]</sup> Interestingly both these cases showed an NRAS mutation (Q61K) in addition to KIT or PDGFRA mutations, respectively. RAS family mutations can rarely occur in GISTs and account for <1% of all GISTs.<sup>[30]</sup>

In comparison to our study, other studies showed a slightly lesser number of cases in the high-risk category while there was the similar distribution of cases in the intermediate risk category [Table 9].<sup>[14,18,22]</sup>

A study by Zhao *et al.*<sup>[31]</sup> suggested that a cutoff value of 8% for Ki67 can effectively sub-divide high-risk patients of GIST who was substantiated in this study. Therefore, Ki67 can be used as an adverse prognostic marker in GIST.

## CONCLUSION

The following conclusions were drawn from this study

- Out of all the true mesenchymal tumors of the GIT, the gastrointestinal stromal tumor was the most common.
- The age of presentation was earlier in this study as well as Indian studies when compared to global data. This study showed a slight male predominance similar to other Indian studies whereas global data showed equal sex distribution.
- GISTs commonly present with pain abdomen. Metastatic disease was present in 16.2% of cases while

- the recurrence of GISTs was seen in 13.5% of cases.
- Stomach was the most common site of involvement, and the mean tumor size was 10.7 cms.
- Spindle cell morphology was more commonly present while epithelioid and mixed morphology carried a higher recurrence rate.
- Although KIT is still the most specific marker for GIST, the combination of KIT and DOG1 highly improved the sensitivity of identifying cases of GIST.
- Mutation analysis in KIT-negative cases can be helpful in identifying KIT, PDGFRA, and other associated mutations in GIST.
- Ki67 can be used as an adverse prognostic marker for identifying high-risk cases of GIST.

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# A Prospective Clinical Study on Types and Diagnostic Criteria of Fungal Rhinosinusitis used in Tertiary Teaching Hospital of Telangana

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## Abstract

**Background:** Fungal rhinosinusitis (FRS) is a disease of a wide spectrum of immune and pathological responses and includes invasive, chronic, granulomatous, and allergic variants. Consensus on its terminology, pathogenesis, and optimal management is not uniform among the surgeons. Based on the criteria of the International Society for Human and Animal Mycology, a clinical study was conducted on FRS.

**Aim of the Study:** The aim is to study and determine clinically and radiologically the various types of FRS and analyze them with the help of laboratory tests for confirmation in a clinical setting.

**Materials and Methods:** A total of 237 patients with FRS were included, and a detailed clinical history, demographic data, clinical examination, and direct sinonasal endoscopy were done. Radiological evaluation was done and the findings considered were air-fluid levels, opacities, mucosal thickening, and sinus wall erosion; expansion of the sinus walls, variegated densities, and other sinuses involved were studied. Fungal studies and histopathological studies were done. Treatment given to all the patients was recorded, and all the patients were followed up for 12 months. All the data were analyzed using standard statistical methods.

**Observations and Results:** Among the 237 consecutive patients included, there were 144 males (60.75%) and 93 females (39.24%). The mean age in males was  $37.62 \pm 4.73$  years, and in females, it was  $39.18 \pm 3.64$  years. 69/237 (29.11%) belonged to 33–42 years, 53/237 (22.36%) belonged to 23–32 years, 35/237 (14.76%) patients to 13–22 years, 23/237 (9.70%) patients to 53–62 years, and 20/237 (8.43%) patients to 63–72 years age group. Construction workers were 29/237 (12.23%), factory workers were 45/237 (19.40%), agriculture workers were 50/237 (21.09%), students were 23/237 (9.70%), office-goers were 50/237 (21.09%), and homemakers were 40/237 (16.87%) in number. Allergy was present in 94/237 (39.66%) and bronchial asthma in 52 (21.94%) patients. Diabetes mellitus was present in 44/237 (18.56%), tuberculosis in (6.32%), previous surgeries in 74 (31.22%), malignancies in 21 (8.86%), and psychiatric illnesses in 32 (13.50%) patients.

**Conclusions:** The diagnosis of FRS is challenging due to its wide spectrum of clinical symptoms and signs. Radiological features such as hyperattenuation, neo-osteogenesis, air-fluid level, bone erosion, and extra sinus extension are the parameters that will help routinely assess and differentiate fungal sinusitis from non-fungal sinusitis with considerable accuracy. Thorough clinical history, clinical examination, and laboratory evaluation hold the key to successful provisional diagnosis. Post-treatment assessment in India is difficult due to non-availability of patients for follow-up.

**Key words:** Allergic fungal sinusitis, Chronic sinusitis, Functional endoscopic sinus surgery, Fungal ball and invasive fungal sinusitis, Fungal rhinosinusitis

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## INTRODUCTION

Fungal rhinosinusitis (FRS) can be acute invasive FRS (AIFRS) refers to disease of <4 weeks duration in immunocompromised patients; chronic invasive rhinosinusitis and granulomatous rhinosinusitis are terms denoting locally invasive disease over at least 3 months<sup>1</sup>

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duration, with differing pathology and clinical settings; fungal ball of the sinus is preferred to either mycetoma or aspergilloma of the sinuses. Localized fungal colonization of nasal or paranasal mucosa refers to localized infection visualized endoscopically; eosinophilic mucin refers to allergic mucin; and allergic FRS (AFRS), eosinophilic FRS (EFRS), and eosinophilic mucin rhinosinusitis (EMRS) are imprecise and require better definition.<sup>[1]</sup> In 1965, Hora published to classify FRS into two categories: Noninvasive, clinically similar to chronic bacterial sinusitis, and invasive, in which the infection results in a mass that behaves such as malignant neoplasm, eroding bone, and spreading into adjacent tissue.<sup>[2]</sup> The invasive nature of the disease was further confirmed on histopathology.<sup>[3,4]</sup> A fulminant type of rhinosinusitis with rapid and malignant course was reported by McGill *et al.*, in 1980, in immunocompromised patients.<sup>[5]</sup> Allergic bronchopulmonary aspergillosis (ABPA) was reported by Safirstein<sup>[6]</sup> in 1976 which was a combination of nasal polyposis, crust formation, and sinus cultures yielding *Aspergillus* species. This clinical similarity with a constellation of findings was shared in 1981 by Millar *et al.*<sup>[7]</sup> In 1983, Katzenstein *et al.*<sup>[8]</sup> independently described a pathophysiologic resemblance in few cases of CRS associated with a mucosal plug in the sinuses of patients with ABPA leading to the description of a fourth type of FRS, namely allergic *Aspergillus sinusitis*. It became apparent later that melanized fungi are common etiological agents of this allergic type of sinusitis, which led to the renaming of this type of FRS as allergic fungal sinusitis or rhinosinusitis (AFS or AFRS).<sup>[9-11]</sup> With the demonstration of fungi in eosinophilic mucin independently from Type I hypersensitivity in most cases of CRS in recent years, the definition of AFRS has faced a greater challenge.<sup>[12,13]</sup> Hence, Ponikau *et al.*<sup>[12]</sup> proposed a new term for this condition, namely EFRS, to reflect the striking role of eosinophils.<sup>[12]</sup> The granulomatous invasive type of rhinosinusitis has to be differentiated from chronic invasive FRS (CIFRS). The former occurs in the patients who are immunocompetent, exclusively identified with *Aspergillus flavus*, and present as non-caseating granuloma with proptosis, whereas the latter often occurs in subtly immunocompromised patients, such as those with diabetes mellitus and corticosteroid treatment, with dense accumulation of hyphae invading tissue, and sometimes in association with the orbital apex syndrome.<sup>[13]</sup> The non-invasive FRS disorder consists of three types: Saprophytic fungal infestation, fungal ball, and fungus-related eosinophilic rhinosinusitis including AFRS.<sup>[14]</sup> Fungal ball is more or less a clear-cut entity. However, the confusion surrounds fungus-related eosinophilic rhinosinusitis and the definition of AFRS. As originally described, the detection of fungi in allergic mucin is considered important in the diagnosis of AFRS, although occasionally hyphae are sparse in the sinus contents. This leads to confusion and potential overlap with EMRS, as

described by Ferguson in 2000.<sup>[15]</sup> Ferguson speculated that EMRS is a systemic disease with dysregulation of immunological control where eosinophilic mucin could be present without the presence of fungi.<sup>[15]</sup>

### Type of the Study

This was a prospective, cross-sectional, and analytical study.

### Institute of the Study

The study was conducted at the Department of ENT and Head and Neck Surgery, Gandhi Medical College/Gandhi Hospital, Hyderabad, Telangana.

### Period of the Study

The study duration was from July 2013 to June 2015.

## MATERIALS AND METHODS

A total of 237 consecutive patients attending the OPD of the Department of ENT, Gandhi Medical College/Gandhi Hospital, tertiary teaching institutes, were selected. Patients with FRS were included in this study over 2 years. An Ethical Committee Clearance was obtained before the commencement of the study. An Ethical Committee cleared consent form was used during the study.

### Inclusion Criteria

1. Patients aged between 13 and 75 years were included.
2. Patients with acute as well as chronic FRS (CFRS) were included.
3. Patients with immunocompromised status were included.
4. Patients with diabetes mellitus and immunosuppressive drugs were included.
5. Patients with all types of FRS were included.
6. Patients with recurrent disease were included in the study.

### Exclusion Criteria

1. Patients below 13 years and above 75 years were excluded.
2. Patients with bacterial chronic or acute rhinosinusitis were excluded.
3. Patients with acute fulminant systemic diseases were excluded from the study.

Patients included in this study were enquired about their detail clinical history and demographic data followed by clinical examination including direct sinonasal endoscopy. This was followed by plain and/or contrast-enhanced computed tomography (CT) paranasal sinuses (PNS), with axial, coronal, and sagittal cuts in all patients. The radiological findings that were observed were, air-fluid levels, opacities, mucosal thickening, and sinus wall erosion,



Expansion of the sinus walls, Variegated densities, other sinuses involved, Anatomical abnormalities, intra-cranial extension, orbital involvement and laterality to classify the types of AFS.

### Sample Collection

Microbiology and pathology samples were collected such as exudates from nasal debris, discharge, and intraoperative tissue (polyps) sample, respectively. The samples were collected in two sterile containers, one containing normal saline for microbiology examination and the other containing 10% formalin for fixation. Samples received in microbiology were subjected to direct microscopy using KOH and calcofluor white as well as culture onto two sets of tubes of Sabouraud's dextrose agar with and without antibiotics. Samples sent in formalin to the pathology department were put up for histopathological examination (HPE). Fungal elements and yeasts were identified by colony morphology, gram staining, and lactophenol cotton blue standard preparations. Identification of the yeasts was done on the basis of germ tube production and morphology corn meal agar.<sup>[16]</sup> Treatment given to the all the patients was recorded, and all the patients were followed up for 12 months. All the data were analyzed using standard statistical methods.

## OBSERVATIONS AND RESULTS

The study was conducted in a tertiary teaching hospital attached to Gandhi Medical College. The total number of patients attending the ENT department OPD was 86,490 over a period of 3 years. Among them, the patients with nasal complaints were 19,426 (22.46%). Patients with symptoms and signs of chronic rhinosinusitis were 2269 (11.68%). 237 consecutive patients among 2269, who were willing to participate in the study, were included. There were 144 males (60.75%) and 93 females (39.24%). The mean age in males was  $37.62 \pm 4.73$  years, and in females, it was  $39.18 \pm 3.64$  years. The youngest patient was 14-year-old female and the eldest one was 73-year-old male. 69/237 (29.11%) patients belonged to the age group of 33–42 years, 53/237 (22.36%) patients belonged to the age group of 23–32 years, 35/237 (14.76%) patients to the age group of 13–22 years, followed by 23/237 (9.70%) in 53–62 years and 20/237 (8.43%) in 63–72 years age group [Table 1]. In this study, construction workers were 29/23 (12.23%), factory workers were 45/237 (19.40%), agriculture workers were 50/237 (21.09%), students were 23/237 (9.70%), office-goers were 50/237 (21.09%), and home-makers were 40/237 (16.87%) in number [Table 1]. Allergy was present in 94/237 (39.66%) and bronchial asthma in 52 (21.94%) patients. Diabetes mellitus was present in 44/237 (18.56%), tuberculosis in (6.32%), previous surgeries in 74 (31.22%), malignancies in 21 (8.86%), and psychiatric illnesses in 32 (13.50%) patients

[Table 1].

The study revealed that the complaint of nasal stuffiness was present in 87.76%, rhinorrhea in 76.79%, postnasal drip in 71.72%, cough in 53.58%, purulent rhinorrhea in 49.36%, headaches in 45.52%, fever in 44.72%, facial pains in 33.75%, and toothache in 13.50% of patients [Table 2].

CT PNS with or without contrast showed hyperattenuation in 36.28%, fluid levels in 29.53%, sinuses expansion in 21.51%, variegated appearance in 12.65%, bone erosion in 9.70%, extra sinus extension in 6.32%, and osteoneogenesis in 5.48% of patients [Table 3].

Mucosal thickening, variegated appearance, sinuses expansion, bone erosion, and intracranial or intraorbital

**Table 1: The gender incidence and other demographic incidences of the study group (n - 237)**

Observation	Male - 144 (60.75%)	Female - 93 (39.24%)	Total (%) 237 (100%)
Mean age	37.62±4.73	39.18±3.64	
Age groups			
13–22	22 (15.27)	13 (13.97)	35 (14.76)
23–32	34 (23.61)	19 (20.43)	53 (22.36)
33–42	41 (28.47)	28 (30.10)	69 (29.11)
43–52	16 (11.11)	8 (8.60)	24 (10.12)
53–62	13 (9.02)	10 (10.75)	23 (9.70)
63–72	11 (7.63)	9 (9.67)	20 (8.43)
>72	7 (4.86)	6 (6.45)	13 (5.48)
Profession			
Construction worker	18 (12.5)	11 (11.82)	29 (12.23)
Factory worker	26 (18.05)	19 (20.43)	45 (19.40)
Agriculture	30 (20.83)	20 (21.50)	50 (21.09)
Student	12 (8.33)	11 (11.82)	23 (9.70)
Office-goers	29 (20.13)	21 (22.08)	50 (21.09)
Home-maker	29 (20.13)	11 (11.82)	40 (16.87)
Allergy			
Present	67 (46.52)	27 (29.03)	94 (39.66)
Absent	77 (53.47)	66 (70.96)	143 (60.33)
Bronchial asthma			
Present	31 (21.02)	21 (22.58)	52 (21.94)
Absent	113 (78.47)	72 (77.41)	185 (78.05)
Diabetes mellitus			
Present	34 (14.34)	13 (13.97)	44 (18.56)
Absent	120 (50.63)	80 (86.02)	200 (84.23)
Immunocompromised			
Present	9 (06.02)	7 (07.52)	16 (6.75)
Absent	135 (93.75)	86 (92.47)	221 (93.24)
Tuberculosis			
Present	10 (06.94)	5 (05.37)	15 (6.32)
Absent	134 (93.05)	88 (94.62)	222 (93.67)
Previous surgeries			
Present	46 (31.94)	28 (30.10)	74 (31.22)
Absent	98 (68.05)	65 (69.89)	163 (68.77)
Malignancies			
Present	13 (9.02)	8 (8.60)	21 (8.86)
Absent	131 (90.97)	87 (93.54)	116 (48.94)
Psychiatric illnesses			
Present	20 (13.88)	12 (12.90)	32 (13.50)
Absent	124 (86.11)	81 (87.09)	205 (86.49)

**Table 2: The incidence of different symptoms in the patients (n - 237)**

Observation	Male - 144	Female - 93	Total (%)
Stuffiness	121	87	208 (87.76)
Watery rhinorrhea	103	79	182 (76.79)
Postnasal drips	98	72	170 (71.72)
Coughs	76	51	127 (53.58)
Purulent rhinorrhea	68	49	117 (49.36)
Headaches	67	48	115 (45.52)
Fevers	59	47	106 (44.72)
Facial pains	44	36	80 (33.75)
Toothaches	19	13	32 (13.50)
Diplopia	17	8	25 (10.54)
Visual loss	12	5	17 (7.17)

**Table 3: Radiological findings of CT PNS in the study group (n - 237)**

Observation	Male - 144	Female - 93	Total (%)
Hyperattenuation	61	25	86 (36.28)
Fluid levels	48	22	70 (29.53)
Sinuses expansion	38	13	51 (21.51)
Variegated appearance	19	11	30 (12.65)
Bone erosion	16	7	23 (9.70)
Extra sinus extension	9	4	13 (05.48)
Osteoneogenesis	3	0	03 (01.26)

CT: Computed tomography, PNS: Paranasal sinuses

extensions were more common in AIFRS than in chronic fungal sinusitis. Variegated appearance in soft tissue densities filling the sinuses was noted in AFRS. CT PNS features of bone erosion, invasion into extra sinus areas, and hyperattenuation were seen in CIFRS. Saprophytic fungal infestation patients showed unilateral variegated, circumscribed masses in one or many sinuses, usually maxillary sinus followed by the frontal sinus. EMRS showed mucosal thickening, sinus expansion, and hyperattenuation on CT PNS. Taking into consideration of clinical symptoms, microbiological, pathological, and CT PNS findings, the diagnosis was made and it showed AFRS in 85/237 (35.86%), chronic invasive fungal sinusitis in 58/237 (24.47%), chronic granulomatous sinusitis in 43/237 (18.14%), fungal ball in 20/237 (8.43%), saprophytic fungal infestation in 12/237 (5.406%), EMRS in 10/237 (4.21%), and acute invasive fungal sinusitis in 9 (03.79%) patients [Table 4].

Mycological examination revealed fungal elements of *Mucor* species, *A. flavus*, and *Rhizopus* species in the order of frequency in majority of the AIFRS patients. In chronic invasive, FRS <50% showed fungal elements. In addition to the above fungi, *Aspergillus niger*, *Candida albicans*, and *Penicillium* species were found in CIFRS patients. Histopathological specimens collected revealed fungal colonies in submucosal areas and bony erosion areas. Highly vascular areas and areas of necrosis were found in

**Table 4: The final diagnosis of FRS in the study group (n - 237)**

Observation	Male - 144	Female - 93	Total (%)
Allergic fungal rhinosinusitis - 115	52	33	85 (35.86)
Chronic invasive fungal sinusitis	32	26	58 (24.47)
Chronic granulomatous sinusitis	22	21	43 (18.14)
Fungal ball	14	6	20 (8.43)
Saprophytic fungal infestation	9	3	12 (5.06)
Eosinophilic mucin rhinosinusitis	8	2	10 (4.21)
Acute invasive fungal sinusitis	7	2	09 (3.79)

AIFRS. Fungal colonies were aseptate type in majority of AIFRS and CIFRS specimens. No evidence or evidence of occasional fungal elements was noted in AFRS and EMRS. Treatment consisted of functional endoscopic sinus surgery with debridement and clearance of the diseased tissue with adequate ventilation of all the sinuses, avoiding damage to the normal respiratory mucosa. Intraoperatively, Amphotericin B was given parenterally followed by post-operative antifungal antibiotics for 6 weeks in patients with AIFRS and CIFRS. In AFRS patients, itraconazole combined with steroid and antihistamine nasal spray and systemic steroids like methyl prednisolone was given to the patients for 6 months. Treatment of fungal ball consisted of FESS with middle meatus antrostomy and excision of the fungal ball followed by Antral lavage.

## DISCUSSION

Various types of microorganism enter the upper airway tract and tend to colonize in the nasal cavity, PNS, and nasopharynx. In the PNS, fungi are the most common organism which would colonize as their spores are inhaled from the atmospheric air. Absence or minimal immune host reaction toward fungi plays a major role in the symptomatic manifestations of FRS, both invasive and non-invasive.<sup>[16]</sup> Invasive FRS is of two types: Acute (AIFRS) and CFRS, whereas non-invasive are typed as AFRS, fungal mycetoma (fungal ball), saprophytic variant, and EMRS.<sup>[17]</sup> Based on the clinical condition, immune status, histopathology, and fungus infection, de Shazo *et al.*<sup>[14]</sup> suggested a classification for tissue of IFRS as AIFRS, chronic granulomatous FRS (CGFRS), and CIFRS types, with a disease course of <4 weeks which is seen in AIFRS cases in an immunocompromised setting. He proposed that a disease course of >12 weeks, dense infiltration of fungal hyphae, occasional vascular invasion, and sparse inflammatory reaction destroying the local sinus walls are typical of CIFRS cases. The presence of granulomatous

reaction and fibrosis suggests a CGFRS.<sup>[18]</sup> In the present study, there were 144 males (60.75%) and 93 females (39.24%). The mean age in males was  $37.62 \pm 4.73$  years, and in females, it was  $39.18 \pm 3.64$  years. The youngest patient was 14 years old female and the eldest one was 73 years old male. In this study, AFRS accounted for 85/237 (35.86%) of the total patients with female-to-male preponderance of 1.5:1. In a study from Thailand among the patients of AIFRS, the age range was 22–75 years with a mean age of 54 years and sex ratio (Male:Female) of 1:1.33.<sup>[18]</sup> Chakrabarti *et al.*<sup>[19]</sup> reported a mean age of 54 years (24–82) and Male:Female ratio of 1.5:1; this was similar to the present study. In the same study among CIFRS patients, the age range was 20–63 years, mean age being 45 years and sex ratio (Male:Female) 1:2. In the present study, the Male: Female ratio among the CIFRS patients was 1.23:1. Review of literature showed that patients of CIFRS present clinically with an enlarging mass in cheek, orbit, nose, and PNS regions and intracranial extension will change the clinical picture to associated symptoms such as headache, localizing, neurological findings, seizures, proptosis, and facial pain. Acute fulminant type presents with fever and headache in initial stages and proptosis, blindness, conjugal chemosis, ophthalmoplegia, signs and symptoms of meningeal involvement, cerebral infarction, and multiple cranial nerve palsies on invasion to different sites.<sup>[20,21,22]</sup> The present study revealed that the complaint of nasal stuffiness was present in 87.76%, rhinorrhea in 76.79%, postnasal drip in 71.72%, cough in 53.58%, purulent rhinorrhea in 49.36%, headaches in 45.52%, fever in 44.72%, facial pains in 33.75%, and toothache in 13.50% of patients, whereas Piromchai from Thailand<sup>[23]</sup> in 2008 from his study concluded that headache (59.3%) was the most common symptom, followed by visual loss (47.5%), facial pain (35.6%), and fever (33.9%). There were 9/237 (03.79%) patients in this study presenting with AIFRS who were immunocompromised unlike all other types of FRS 228/237 (96.20%), who were immunocompetent. Among the 9 cases of AIFRS, all were immunocompromised accounting to 100%. This was similar to the study conducted in the USA in 2008<sup>[22]</sup> wherein they found that all their patients with AIFRS were immunocompromised. As described by de Shazo *et al.*,<sup>[14]</sup> AIFRS occurs in immunocompromised patients most frequently. The comorbidities encountered in this study of FRS were diabetes mellitus, tuberculosis, allergy, bronchial asthma, and malignancies. Allergy was present in 94/237 (39.66%) and bronchial asthma in 52 (21.94%) patients. Diabetes mellitus was present in 44/237 (18.56%), tuberculosis in 15/237 (06.32%). previous surgeries in 74 (31.22%), malignancies in 21 (08.86%), and psychiatric illnesses in 32 (13.50%) patients. In Thailand (2008) study, diabetes mellitus was present in 66.6% of their AIFRS cases. Pagella *et al.*<sup>[24]</sup> reported that, in AIFRS cases,

hematological malignancies represented the principal comorbidity (100%), and Montone *et al.*<sup>[22]</sup> from the USA also found hematological disorders (84%) to be more commonly associated with AIFRS patients. Furthermore, Michael *et al.*<sup>[24]</sup> in their patients found an association of diabetes in 62.7% of AIFRS cases. In CIFRS cases, diabetes was present in 22.2% and hypertension in 11.1% of cases, while Pagella *et al.*<sup>[25]</sup> reported that, in chronic form, diabetes mellitus (87.5%) to be the principal comorbidity. Radiological evaluation in this study showed CT PNS with or without contrast showed hyperattenuation in 36.28%, fluid levels in 29.53%, sinuses expansion in 21.51%, variegated appearance in 12.65%, bone erosion in 9.70%, extra sinus extension in 6.32%, and osteoneogenesis in 5.48% of patients. In AIFRS patients in this study, bone erosions, intraorbital and intracranial extension, mucosal thickening, and variegated opacities on bilateral sides were present. Unilateral homogenous opacities are described as characteristic radiological feature of fungal ball which was significantly present in this study. Aribandi *et al.*<sup>[26]</sup> documented features of the findings such as heterogeneous opacities, mucosal thickening, and calcifications in patients of fungal ball diseases. All the patients with AFRS in this study showed bilateral sinus involvement with heterogeneous opacities and variegated appearances and calcifications indicating a systemic disease rather than local infection with fungus. This finding is in agreement with the work of authors such as Aribandi *et al.*,<sup>[26]</sup> Michael *et al.*,<sup>[25]</sup> and Piromchai and Thanaviratnanich.<sup>[23]</sup> Heterogeneous opacities were the most common finding in CIFRS cases followed by mucosal thickening and calcification. The CT findings seen in this study were showing such changes in CIFRS patients. Review of the study by Aribandi *et al.*<sup>[26]</sup> showed that the features of CGFRS were similar to CIFRS cases in their study. On HPE of the tissue from AFRS showed necrosis of sub-mucosa, bone, and vascular tissue in all the patients. All patients with AIFRS showed 100% of cases of AIFRS, and 65/85 (76.47%) of the AFRS patients evidenced accumulation of hyphae invading tissue. Only 148/237 (62.44%) patients could be followed up following surgical and medical treatment on this study. The incidence of recurrence among these 148 patients was 11/148 (07.43%). Post-treatment of this study remains the drawback of the present study.

## CONCLUSION

The diagnosis of FRS is challenging due to its wide spectrum of clinical symptoms and signs. Radiological features such as hyperattenuation, neo-osteogenesis, air-fluid level, bone erosion, and extra sinus extension are the parameters that will help routinely assess and differentiate fungal sinusitis from non-fungal sinusitis with considerable

accuracy. Thorough clinical history, clinical examination, and laboratory evaluation hold the key to a successful provisional diagnosis. Post-treatment assessment in India is difficult due to the non-availability of patients for follow-up.

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# Prevalence of Signs and Symptoms of Temporomandibular Joint Disorders among Saudi Population - A Cross-sectional Study

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## Abstract

**Background:** This cross-sectional study evaluated the prevalence of the signs and symptoms of temporomandibular joint (TMJ) disorder (TMD) among Saudi patients with TMD symptoms.

**Methods:** A total of 300 patients were screened; and of which 243 patients, 116 were males and 127 were females, with the age group of 15–30 years and above, who were randomly picked from the different school and colleges and also patients visiting the college of dentistry, King Khalid University, Abha, Saudi Arabia. A detailed questionnaire was distributed among the subjects asking about the presence of TMJ pain and related habits. The data obtained were compiled and statistically analyzed using Statistical Package for the Social Sciences software version 16.0. The *P* value was analyzed using the Pearson Chi-square test.

**Results:** About 20 patients (7 male and 13 female, i.e., 8.23%) had pain in TMJ or related or facial region, with a *P* = 0.0015 which is statistically significant.

**Conclusion:** Females with age group above 30 years had TMD signs and symptoms more frequently than males in the study population. The most common problem in both genders was pain.

**Key words:** Chewing habit, Headache, Pain

## INTRODUCTION

Temporomandibular joint (TMJ) disorders (TMD) are one of the common conditions which affect the orofacial region. The American Dental Association in 1983 has suggested a broader term TMD refers to a group of disorders characterized by pain in TMJ, the periauricular area, or the muscles of mastication based on various risk factors [1]. In the past few years, the risk factors underlying the etiology of TMJ is subject of debate. [2,3] In general, the risk factors such as parafunctional habits, emotional stress,

genetic and psychosocial factors, age, and gender have gained an important role in the etiology of TMD. [4,5] The most common signs are noises during opening and closing of mandible and deviation or restriction in mandibular range of motion. Most common symptom of TMD is pain during mandibular movements, at rest, or on palpation of the muscles. Pain results from the changes in muscle activity that limits the movements of the mandible and protects it from further damage while trying to promote healing. [6] TMD can also occur as a consequence of pain of non-dental origin in the orofacial region, including the head, face, and related structures. TMD is a possible cause of headache and vice versa as a positive correlation was found between TMD and the prevalence of headaches. [7] The prevalence of TMD varies from 9.8 to 80% from published data, according to epidemiological studies in different population age group based on risk factors. Few studies have been reported on the prevalence of TMD in

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Saudi Arabia in normal children, during the primary, mixed, and permanent dentition population group.<sup>[8-10]</sup> Other Saudi reports were on signs and symptoms of TMD in a specific patient and non-patient subjects such as military students, female patients seeking orthodontic treatment, and dental students.<sup>[11]</sup> The prevalence of TMD is still not well known, and more studies and comparisons are necessary to allow better understanding of the pathological aspects so as to address effective preventive and therapeutic measures. The aim of this questionnaire study is to assess the common predisposing or risk factors for TMJ pain in Saudi population.

## MATERIALS AND METHODOLOGY

The present study followed a cross-sectional design. Ethical clearance was obtained from the Institutional Review Board (SRC ETH/2012-13/022). The study sample consists of 300 subjects, Saudi nationals (both male and female) who were randomly picked from the different school and colleges and also patients visiting the College of Dentistry, King Khalid University, Abha, Saudi Arabia. A detailed questionnaire was distributed among the subjects asking about the presence of TMJ pain and related habits. All the subjects were informed regarding the purpose of the study, and written consent was obtained from participants. The subject sample that did not complete the questionnaire was excluded from the study. The final sample size was 243 (116 males and 127 females).

## DATA AND STATISTICAL ANALYSIS

Data were collected by questionnaire and were entered into a spreadsheet (Excel 2000; Microsoft, US) and analyzed subsequently using Statistical Package for the Social Sciences version 16.0. The *P* value was analyzed using the Pearson Chi-square test.

## RESULTS

A total of 243 subjects were questioned regarding the presence of TMJ pain, and about 20 patients (7 male and 13 female [8.23%]) had pain in TMJ or related or facial region, with  $P = 0.0015$  which is statistically significant. In age group between 15 and 30 years, 5 females and 7 males were suffering from the TMJ pain. In age group above 30 years, no males had TMJ problem, but eight females had pain [Table 1].

Of 243 subjects, about 40% had regular headache from time to time, and among them, male subjects in the age group of 15–30 years had higher prevalence followed by

female subjects. About 11.5% of patients had TMJ noise (clicking) while opening or closing the mouth, whereas 7.7% of patients had pain on the wide opening of the mouth. Moreover, 10% of the population were suffering from arthritis, 5.5% had a previous history of blow to the jaws, 6.8% had pain while chewing food, while 13% of the patients expressed pain while eating a big meal. Rest of the subjects, i.e., 10.7% felt pain in the jaw joint when they visited the dentist [Table 2].

Regarding the habits as recorded by the questionnaire, about 26% had chewing on one side, of which males of 15–30 years had higher prevalence making about 46.6%. Moreover, 41% of the subjects had a habit of using chewing gum more than an hour per day, of which female students had a higher incidence of 69%, whereas 23% of subjects had the habit of biting their nails, of which female population was more (25%). The prevalence of biting some article like pen or pencil with their teeth was 28%. A large number of samples about 52% of subjects had the habit of supporting their hand on TMJ area while relaxing or watching television. Bruxism accounted for 4% and stress biting for 3.4% [Table 3].

## DISCUSSION

Risk factors are pathophysiologic, psychological, or structural processes that alter the masticatory system sufficiently to increase the risk of development of TMD.<sup>[12,13]</sup> “We have been taught that pain is a symptom and the way to relieve a symptom is to remove the cause. If no somatic cause can be found, we may give up and abandon the patient else we may hypothesize a cause and treat it, either conservatively or less conservatively. If the treatment fails, we may try something else or tell the patient to learn to live with the pain.”

The present study examined 243 subjects by questionnaire consisting of risk factors, out of which 20 subjects, both

**Table 1: Age group**

Age	Sample	TMJ complaint (%)
15–30	Males - 78	7 (8.9)
	Female - 106	5 (4.7)
30 and above	Male - 38	0
	Females - 21	8 (38.9)

TMJ: Temporomandibular joint

## Chi-square tests

	Value	df	Asymptotic significant (two-sided) (P value)
Pearson Chi-square	9.88 (a)	6	0.003

**Table 2: TMJ symptoms**

S. No.	Symptoms	Males		Females		Total (%)
		15–30 (a)	30 ab (b)	15–30 (a)	30 ab (b)	
1	Head ache	46	4	38	5	93 (40)
2	Rheumatoid arthritis	18	2	2	1	23 (10)
3	Accident or a blow on the jaw	11	0	2	0	13 (5.5)
4	Clicking	18	3	3	3	27 (11.5)
5	Pain on opening mouth widely	10	2	5	1	18 (7.7)
6	Pain when chewing	4	5	2	5	16 (6.8)
7	Feel pain while eating a big meal	12	4	12	3	31 (13)
8	Pain in the jaw joint when you visit the dentist	10	4	8	3	25 (10.7)

TMJ: Temporomandibular joint

**Chi-square tests**

	Value	df	Asymptotic significant (two-sided)
Pearson Chi-square	13.518 (a)	9	0.141

**Table 3: Habits**

S. No.	Habits	Males		Females		Total (%)
		15-30 year (a)	30 ab (b)	15–30 (a)	30 ab (b)	
1	Chewing on one side	26	10	18	7	61 (26)
2	Bruxism	3	1	5	1	10 (4)
3	Use of chewing gum	23	2	65	4	94 (41)
4	Nail biting	25	4	18	6	53 (23)
5	Biting articles	33	2	27	4	66 (28)
6	Jaw enforcement	49	3	65	6	123 (52)
7	Stress biting	3	1	3	1	8 (3.4)

**Chi-square tests**

	Value	df	Asymptotic significant (two-sided)
Pearson Chi-square	8.735 (a)	9	0.462 (non-significant)

male and female, had the complaint of pain in TMJ or orofacial region, broken down by age and by gender. 14.5% of the subjects experienced pain in periauricular region which were in contrary to the previous study.<sup>[14]</sup>

Headache is one of the common symptoms seen with TMD. In the present study, 40% of the subjects experienced headache. The younger age groups had higher prevalence rate compared to older age group. 40% of male and female subjects in the age group of 15–30 years had higher when compared to above 30 years of age. This was at higher rate when compared to previous studies.<sup>[15]</sup> The prevalence of TMJ pain in younger age group is due to parafunctional habits such as chewing on one side and jaw enforcement, and the results were correlating with previous studies and possible causative mechanism for head ache, namely, TMD and TMD-induced sensitization in the central and peripheral nervous systems.<sup>[16]</sup> Clicking while opening and closing of the mouth was prevalent in 11.5% of population where the higher prevalent group was males under 30 years of age, with 66% which was contrary to the

study conducted on adults in West Bothnia.<sup>[17]</sup> A history of rheumatoid arthritis was found in 10% of population, but a strange finding was more number of sufferers who were below 30 years' male, and this may not be clinical finding instead it was a questionnaire which sample group might have mistaken for other pain. 13% of population had pain in temporomandibular area after a big meal where both males and females under 30 years had similar prevalence rate. 10% of population had pain after long dentist appointments. Questionnaire on the personal habits we found that 52% of population (123 out of 243) had a habit of placing their palm on TMJ area and supporting on elbow while relaxing or watching television. 41% of population, 94 patients, had a habit of chewing gums for longer period affecting the masticatory system. Female below 30 years were more compared to other groups. 28% of population had a habit of biting articles such as pen and pencil, which was more common among males below 30 years of age. In a study conducted in Jeddah, Saudi Arabia, the prevalence of parafunctional habits like nail biting was 41%. 26% of population had a habit of chewing

on one side of the jaw which had led to unilateral pain on temporomandibular areas in this group. A common habit of biting nail or trimming the nail with the teeth was found in 23% of population. Other habits such as bruxism and stress biting or psychological stress lead to bit the upper and lower teeth which were found in few patients about 4% and 3.4% of population, respectively.<sup>[18]</sup>

## SUMMARY AND CONCLUSION

The prevalence of TMD among Saudi population in Asir region Abha females were comparatively more affected than the males. Females with age group above 30 years were found to have more prevalence when compared to 15–30 years age group. Common symptoms in these patients were headache, pain after a big meal, clicking of joints, and pain in the preauricular area after prolonged dentist appointment. To some extent, these patients also had symptoms like pain on opening wide and chewing. The most common etiological factors for TMD in descending order were found to be pressure on TMJ while relaxing or watching television, use of chewing gum for longer period, biting articles such as pen or pencil, unilateral chewing, nail biting, bruxism, and psychological stress for lesser extent.

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# No Cost Vacuum-assisted Closure Therapy in Government Hospital

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## Abstract

Majority of the patients in India who avail facilities in government hospitals belong to low socioeconomic status. The incidence of diabetic foot cases in government hospitals is showing an increasing trend. The standard treatment for diabetic foot is thorough surgical debridement followed by daily antiseptic dressings. In the management of diabetic foot abscess, if controlled negative pressure is applied after surgical debridement healing process would be faster than conventional therapy. Negative pressure wound therapy is a newer non-invasive adjuvant therapy system that uses controlled negative pressure using vacuum-assisted closure device (VAC) to promote healing process. Use of VAC therapy reduces the hospital stay, thereby reducing the overall cost to the patient. However, the high cost of VAC therapy unit and disposables become a constraint in using this modality in government hospitals with limited resources. In view of this, a simple but novel technique is developed using suction apparatus and other disposables which are readily available in all government hospitals including Primary Health Centres with good outcome.

**Key words:** Diabetic foot, Negative pressure, Suction apparatus, Vacuum-assisted closure therapy

## INTRODUCTION

Delayed intervention in diabetic foot abscess may end up in complications such as gangrene and osteomyelitis requiring amputation. Therefore, early intervention is recommended to prevent such complications. Application of negative pressure using vacuum-assisted closure (VAC) therapy after thorough debridement along with appropriate antibiotics and controlling the blood sugar improves the outcome. In developing countries like India, it may not be possible to make VAC therapy units available in all government hospitals due to the high cost of unit and disposables required. Hence, an effort is made by employing the materials readily available in government hospital. This can be used where VAC therapy units are not available or cost of therapy of VAC not affordable by the patient. The results are good with no extra cost to the patient since all materials used are available in government hospitals including Primary Health Centres (PHCs).<sup>[1-4]</sup>

## MATERIALS AND METHODS

### Materials

1. Roller gauge - autoclaved.
2. Gamgee pad - autoclaved.
3. Ryle's tube 16–18 G.
4. Urosac bags.
5. Dyna plast/plaster.
6. Bedside suction apparatus.

### Method

After prepping and draping the involved lower 1/3 of leg, ankle and foot adequate surgical debridement was done under suitable anesthesia followed by antiseptic dressing with Gamgee pads and roller gauze. The dressing is opened after 8–12 h while ensuring thorough and complete hemostasis. Place 2–3 layers of gauze over the ulcer. Size of the gauze should be more than the ulcerated area. Place a Ryle's tube with multiple holes (additional holes were made) over the gauze. Gamgee pad is placed over the Ryle's tube. Dressing is done with roller gauze. At this stage, one end of urosac was cut to open it and covers the ulcerated wound up to the ankle. The another end of Ryle's tube should be brought out through the open end of the urosac. Opening of the urosac is folded and closed at ankle level with dyna plast/plaster, thus making the entire wrapping airtight. The

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**Figure 1:** (a) Diabetic foot ulcer, (b) 2–3 layers of Gauze applied over ulcer, (c) Ryle's tube is placed, (d) Gamgee pad is placed over it, (e) tied with roller gauze, (f) covered with urosac, (g) dyna plast is applied at opening of urosac to make airtight, (h) other ends of Ryle's tube attached to bedside suction apparatus



**Figure 2:** (a) At the time of admission, (b) at the time of admission, (c) 24 h after incision and drainage, (d) 48 h after applying vacuum-assisted closure therapy, (e) at the time of discharge (10 days after admission)

Ryle's tube is connected to bedside suction apparatus where negative pressure of  $-100$ – $-125$  mm Hg is maintained in the ulcerated area.<sup>[5]</sup>

### Method of Application of Device [Figure 1]

*Diabetic foot abscess treated with no cost vacuum-assisted closure therapy [Figure 2].*

Vacuum-assisted closure therapy or negative pressure wound therapy is a newer non invasive adjuvant therapy that uses controlled negative pressure to enhance healing process in wound healing. It reduces bacterial burden, interstitial wound fluid and increases vascularity. Increased blood flow to the wound bed results in delivery of fresh leukocytes and plasma that augments wound healing.

### RESULTS

It was noticed that healthy granulation tissue developed within 36–48 h after the procedure. Daily dressing was done and the condition of wound is assessed. There is no extra cost to the patient as all materials used in this procedure were available in all government hospitals including PHCs. Response to the treatment of the diabetic foot ulcers. The results are good with no extra cost to the patient since all materials used are available in government hospitals including PHCs.

Contraindications are similar to VAC therapy like:

- Patient on anticoagulants.
- Patient on antiplatelet aggregators (use with caution).

- High risk for bleeding.
- Exposed blood vessels/nerves.
- Untreated osteomyelitis.

## CONCLUSION

This can be used where VAC therapy units are not available or cost of therapy of VAC not affordable by the patient. Suction VAC therapy can be done in any government hospital with no extra cost to the patient. Hospital stay could be minimized with this therapy, thereby decreasing the expenditure to the government.

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# Assessment of Left Main Coronary Stenosis by Transesophageal Echocardiography

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## Abstract

**Introduction:** Coronary angiography is, and remains, the gold standard for evaluating the left main coronary artery (LMCA) stenosis. Transthoracic echocardiography has been shown to be of value in demonstrating LMCA anatomy and arteriosclerotic lesions.

**Aim:** The purpose of the study was the utility of transesophageal echocardiography in assessing LMCA stenosis.

**Methods:** The study was conducted in the Department of Cardiology, Government Rajaji Hospital, Madurai. Transesophageal echocardiography was done and LMCA visualized at midesophageal transverse view at the base of the heart and the level of the left sinus of Valsalva and flow was recorded with pulsed wave Doppler.

**Results:** We studied 25 patients of whom 20 were male, and 5 were female. 16 patients presented as inferior wall myocardial infarction, six as anterior wall myocardial infarction, and three as stable angina. The mean size of the LMCA at the level of the ostium is 3.27 mm + 0.6 mm, shaft level is 3.7 mm + 0.74 mm, and at the level of bifurcation is 2.87 mm + 0.34 mm. The length of the LMCA was 7 mm + 1.83 mm. All patients show stenosis of the LMCA and turbulence. The diastolic flow velocity before the stenosis was 84 cm/s + 16.7 cm/s and after the level of stenosis was 343 cm/s + 43.4 cm/s. The diastolic flow velocity ratio between LMCA and LAD is 1.24%. All patients underwent quantitative coronary angiogram and showed LMCA stenosis.

**Conclusion:** Transesophageal Doppler assessment of coronary blood flow is a highly sensitive and specific non-invasive method in the diagnosis of stenotic and occlusive atherosclerosis of the main coronary arteries.

**Key words:** Coronary stenosis, Left main coronary artery, Transthoracic echo

## INTRODUCTION

Quantitative evaluation of coronary stenosis is clinically important. Quantitative coronary angiography is usually performed for estimating the severity of coronary stenosis. Intracoronary blood flow velocity measurements using Doppler catheters or Doppler ultrasound guide systems have also been proposed as an alternative method for evaluating the functional severity of coronary stenosis at

baseline as well as for assessing the results of interventional procedures.<sup>[1-3]</sup> Johnson *et al.* demonstrated in a canine model that the cross-sectional area (CSA) of the coronary stenosis could be calculated with a Doppler catheter using the continuity equation, which was originally introduced for measuring stenotic valve area more recently, Nakatani *et al.* showed in 13 patients with mild-to-moderate stenosis that application of the continuity equation to Doppler catheter measurement of coronary flow velocity could be used to compute the severity of coronary stenosis successfully.<sup>[4,5]</sup> These methods, however, remain invasive, requiring cardiac catheterization, and cannot be repeated without risk during serial follow-up studies. Furthermore, in a consecutive series of 52 patients undergoing percutaneous transluminal coronary angioplasty, Di Mario *et al.* found that although the percent CSA stenosis derived from the intracoronary

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guidewire Doppler measurements based on the continuity equation was significantly correlated with the corresponding quantitative angiographic measurements, this determination could be achieved in only 16% of cases.<sup>[6]</sup> Recently, it has been demonstrated that coronary blood flow velocity can be recorded in the proximal part of the left coronary artery (LCA) with the use of transesophageal Doppler echocardiography (TEDE). In the present study, we tested whether the percent reduction of CSA of the stenosis can be quantitated by TEDE using the continuity equation.

### Aim

The purpose of the study was the utility of transesophageal echocardiography in assessing the left main coronary artery (LMCA) stenosis.

## MATERIALS AND METHODS

The study was conducted in the Department of Cardiology, Government Rajaji Hospital, Madurai, between January 2009 and April 2010. All patients underwent coronary angiogram and transechocardiography was done and LMCA visualized at midesophageal transverse view at base of the heart and the level of the left sinus of Valsalva and flow was recorded with pulsed wave Doppler.

**Study group:** A total of 50 patients with an LMCA stenosis were prospectively studied from January 2009 to April 2010. We chose patients with LMCA because TEDE recordings are easier to obtain in these portions of the LCA. A high-quality TEDE signal was obtained in 50 patients (45 men and 5 women, mean age 53 years [range 36–70]). Written informed consent for TEDE examination was obtained in all patients.

### Coronary Angiography and Quantitative Coronary Angiography

Coronary angiography was performed using the standard Judkins method with the femoral artery approach. Coronary injections were performed using multiple views, and images were recorded on TOSHIBA flat panel direct digital acquisition system. This quantitative coronary angiographic system has been validated previously. Quantitative analysis of stenosis was performed using the average of results obtained from two orthogonal projections, when available, or the most severe narrowing of several non-orthogonal angiographic projections. Three recognized quantitative variables of stenosis severity were automatically computed by the software: Percent diameter stenosis (DS), minimal lumen diameter, and percent CSA stenosis.

### Transesophageal Doppler Echocardiographic Measurements

Transesophageal echocardiography was performed with a 7-MHz probe connected to a Philips IE33 echocardiographic system within 24 h of the angiographic

**Table 1: Distribution of age**

Age group (in years)	Cases (n)%
Up to 40	4 (8)
41–50	16 (32)
51–60	21 (42)
>60	9 (18)
Total	50 (100)
Range	36–70
Mean±SD	53.3±8.1

SD: Standard deviation

**Table 2: Distribution of LVID and LVEF**

Parameter	Mean±S.D	Range
LVID (D)	5.1±0.67	3.5–7.1
LVID (S)	3.8±0.86	1.9–6
LVEF (T)	46.5±13.9	17–73
LVEF (QLAB)	44.7±11.3	25–73

LVEF: Left ventricular ejection fraction, LVID: Left ventricular internal diameter, SD: Standard deviation

**Table 3: Distribution of E/A/DT**

Parameter	Mean±S.D	Range
E	64.2±15.4	36–110
A	61±10.9	27–79
DT	139±33.5	56–238

study. A multiplane probe was used in all patients. Transesophageal examination was performed in each patient after oropharyngeal anesthesia by lidocaine. The LMCA was visualized by placing the transducer just above the aortic leaflets. Small adjustments in transducer orientation were necessary to visualize the bifurcation of the vessel into the LAD and circumflex artery. The length and diameter of LMCA (at the level of ostium, shaft, and distal LMCA) were measured. Pre-stenotic and transstenotic coronary flow velocities were then measured as follows: Coronary blood flow was first visualized by color flow imaging and a localized color aliasing phenomenon corresponding to a local flow acceleration was searched; pulsed wave Doppler echocardiography was then sampled in the site immediately upstream from the area of color aliasing; second, the sample volume was moved slightly downward in the area of color aliasing. High pulse repetition frequency or continuous wave Doppler echocardiography was used to quantitate the magnitude of transstenotic velocities if these velocities were too high to be measured by pulsed Doppler echocardiography without aliasing. Small adjustments in the transducer orientation allowed alignment of the ultrasound beam with the long axis of the interrogated proximal portion of the LCA. The peak flow velocity curve was traced from the outer border of the Doppler spectral signal, and the time-velocity integral (TVI) was obtained by planimetry

as the area under this peak flow-velocity curve during diastole. Other investigators have previously reported good interobserver and intraobserver reproducibility of coronary flow transesophageal Doppler velocity recording in the proximal part of the LCA 9, 10, 11, 12, 13, 14, 15.

The parameters assessed in T.E.E are as follows:

- Diameter of LMCA at ostial level, at the level of bifurcation.
- Length of LMCA.
- Presence of atheroma.
- Presence of turbulence.
- Diastolic flow velocity before the level of stenosis at the level of stenosis and after the level of stenosis.

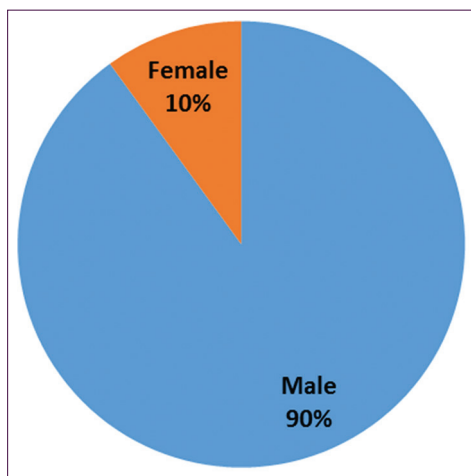


Figure 1: Distribution of gender

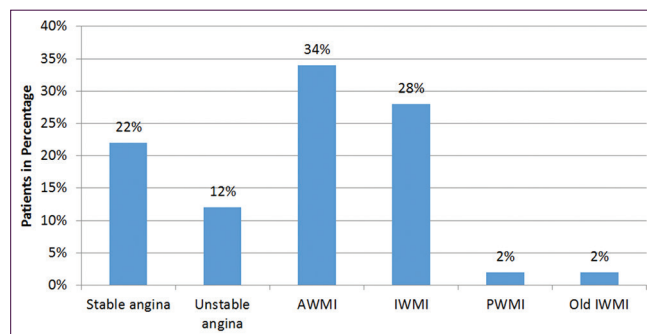


Figure 2: Distribution of diagnosis

- TVI before the level of stenosis and at the transstenotic level was measured.

## RESULTS

A total of 50 patients with an LMCA stenosis were included in the study. 42% of patients were more than 51 years followed by 32% in 41 to 50 years [Table 1]. 90% of patients were male [Figure 1]. AAMI and IAMI were most commonest diagnosis in the study group. Left ventricular internal diameter end diastole and end systole and LV ejection fraction of study patients were distributed in Table 2. E/A ratio and deceleration time of LV were distributed in Table 3.

### Coronary Angiographic Data

The length of the LMCA in angiogram varies between 4.5 and 22 mm with a mean of 11.5 and a standard deviation (SD) of 4.2. The diameter of the LMCA at ostial level ranges from 0.96 to 5.31 mm with a mean of 3.28 mm and an SD of 0.84. The diameter of the LMCA at shaft level ranges from 1.4 to 5.03 mm with a mean of 3.04 mm and an SD of 0.89. The diameter of the LMCA at the distal level ranges from 1.11–4.37 mm with a mean of 2.54 mm and an SD of 0.84. The calculated percent DS ranged from 20% to 90% (mean 43.2 and an SD of 15.7) [Table 4].

### Transesophageal Doppler Echocardiographic Data

A localized increase in velocity appeared on Doppler color flow mapping as a localized area of aliases, and disturbed signal in all 50 patients studied. In all patients, peak diastolic velocity and diastolic TVI at the pre-stenotic site were obtained by pulsed Doppler echocardiography; transstenotic diastolic peak velocity and TVI were obtained in all patients with the use of either pulsed Doppler echocardiography or high pulse repetition frequency Doppler or continuous wave Doppler echocardiography. The peak diastolic velocity at the stenotic region was 12–103 cm/s with a mean of 51.8 and SD of 21.4 and was significantly higher than that measured at the pre-stenotic segment 5–53 cm/s with a mean of 25.2 and SD of 11.4. A good linear correlation was found between the

Table 4: Correlation between echo findings and angiogram findings

Parameter	Values as per				Correlation coefficient between echo and angiogram values
	Echo		Angiogram		
	Range	Mean±SD	Range	Mean±SD	
LMCA (L)	3.9–18.8	10±3.2	4.5–22	11.5±4.2	0.7137
Diameter (O)	2–6.9	3.78±1.12	0.96–5.31	3.28±0.84	0.3562
Shaft	1.7–5.2	3.5±0.97	1.4–5.03	3.04±0.89	0.0267
Bifurca	1.3–6.3	2.99±0.87	1.11–4.37	2.54±0.84	0.3817
% stenosis	12–89	47.8±19.1	20–90	43.2±15.7	0.6007

LMCA: Left main coronary artery, SD: Standard deviation

catheterization-derived and TEDE-derived percent CSA stenosis (correlation coefficient of 0.6007) (significant >0.5) and length of the LMCA (correlation coefficient of 0.7137) (significant >0.5). A good linear relationship was also found between the catheterization-derived percent DS and the simple pre-stenotic to stenotic TVI ratio, which was a good discriminator for distinguishing patients with = 50% diameter reduction from those with <50% diameter reduction. All patients with = 50% diameter reduction stenosis at catheterization had a TVI ratio = 0.5 and only four of the 50 patients with <50% diameter reduction had a TVI ratio = 0.5. Thus, ratio = 0.5 predicted = 50% diameter reduction with 90% sensitivity and 85% specificity. The diameter of the coronary vessels did not correlate because the lateral resolution of the two-dimensional sector scan is too low to allow reliable measurements of dimensions of coronary arteries. The present study demonstrates that velocity measurements derived from TEDE can be used for quantitating stenosis of the LMCA [Tables 5 and 6].

## DISCUSSION

### Use of the Continuity Equation

Based on invasive Doppler measurements have proposed the application of the continuity equation to estimate the severity of coronary stenosis.<sup>[4,5,7]</sup> However, the methods used in these previously published studies remain invasive requiring cardiac catheterization and cannot be repeated without risk during serial follow-up studies.<sup>[4-6]</sup> Furthermore, in their consecutive series of 52 patients undergoing percutaneous transluminal coronary angioplasty, Di Mario *et al.* found that, although accurate for quantitation of lesion significance, use of the continuity equation employing intracoronary guide wire Doppler measurements is difficult and impractical for clinical application because high-quality intrastenotic Doppler signals are obtained in only a minority of cases.<sup>[6]</sup>

In our study, we used a non-invasive approach - TEDE - which can be used more easily in a clinical setting. We found a good linear relation between catheterization-derived and TEDE-derived percent CSA stenosis using the continuity equation. Despite this good linear relation, TEDE measurements significantly underestimated the actual percent CSA stenosis. This discrepancy between transesophageal Doppler measurements and the actual percent CSA may be explained by differences in the cross-sectional velocity profile that may occur between the pre-stenotic and stenotic segment sites. Fluid mechanics theory and previously published experimental studies suggest that cross-sectional velocity profile in a small conduit, like coronary arteries, is parabolic at a low Reynolds number, but flattens when velocities increase, like in stenosis where

flow becomes turbulent.<sup>[8-12]</sup> We have recently confirmed in a clinical study, based on computer analysis of digitally transferred transesophageal color coronary flow maps, that the cross-sectional velocity profile is parabolic in the normal proximal LAD, whereas it becomes flattened when velocities increase like at the site of the stenosis or after intravenous injection of dipyridamole. For clinical purposes, however, the simple TVI ratio may be used for predicting with good accuracy the percent DS, which is also a well-recognized variable of stenosis severity.

### Clinical Implications

Our data suggest that TEDE allows quantitation of stenosis of the LMCA. This method offers the advantage of a non-invasive technique, which can be applied to many echocardiographic laboratories. Our TEDE method might also represent an adjacent angiography to evaluate mild-to-moderate stenosis. Conventional angiography with visual interpretation, as currently used in many catheterization laboratories, has significant limitations in the assessment of coronary stenosis. In patients with severe coronary diameter reduction on the angiogram, there is usually no difficulty in ascertaining the functional severity of the lesion and in making clinical decisions. In contrast, in some patients with angiographically documented mild-to-moderate stenosis, it is sometimes difficult to evaluate the actual physiologic consequences of the obstruction. Furthermore, contrast angiography, even when using quantitative angiography, is not necessarily suitable for evaluating the results of catheter TEDE measurements using the continuity equation do not rely on any geometric assumption, it might help to confirm the functional severity of stenosis visualized by angiography, especially in cases of mild-to-moderate lesions and after

**Table 5: Relationship between pre-/post-TVI stenosis as per angiogram findings**

Pre-/post-TVI	Number of cases	% stenosis as per angiogram	
		<50%	≥50%
		n (%)	n (%)
<0.5	27	3 (11.1)	24 (88.9)
≥0.5	23	19 (82.6)	4 (17.4)
p		0.0001 Significant	

**Table 6: Difference in the values of % stenosis between echo findings and angiogram findings**

% stenosis difference between echo findings and angiogram values	Cases n (%)
<10%	30 (60)
>10%	20 (40)
Total	50 (100)
Range	-31-(+59)
Mean±SD	4.6±15.8

SD: Standard deviation

catheter-based interventions. TEDE also provides a method for quantitating the severity of the stenosis without inserting any catheter or guide wire into the stenotic segment. In contrast, Doppler catheters or guide wires reduce the actual CSA of the stenosis and may disturb flow field, thus leading to some errors in measurements.

## CONCLUSION

Transesophageal Doppler assessment of coronary blood flow is a highly sensitive and specific non-invasive method in the diagnosis of stenotic and occlusive atherosclerosis of the main coronary arteries. A modified continuity equation is hemodynamically correct and allows with the application of transesophageal Doppler allows the accurate calculation of the coronary artery stenosis percentage. The peak diastolic velocity of coronary blood flow (equal to  $1.4 \text{ ms}^{-1}$  in the LMCA,  $0.9 \text{ m.s}^{-1}$  in the LAD, and  $1.1 \text{ m.s}^{-1}$  in the LCX) alongside the aliasing phenomenon is a Doppler criterion of hemodynamically significant stenosis. Break of color mapping absence of Doppler spectrum and registration of retrograde blood flow during late diastole are Doppler echocardiographic criteria for coronary artery occlusion.

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# A Prospective Analysis of Toxicities and Quality of Life after Treatment in Advanced Carcinoma Cervix Patients Following Concurrent Chemoradiation with Weekly Cisplatin

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## Abstract

**Introduction:** Cervical cancer is the most frequently diagnosed cancer among women in India. Understanding quality of life (QOL) in women undergoing Chemoradiotherapy for cervical cancer will help in introducing interventions for better care and outcomes in these women.

**Aim:** To study toxicities and quality of life after treatment in advanced carcinoma cervix patients following concurrent chemoradiation with weekly cisplatin

**Patients and Methods:** Newly diagnosed patients with histologically confirmed carcinoma cervix, Patients with FIGO STAGE IIB TO IVA and no evidence of distant metastasis. Gynecological Oncologic group performance status of 0-3, Age less than 70 years, WBC count greater than 4000 cells/ml, An absolute neutrophil count greater than 37.5%, Platelet count of 100000 platelets/ml, Serum creatinine < 1.5mg/dl, Creatinine clearance more than 80 ml/min, Hemoglobin value >8 gm%. The patient treated with concurrent chemoradiation with weekly cisplatin

**Results:** Out of the 45 patients only 6 patients developed grade 3 neutropenia (13.3%), 12 patients (26.7%) developed grade 2 neutropenia, and there were no incidences of grade 4 neutropenia, during radiation, 4(8.9%) patients developed grade 3 skin reaction and 3(6.7%) patients developed grade 1 skin reaction. The quality of life decreased during treatment.

**Conclusion:** The patients who underwent chemoradiation experienced the reduction in quality of life during the treatment, but it was transient. The symptoms subsided and after the treatment patients have a better quality of life compared to pretreatment status. the toxicities of the treatment can be managed conservatively., which is comparable with global standards

**Key words:** Pelvic radiation toxicity, Quality of life, Cisplatin, Cervical cancer, Concurrent chemo radiotherapy

## INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide and the major cause of death,

particularly in the developing countries.<sup>[1]</sup> The global yearly incidence of cervical cancer in 2012 was 528,000; the annual death rate was 26600.<sup>[2]</sup> The incidence of cervical cancer per 1 lakh women in India is 30.7. The highest rate of incidence is seen in Latin American women. Poor nutritional status, multiple sexual partners, first coitus in young age, early childbirth, promiscuity of the spouse, HPV infections, sexually transmitted diseases, and immunocompromised states are cited as main risk factors.<sup>[3]</sup> Introduction of cervical screening tests reduces the incidence of invasive cervical cancer in the Western world. In developing or less developed countries, over

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80% of women with cervical cancer are diagnosed at the advanced stage which is associated with poor prognosis.<sup>[4]</sup> Radiation therapy (RT) alone was being used as a primary treatment for patients with locally advanced - the International Federation of Gynecology and Obstetrics (FIGO)<sup>[5]</sup> Stage IIB to IV - cervical cancer, but failure rates were high, suggesting the need of additional therapeutic modalities.<sup>[6]</sup> Many randomized studies suggest that a combination of chemotherapy with radiation will increase the effect of radiation.<sup>[7]</sup> Prognosis depends on the initial disease stage (FIGO), tumor volume, nodal status, radiation dose, treatment duration, hemoglobin level, and optimum use of intracavitary brachytherapy.<sup>[8]</sup> There are many randomized studies which incorporate chemo with radiation; in the 1980s, result of these studies shows that concurrent chemoradiation lowers the risk of recurrence and death.<sup>[9,10]</sup> The most common histological type is squamous cell carcinoma comprising around 80%.

### Aim

The aim is to study the toxicities and quality of life (QOL) after treatment in patients with locally advanced carcinoma cervix.

## MATERIALS AND METHODS

This prospective cohort study was conducted in the Department of Radiotherapy, Government Medical College, Thrissur.

### Inclusion Criteria

Newly diagnosed patients with histologically confirmed carcinoma cervix, patients with FIGO Stage IIB to IVA, and patients with no evidence of distant metastasis, Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, age <70 years, white blood cell (WBC) count >4000 cells/ml, an absolute neutrophil count >37.5%, platelet count of 100000 platelets/ml, serum creatinine <1.5 mg/dl, creatinine clearance >80 ml/min, and hemoglobin value >8 g% were included in the study.

### Exclusion Criteria

The following criteria were excluded from the study: Carcinoma cervix FIGO Stage IA-IIA, history of renal disease, coronary artery diseases, uncontrolled hypertension, presence of distant metastasis, age >70 years, WBC count <4000 cells/ml, an absolute neutrophil count <37.5%, platelet count <100000 cells/ml, serum creatinine >1.5, creatinine clearance <80 ml/min, and hemoglobin value <8 g%.

A thorough clinical examination was performed including per-speculum examination, per vaginal examination, digital rectal examination, and per-abdominal examination. In all patients, investigations such as chest X-ray, ultrasonography

abdomen, magnetic resonance imaging, complete blood count, renal function test, liver function test, urinalysis, cystoscopy, and sigmoidoscopy were performed only in patients clinically suspicious of bowel and bladder invasion.

All patients were monitored closely weekly during concurrent chemoradiation for assessing the toxicity of therapy. Toxicity grading was done according to the RT oncology group grading. The patients require to follow up at 6 weeks from completion of therapy to assess response, toxicity, and disease status. Subsequent follow-up visits were scheduled at monthly. At follow-up, patients underwent a thorough clinical examination for detection of locoregional disease. Patients who drop out or do not complete the planned course of treatment will be excluded.

## RESULTS

Mean age of the study population was 57 years, ranging from 35 to 70 years. Majority of patients (20, 44.1%) are in the age group of 61–70 years old. 11 patients (24.1%) are below the age of 50 years, and 14 patients (31.1%) are the age group of 51–60 years. Bleeding PV and discharge PV were present in 38 (84.4%) patients, and pain was present in 25 (55.6%) of patients. 22 (48.9%) patients of 45 have ECOG 0 and 23 (51.1%) patients have ECOG 1. 20 (44.4%) patients have vaginal involvement; 25 (55.6%) patients do not have vaginal involvement. 21 (46.7%) patient have 4-cm size lesion, 13 (28.9%) have 5-cm lesion, 5 (11.1%) have 6-cm lesion, 3 (6.7%) have 3-cm lesion, 2 (4.4%) have 5.5-cm lesion, and 1 (2.2%) has 2.8-cm lesion. 7 (15.6%) have adjacent structure involvement; 38 (84.4%) patients do not have adjacent structure involvement. 26 (57.8%) patients have initial stage of 2B, 13 (28.9%) have 3B, 5 (11.1%) have 4A, and only 1 (2.2%) have 3A stage. 35 (77.8%) patients received only 4 cycles of concurrent chemotherapy and 10 (22.2%) received 5 cycles of concurrent chemotherapy. 21 (46.7%) developed Grade 2 neutropenia, 12 (26.7%) developed Grade 1 neutropenia, 6 (13.3%) developed Grade 0 neutropenia, and 6 (13.3%) developed Grade 3 neutropenia. 21 (46.7%) developed Grade 1 cystitis during RT and 24 (53.3%) developed Grade 2 cystitis. 21 (46.7%) patients developed Grade 2 nausea, 22 (48.9%) developed Grade 1, and 2 (4.4%) developed Grade 0 reaction. 18 (40%) have Grade 1 diarrhea and 27 (60%) developed Grade 2 diarrhea during radiation. 38 (84.4%) patients developed Grade 2 skin reaction during radiation, 4 (8.9%) developed Grade 3 skin reaction, and 3 (6.7%) developed Grade 1 skin reaction.

### QOL Analysis

Repeated measures ANOVA was carried out for comparing pre-treatment, during treatment, and after treatment parameters of QOL.

F-value (137.202) was found to be significant, indicating that there exists the significant difference in the CXBI (body image scale) measured at 3 times. During the treatment, a significant decrease was noted, and it increased in the after treatment period. *P*-value of the comparison between pre-treatment and after treatment value ( $<0.0001$ ) indicates that there exists significant difference. Mean value before the treatment is 54.3 and it increases to 60.0 after the treatment ( $P < 0.0001$ ).

In the case of sexual activity, during the treatment, a significant increase is noted followed by a significant decrease. *P*-value of the comparison between pre-treatment and after treatment (0.323) indicates that there is no significant difference between sexual activity before and after the treatment. The mean value is 71.1, 100, and 73.3 before, during, and after the treatment, respectively (F-value = 45.150).

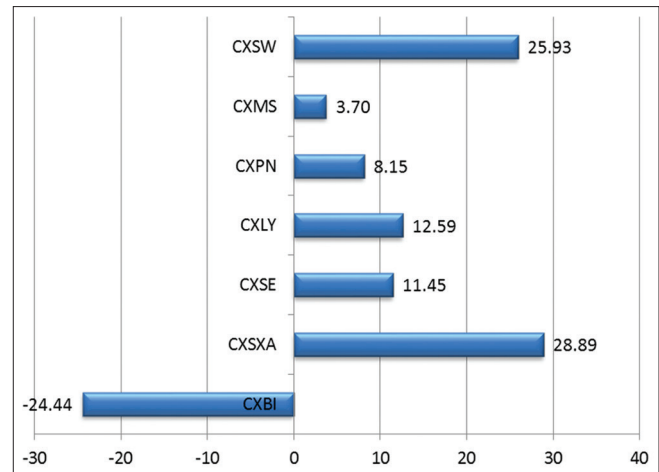
During the treatment, there are a significant increase in symptom experience and a significant decrease thereafter. *P*-value of the comparison between pre- and post-treatment ( $<0.001$ ) indicates that there is a significant decrease in symptoms after the treatment. The mean values are 48.89, 60.34, and 44.58 before, during, and after the treatment, respectively (F-value = 145.438).

During the treatment, there are a significant increase in lymphedema and a significant decrease thereafter. *P*-value of the comparison between pre-treatment and after treatment (0.013) indicates that there is a significant increase in lymphedema. The mean value is 0.74, 13.33, and 5.9 before, during, and after the treatment, respectively (F-value = 15.525).

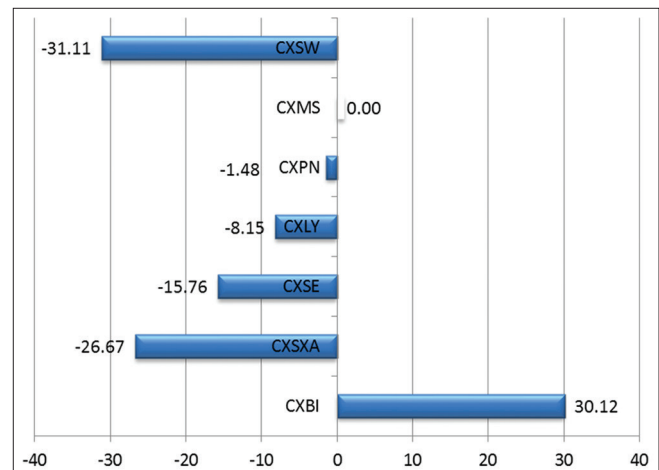
During the treatment, there are a significant increase in peripheral neuropathy and a significant decrease thereafter. *P*-value of the comparison between pre- and post-treatment (0.002) indicates that there is a significant increase in the peripheral neuropathy. The mean values are 0, 8.15, and 6.67 before, during, and after the treatment, respectively (F-value = 9.402).

During the treatment, there is a significant increase in menopausal symptoms, and after the treatment, there is no change in the menopausal symptoms. The mean values are 42.96, 46.67, and 46.67, respectively, before, during, and after the treatment (F-value = 1.583).

During the treatment, there is a significant increase in sexual worry followed by a significant decrease in post-treatment. There is no significant difference in sexual worry before and after the treatment ( $P = 0.051$ ). The mean values are 28.59, 54.81, and 23.70, respectively, before, during, and after the treatment (F-value = 39.878) [Figures 1-4].



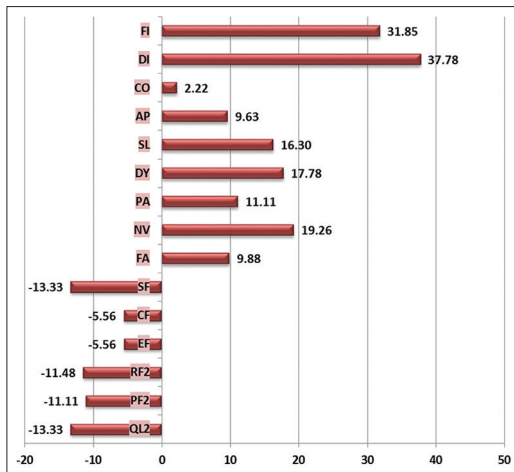
**Figure 1: Difference in mean quality of life during radiation therapy (RT) and before RT. CXSW - Sexual worry, CXMS - Menopausal symptoms, CXPN - Peripheral neuropathy, CXLY - Lymphedema, CXSE - Symptom experience, CXSXA - Sexual activity, CXBI - Body image**



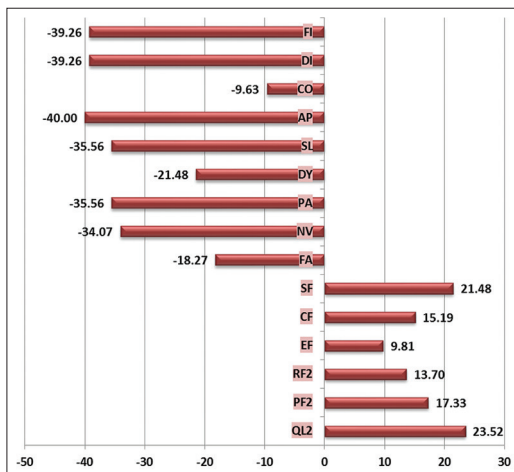
**Figure 2: Difference in mean quality of life after radiation therapy (RT) and during RT. CXSW - Sexual worry, CXMS - Menopausal symptoms, CXPN - Peripheral neuropathy, CXLY - Lymphedema, CXSE - Symptom experience, CXSXA - Sexual activity, CXBI - Body image**

During the treatment, there is a significant decrease in global health status followed by a significant increase. *P*-value of the comparison between pre- and post-treatment is  $<0.001$ , indicating that there is a significant increase in global health status after the treatment. Mean values are 42.04, 28.70, and 52.22, respectively, before, during, and after the treatment.

During the treatment, there is a significant decrease in physical functioning, with a significant increase in post-treatment. *P*-value of the comparison between pre- and post-treatment ( $<0.001$ ) indicates that there is a significant improvement in the physical functioning after the treatment, and the mean values are 68.44, 57.33, and 74.67, respectively, before, during, and after the treatment.



**Figure 3: Difference in mean quality of life during radiation therapy (RT) and before RT. QL2 - Global health status, PF2 - Physical functioning, RF2 - Role of functioning, EF - Emotional functioning, CF - Cognitive functioning, SF - Social functioning, FA - Fatigue, NV - Nausea and vomiting, PA - Pain, DY - Dyspnea, CO - Constipation, SL - Insomnia, AP - Appetite, DI - Diarrhea, FI - Financial difficulties**



**Figure 4: Difference in mean quality of life after radiation therapy (RT) and during RT. QL2 - Global health status, PF2 - Physical functioning, RF2 - Role of functioning, EF - Emotional functioning, CF - Cognitive functioning, SF - Social functioning, FA - Fatigue, NV - Nausea and vomiting, PA - Pain, DY - Dyspnea, CO - Constipation, SL - Insomnia, AP - Appetite, DI - Diarrhea, FI - Financial difficulties**

During the treatment, there is a significant decrease in the role of functioning, after that there is a significant increase. *P*-value of the comparison between pre- and post-treatment (0.294) indicates that there is no significant difference between the roles of functioning after the treatment, and the mean values are 41.85, 30.37, and 44.07, respectively, before, during, and after the treatment (*F*-value = 19.702).

During the treatment, there was a significant decrease in the emotional functioning, with a significant increase

after treatment. *P*-value of the comparison between pre-treatment and after treatment ( $<0.001$ ) indicates that there is a significant increase in emotional functioning after the treatment, and the mean values are 60.93, 55.37, and 65.19, respectively, before, during, and after the treatment (*F*-value = 31.435).

During the treatment, there were a significant decrease in the cognitive functioning and a significant increase afterward. *P*-value of the comparison between pre- and post-treatment (0.001) indicates that there is a significant improvement in the cognitive function after the treatment, and the mean values are 46.67, 41.11, and 56.30, respectively, before, during, and after the treatment (*F*-value = 34.764).

During the treatment, the social functioning score shows a significant decrease after that there is a significant increase. *P*-value of the comparison between pre- and post-treatment ( $<0.001$ ) indicates that there is a significant increase in social functioning score after the treatment, and the mean values are 57.04, 43.70, and 65.19, respectively, before, during, and after the treatment (*F*-value = 43.00).

During the treatment, there was a significant increase in fatigue, with a decrease after treatment. *P*-value of the comparison between pre-treatment and after treatment ( $<0.001$ ) indicates that there is a significant decrease in fatigue after the treatment, and the mean values are 49.38, 59.26, and 40.99, respectively, before, during, and after the treatment (*F*-value = 81.249).

During the treatment, there was a significant increase in nausea and vomiting, with a significant decrease after treatment. *P*-value of the comparison between pre- and post-treatment ( $<0.001$ ) indicates that there was a significant decrease in nausea and vomiting after the treatment, and the mean values are 43.33, 62.59, and 28.52, respectively, before, during, and after the treatment (*F*-value = 115.310).

During the treatment, there was a significant increase in pain with a significant decrease in pain after treatment. *P*-value of the comparison between pre-treatment and after treatment ( $<0.001$ ) indicates that there was a significant decrease in pain, and the mean values are 57.04, 68.15, and 32.59, respectively, before, during, and after the treatment (*F*-value = 113.749).

During the treatment, there were a significant increase in dyspnea and a significant decrease in dyspnea after treatment. *P*-value of the comparison between pre- and post-treatment (0.024) indicates that there was a significant decrease in dyspnea after the treatment, and the mean value are 27.41, 45.19, and 23.70, respectively, before, during, and after the treatment (*F*-value = 47.068).



There was no significant increase in constipation during treatment. *P*-value of the comparison between pre- and post-treatment (0.017) indicates that there was a significant decrease in constipation after the treatment, and the mean values are 20, 22.22, and 12.59, respectively, before, during, and after the treatment (*F*-value = 6.499).

During the treatment, there was a significant increase in insomnia followed by a significant decrease after treatment. *P*-value of the comparison between pre- and post-treatment (<0.001) indicates that there was a significant decrease in insomnia after the treatment; the mean values are 45.19, 61.48, and 25.93, respectively, before, during, and after the treatment (*F*-value = 66.383).

During the treatment, there was significant appetite loss with a significant improvement in appetite post-treatment. *P*-value of the comparison between pre- and post-treatment (<0.001) indicates that there was a significant improvement in appetite after treatment; the mean values are 49.63, 59.26, and 19.26, respectively, before, during, and after the treatment (*F*-value = 43.00).

During the treatment, there was a significant increase in diarrhea, and after the treatment, there was a significant reduction in diarrhea. *P*-value of the comparison between pre-treatment and after treatment (0.623) indicates that there was no significant decrease in diarrhea after the treatment; the mean values are 12.59, 50.37, and 11.11, respectively, before, during, and after the treatment (*F*-value = 43.00).

During the treatment, there was a significant increase in financial difficulties, and after the treatment, there was a significant decrease in financial difficulties. *P*-value of the comparison between pre- and post-treatment (0.006) indicates that there was a significant decrease in financial difficulties after the treatment, and the mean values are 25.93, 57.78, and 18.52, respectively, before, during, and after the treatment (*F* value = 43.00).

## DISCUSSION

QOL assessment reveals that there are an increase in the body image score and a decrease in the symptom score after treatment. There was an increase in lymphedema after the treatment, which may be attributed to radiation. There was also an increase in peripheral neuropathy after the treatment which may be due to the concurrent use of cisplatin. There were no significant changes in menopausal symptoms, sexual worry, and sexual activity when compared to the pre-treatment status. Aggravation of symptoms was observed during the treatment. The global health status, physical functioning, emotional functioning, cognitive functioning,

and social functioning decreased during treatment but significantly improved after treatment. Fatigue, nausea, vomiting, pain, insomnia, diarrhea, and financial difficulties increased during treatment but significantly reduced after treatment. There was no significant change in the occurrence of diarrhea compared to the pre-treatment status.

Monitoring the QOL in disease-free period after radiotherapy should include the information about the treatment complications since it might help the patients deal with them and cure the disease symptoms. It is important to monitor the mental status of cervical cancer patients in the assessment of their QOL. While some studies indicate a low mental status with irradiated patients, this study reveals significant improvements of emotional functions, higher role function, and better social integration, which significantly affect a mental status. Due to tumor regression, pain and fatigue were significantly reduced in patients after the irradiation.<sup>[11-13]</sup>

## CONCLUSION

The patients who underwent chemoradiation experienced reduction in QOL during the treatment, but it was transient. The symptoms subsided, and after the treatment, patients had better QOL compared to pre-treatment status.

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# A Prospective Randomized Double-blind Controlled Study Comparing Intravenous Paracetamol Plus Fentanyl and Intravenous Fentanyl Alone for Post-operative Analgesia for Laparoscopic Cholecystectomy

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## Abstract

**Background:** Acute pain after laparoscopic cholecystectomy is complex in nature which shows individual variation in intensity and duration; therefore, adequate pain control is mainstay during post-operative period. This study compares the effect of intravenous (IV) paracetamol plus IV fentanyl and fentanyl alone for analgesic efficacy, intraoperative hemodynamic, opioids sparing effects, and opioid-related side effects after laparoscopic cholecystectomy.

**Aim of the Study:** The aim of the study was to determine the efficacy of IV paracetamol for post-operative analgesia in patients undergoing elective laparoscopic cholecystectomy under general anesthesia and to compare the occurrence of opioid-sparing effects in patients receiving IV fentanyl plus IV paracetamol and IV fentanyl alone postoperatively.

**Materials and Methods:** A total of 60 patients undergoing laparoscopic cholecystectomy were randomized into two groups. In Group A, IV paracetamol 1 g (100 mL) was administered 10 min before induction. Group B served as a control group and received saline normal saline 100 mL. Both groups received fentanyl during induction. Intraoperative hemodynamic such as heart rate, mean arterial pressure, and intraoperative fentanyl consumption was measured and recorded. The post-operative pain relief was evaluated by a visual analog scale (VAS) score, consumption of fentanyl as rescue analgesia, and sedation scores, the incidence of post-operative nausea and vomiting (PONV) and pruritus was measured in the post-operative period.

**Observations and Results:** The mean VAS score in immediate and 1 h after surgery was less in the group receiving IV paracetamol ( $3.03 \pm 0.41^*$  vs.  $3.53 \pm 1.04$ ;  $3.13 \pm 0.57^*$  vs.  $3.90 \pm 1.21$ ); the fentanyl consumption intraoperatively was less in the paracetamol group ( $41.50 \pm 32.40^*$  vs.  $84.66 \pm 32.32^*$ ), overall intraoperative hemodynamic was stable in paracetamol group. The time requirement of the first dose of rescue analgesic in the post-operative period was also significantly prolonged in the group receiving IV paracetamol ( $5.84 \pm 4.44^*$  vs.  $1.83 \pm 1.09$ ). The sedation scores at 1<sup>st</sup>, 6<sup>th</sup>, and 12<sup>th</sup> h were less in paracetamol group ( $1.43 \pm 0.67^*$  vs.  $1.83 \pm 0.64$ ;  $1.20 \pm 0.40^*$  vs.  $1.56 \pm 0.72$ ; and  $1.10 \pm 0.30^*$  vs.  $1.43 \pm 0.50$ ). There was no difference in the incidence of PONV and pruritus in the two groups.

**Conclusion:** The use of IV paracetamol 1 g for preemptive analgesia as an adjunct to IV fentanyl in patients undergoing laparoscopic cholecystectomy had better intraoperative hemodynamic parameters, good quality postoperative analgesia, reduced consumption of fentanyl doses, and lesser sedation in post-operative period.

**Key words:** Intravenous paracetamol, Laparoscopic cholecystectomy, Post-operative pain, Post-operative analgesia

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## INTRODUCTION

Surgical pain is a form of acute pain that occurs in response to tissue damage caused by the surgical act, and it is the expression of autonomic responses, that can produce an unpleasant and unwanted sensory-emotional experience. Recent data suggest that at least 30–40% of all surgical

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patients do experience moderate or severe postoperative pain.<sup>[1,2]</sup> Acute pain after laparoscopic cholecystectomy is complex in nature. Pain after laparoscopy is caused by the stretching of the peritoneum, residual gas, the effect of surgery and skin incisions. The pain pattern does not resemble pain after other laparoscopic procedures; hence, the analgesic treatment required after laparoscopic cholecystectomy might be different or multimodal. Thus, effective analgesic treatment after laparoscopic cholecystectomy has remained a clinical challenge.<sup>[3]</sup> In laparoscopic cholecystectomy, overall pain is of three different types mainly clinically divided as: Incisional pain (somatic pain), visceral pain (deep intra-abdominal pain), and shoulder pain (presumably referred visceral pain). Characteristically, there is a high inter-individual variability in intensity and duration in such types of pain. It has been observed in many studies that pain is most intense on the day of surgery and the following day and subsequently declines to low levels within 3–4 days. However, severe pain is found in approximately 13% of patients throughout the 1<sup>st</sup> week after laparoscopic cholecystectomy.<sup>[4]</sup> Hence, this could be one of the reasons for a prolonged duration of stay in the hospital postoperatively. It is found in 17–41% of the patients, pain is the main reason for staying overnight in the hospital on the day of surgery.<sup>[5]</sup> Different combinations of drugs are available for optimal pain management which include local anesthetics, nonsteroidal anti-inflammatory drugs, opioids, and paracetamol. Opioids are very commonly used in the management of moderate to severe post-operative pain extensive use of opioids is associated with a variety of perioperative side effects, such as ventilatory depression, drowsiness and sedation, post-operative nausea and vomiting (PONV), pruritus, urinary retention, ileus, and constipation that can delay hospital discharge.<sup>[6]</sup> Intraoperative use of large bolus doses or continuous infusions of potent opioid analgesics may actually increase post-operative pain as a result of their rapid elimination and/or the development of acute tolerance.<sup>[7]</sup> To avoid the adverse effects of the individual drug at high doses an adjunctive drug may be used. Recent evidence suggests that the reduction in these adverse effects may be best achieved using a combination of protocols involving both central and peripheral acting drugs.<sup>[8]</sup> Recently launched intravenous (IV) paracetamol is commonly used for preemptive analgesia during various operative procedures. The aim of providing preemptive analgesia with IV paracetamol before a painful stimulus is to prevent central sensitization caused by painful stimulus and consequently to decrease the need for post-operative analgesia.<sup>[9]</sup> The analgesic effects of acetaminophen are mediated in the central nervous system by inhibiting the synthesis of prostaglandins. Its IV administration provides rapid and predictable therapeutic plasma

concentration. Initiation of treatment with centrally acting acetaminophen shortly before or during laparoscopic cholecystectomy is optimal.<sup>[10]</sup> The opioids sparing effects of acetaminophen are in the range of 20–30%. Recent data from routine use of acetaminophen suggested hastened and higher quality of recovery along with less use of opioids in cholecystectomy.<sup>[11]</sup> The concept of multimodal “opioid-sparing” analgesic techniques (so-called balanced analgesia) was introduced more than 15 years ago, with the aim of improving analgesia by combining analgesics that have additive or synergistic effects. It involves the use of smaller doses of opioids in combination with non-opioid analgesic drugs (e.g., local anesthetics, ketamine, acetaminophen, and nonsteroidal anti-inflammatory drugs) to prevent pain after surgery. Thus, the present study is done to evaluate the analgesic efficacy of IV paracetamol in patients undergoing laparoscopic cholecystectomy.

### **Aim of the Study**

The aim of the study was to determine the efficacy of IV paracetamol for post-operative analgesia in patients undergoing elective laparoscopic cholecystectomy under general anesthesia and to compare the occurrence of opioid-sparing effects in patients receiving IV fentanyl plus IV paracetamol and IV fentanyl alone postoperatively.

### **Type of Study**

This was a progressive randomized double-blind controlled study.

### **Period of Study**

This study was from May 2012 to May 2013.

### **Institute of Study**

This study was conducted in the Department of Anaesthesiology, C.S.I Holdsworth Memorial Hospital, Mysuru.

## **MATERIALS AND METHODS**

The present study was conducted in the Department of Anaesthesiology, CSI Holdsworth Memorial Hospital, Mysuru - 21. The study was undertaken after obtaining Ethical Committee Clearance as well as informed consent from all patients. 60 patients, scheduled for elective laparoscopic cholecystectomy belonging to ASA Class I and II were included in the study.

### **Inclusion Criteria**

The following criteria were included in the study:

1. Patients aged between 18 and 65 years.
2. Patients with ASA Grades I and II.



3. Patients scheduled for elective laparoscopic cholecystectomy under general anesthesia.

### Exclusion Criteria

The following criteria were excluded from the study:

1. Patients with known hypersensitivity to paracetamol, fentanyl.
2. Patients with abnormal coagulation profile.
3. Patients with hepatic or renal insufficiency.
4. Laparoscopic cholecystectomy converted to open cholecystectomy intraoperatively.

### Randomization

Based on the computer-generated randomization numbers, patients were randomly divided into two groups with 30 patients in each group. Group A ( $n = 30$ , paracetamol + fentanyl group) received 100 mL of paracetamol IV (1 g) 10 min before induction. Group B ( $n = 30$ , fentanyl alone group) received 100 mL of normal saline 10 min before induction. Patients fulfilling selection criteria were selected for the study and briefed about the nature of study and explained about anesthetic procedure. The routine blood investigations were followed and thorough pre-anesthetic evaluation was done on the evening before surgery. All patients included in the study were premedicated with tablet alprazolam 0.5 mg and tablet ranitidine 150 mg orally at bedtime the previous night before surgery. They were kept nil orally 10 pm onward on the previous night. The investigators involved in the study did not know about the content of the 100 mL bottle as the preparation of the study drug was done by an anesthesiologist not involved with the observations made for the study. Patients were explained about the study but did not know which drug was used. On arrival of the patient in the operating room, two IV lines were secured, one 20 G IV cannula in right hand for the infusion and another 18 G IV cannula in left hand for IV fluids and drug administration. 500 mL of crystalloids (ringer lactate) was started. Monitors, electrocardiography, non-invasive blood pressure, pulse oximeter, and  $\text{ETCO}_2$  were attached. HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were monitored before, during and after the surgery. End-tidal carbon dioxide was monitored intraoperatively and kept between 30 and 35 mmHg depending on different stages of laparoscopy. The study drug paracetamol 100 mL (1 g) given to Group A as single dose IV over 10 min just before induction. The Group B patients served as control were given 100 mL normal saline over 10 min just before induction. After the preoxygenation for 3 min, patients in both the groups were induced with injection fentanyl 2  $\mu\text{g}/\text{kg}$ , injection propofol 2  $\text{mg}/\text{kg}$ , and injection rocuronium 0.6  $\text{mg}/\text{kg}$ . Laryngoscopy and endotracheal intubation were done and lungs were mechanically ventilated. Anesthesia was

maintained with  $\text{O}_2$  in  $\text{N}_2\text{O}$  (66%:33%), isoflurane 1% and intermittent bolus dose of rocuronium. Fentanyl was repeated in a dose of 1  $\mu\text{g}/\text{kg}$  intraoperatively if both HR and MAP increased >15–20% from baseline despite maintaining adequate depth of anesthesia. The intraoperative hemodynamic monitoring such as SBP, DBP, MAP, and HR was done after induction of the patient in every 15 min interval. Moreover, intraoperative requirement of injection fentanyl was noted and recorded. (1) Heart rate [HR] in beats per minute (bpm), (2) SBP in mmHg, (3) DBP in mmHg, and (4) MAP in mmHg. The above cardiovascular parameters were monitored in the following time intervals: (1) Baseline parameter recording, (2) at the time of induction, (3) at the time of intubation, (4) during insufflations of  $\text{CO}_2$  (pneumoperitoneum [PNP]), (5) every 15 min after PNP, and (6) deflation of PNP and after extubation. After surgery patients were reversed with injection glycopyrrolate 0.01  $\text{mg}/\text{kg}$  and injection neostigmine 0.05  $\text{mg}/\text{kg}$  and the patients were extubated and transferred to postanesthesia care unit. Post-operative pain was assessed using visual analog scale (VAS: 0 - “no pain” and 10 - “worst pain ever”) and the post-operative rescue analgesia was provided with injection fentanyl 0.5  $\mu\text{g}/\text{kg}$  when VAS score exceeded 3. The degree of sedation was determined by RAMSAY sedation score ranging from 1 to 6 score. The VAS score is assessed at an interval of 1, 2, 4, 6, 12, and 24 h after surgery similarly sedation score assessed at an interval of 1, 2, 4, 6, and 12 h. The total fentanyl consumption at these times for both the group was recorded. The time of first dose of rescue analgesia was recorded. The incidence of PONV and Pruritus was also observed in post-operative period and treated accordingly. Sample size calculation: The number of participants required in each study group,  $m$ , was calculated using the formula as below:

$$m = \frac{2 \times [Z(1 - \alpha / 2) + Z(1 - \beta)]^2}{\Delta^2}$$

Where  $Z(1 - \alpha / 2)$  and  $Z(1 - \beta)$  represent percentage points of the normal distribution for statistical significance level and power, respectively, and  $\Delta$  represents the standardized difference (i.e., the treatment difference divided by its standard deviation).

$$\text{The standardised difference } \Delta = \frac{p1 - p2}{\sqrt{p \times (1 - p)}}$$

Where

$$p = \frac{(p1 + p2)}{2}$$

In our study,  $p_1 = 0.80$  (or 80%),  $p_2 = 0.40$  (or 40%), and

$$p = \frac{0.8 + 0.4}{2} = 0.6$$

so,

$$\text{Hence, } \Delta = \frac{0.8 - 0.4}{\sqrt{0.6 \times (1 - 0.6)}} = 0.82$$

Using the values for a significance level of 5%,  $Z (1 - \alpha/2) = 1.96$ , and a power of 80%,  $Z (1 - \beta) = 0.8416$ ,

$$m = \frac{2 \times [1.96 + 0.8]^2}{(0.82)^2} = 23$$

From the above calculations, the sample size was taken as 23. Hence, it was decided to study 30 patients in each group. Statistical method applied: Frequencies: The frequencies procedure provides statistics and graphical displays that are useful for describing many types of variables. For a frequency report and bar chart, the distinct values arranged in ascending or descending order, or by their frequencies. The frequencies report can be suppressed when a variable has many distinct values. The charts labeled with frequencies (the default) or percentages.

### Descriptives

The descriptives procedure displays univariate summary statistics for several variables in a single table and calculates standardized values (z scores). Variables can be ordered by the size of their means (in ascending or descending order), alphabetically, or by the order in which you select the variables (the default). When z scores are saved, they are added to the data in the Data Editor and are available for charts, data listings, and analyses. When variables are recorded in different units (for example, gross domestic product per capita and percentage literate), a z-score transformation places variables on a common scale for easier visual comparison.

### Paired-samples t-test

The paired-samples t-test procedure compares the means of two variables for a single group. The procedure computes the differences between the values of the two variables for each case and tests whether the average differs from 0.

**Table 1: Demographic data showing mean age, DOS, and weight of patient**

Characteristics	Group A	Group B	P value
Age (years)	43.93±12.90	43.87±11.94	0.984
Weight (kg)	70.47±9.9	68.57±7.9	0.415
Duration of surgery (min)	111±13.98	114±12.20	0.380

DOS: Duration of surgery

### One-way ANOVA

The one-way ANOVA procedure produces a one-way analysis of variance for a quantitative dependent variable by a single factor (independent) variable. Analysis of variance is used to test the hypothesis that several means are equal. This technique is an extension of the two-sample t-test.

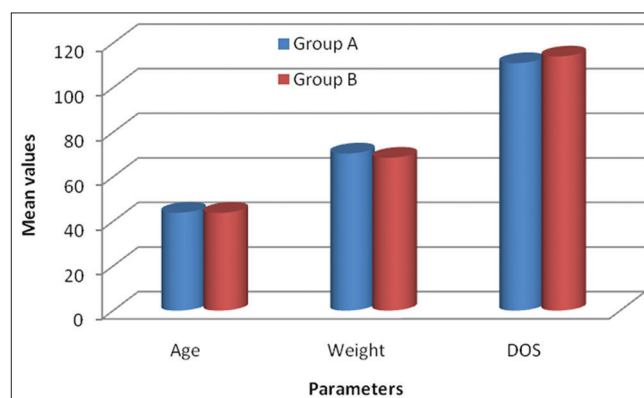
## OBSERVATIONS AND RESULTS

The mean age of the patients observed was  $43.93 \pm 12.90$  in Group A and  $43.87 \pm 11.94$  in Group B with P value 0.984 (not significant statistically). The mean weight in Group A was  $70.47 \pm 9.9$  and  $68.57 \pm 7.9$  in Group B with P value of 0.415 (not significant). The duration of surgery (DOS) in Group A was  $111 \pm 13.98$  and  $114 \pm 12.20$  min in Group B [Table 1 and Figure 1].

In Group B ( $n = 30$ , control), the basal mean HR was  $82.20 \pm 12.58$ . 10 min after bolus drug administration, at induction the mean HR was  $76.47 \pm 10.61$  which is statistically significant ( $P = 0.001$ ). 15 min after PNP and subsequently the mean HR was significantly high compared to basal value ( $P = 0.028$ ). The mean HR after deflation of abdomen was not statistically significant compared to basal value ( $P = 0.277$ ) and soon after extubation mean HR remained significantly high compared to basal value ( $P = 0.003$ ) [Table 2].

In Group A (paracetamol), the basal mean HR was  $78.43 \pm 14.30$ . The mean HR after induction and PNP was statistically insignificant compared to basal HR. After extubation HR was  $85.33 \pm 7.28$  which was statistically significant ( $P = 0.008$ ). In our study, we found the mean HR in paracetamol group with different stages of laparoscopy was maintained with basal HR intraoperatively [Table 3].

The mean HR in control Group(B) after PNP and subsequently at 30, 45, 75, 90, and 105 min and after



**Figure 1: Mean age, duration of surgery, and weight of patient**

**Table 2: Intraoperative comparison of mean HR/min changes in response to laryngoscopy and intubation and PNP in control Group (B) compared to basal HR**

Time interval	HR /min	P value
Basal (M1)	82.20±12.58	
At induction (M2)	76.47±10.61	0.001
Intubation (M3)	79.70±10.09	0.238
PNP (M4)	81.47±11.29	0.695
15 min after PNP (M5)	87.63±10.62	0.028
30 min after PNP (M6)	85.67±9.37	0.167
45 min after PNP (M7)	82.67±9.49	0.835
60 min after PNP (M8)	81.03±7.36	0.617
75 min after PNP (M9)	81.73±7.29	0.847
90 min after PNP (M10)	81.29±7.11	0.464
105 min after PNP (M11)	83.00±8.61	0.195
After abdomen deflation (M12)	84.73±6.98	0.277
After extubation (N1)	88.67±5.57	0.003

HR: Heart rate, PNP: Pneumoperitoneum

**Table 3: Intraoperative comparison of mean HR/min changes in response to laryngoscopy and intubation and PNP in paracetamol Group (A) compared to basal HR**

Time interval	HR /min	P value
Basal (M1)	78.43±14.30	
At induction (M2)	76.23±11.67	0.085
Intubation (M3)	81.57±10.02	0.085
PNP (M4)	80.20±9.65	0.362
15 min after PNP (M5)	83.47±9.64	0.045
30 min after PNP (M6)	80.50±10.93	0.524
45 min after PNP (M7)	77.33±9.20	0.660
60 min after PNP (M8)	78.17±9.69	0.907
75 min after PNP (M9)	76.50±8.90	0.362
90 min after PNP (M10)	74.86±8.78	0.223
105 min after PNP (M11)	76.38±8.30	0.608
After abdomen deflation (M12)	80.87±7.31	0.358
After extubation (N1)	85.33±7.28	0.008

HR: Heart rate, PNP: Pneumoperitoneum

**Table 4: The intergroup comparison of mean HR/min changes in response to laryngoscopy and intubation and PNP between control Group (B) and paracetamol (A) Group**

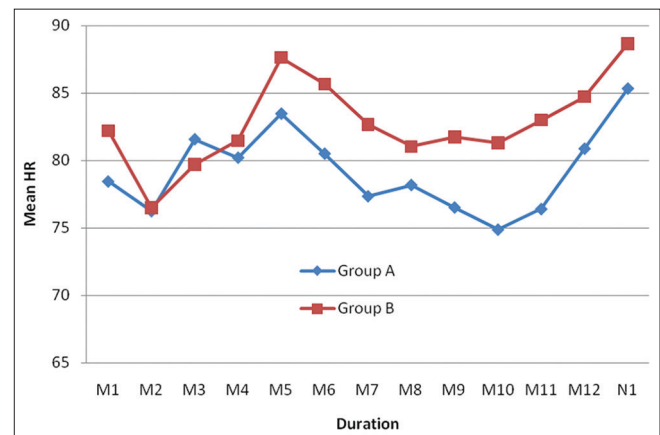
Time interval	Group A	Group B	P value
Basal (M1)	78.43±14.30	82.20±12.58	0.283
At induction (M2)	76.23±11.67	76.47±10.61	0.936
Intubation (M3)	81.57±10.02	79.70±10.09	0.475
PNP (M4)	80.20±9.65	81.47±11.29	0.642
15 min after PNP (M5)	83.47±9.64	87.63±10.62	0.117
30 min after PNP (M6)	80.50±10.93	85.67±9.37	0.054
45 min after PNP (M7)	77.33±9.20	82.67±9.49	0.031
60 min after PNP (M8)	78.17±9.69	81.03±7.36	0.202
75 min after PNP (M9)	76.50±8.90	81.73±7.29	0.016
90 min after PNP (M10)	74.86±8.78	81.29±7.11	0.010
105 min after PNP (M11)	76.38±8.30	83.00±8.61	0.012
After abdomen deflation (M12)	80.87±7.31	84.73±6.98	0.041
After extubation (N1)	85.33±7.28	88.67±5.57	0.051

HR: Heart rate, PNP: Pneumoperitoneum

**Table 5: Intraoperative comparison of MAP in mmHg changes in response to laryngoscopy and intubation and PNP in control Group (B) compared to basal MAP**

Time interval	MAP (mmHg)	P value
Basal (M1)	93.67±10.41	
At induction (M2)	85.97±10.19	0.000
Intubation (M3)	90.37±7.94	0.074
PNP (M4)	93.77±9.28	0.965
15 min after PNP (M5)	101.67±9.65	0.000
30 min after PNP (M6)	99.20±8.66	0.019
45 min after PNP (M7)	95.07±6.01	0.462
60 min after PNP (M8)	93.57±5.62	0.961
75 min after PNP (M9)	92.80±5.53	0.671
90 min after PNP (M10)	93.13±5.18	0.739
105 min after PNP (M11)	95.25±7.70	0.593
After abdomen deflation (M12)	95.60±6.81	0.327
After extubation (N1)	101.07±5.74	0.000

MPA: Mean arterial pressure, PNP: Pneumoperitoneum



**Figure 2: The intergroup comparison of mean heart rate (HR/min) changes in response to laryngoscopy and intubation and pneumoperitoneum between control Group (B) and paracetamol (A) Group**

extubation was increased compared to basal value and mean HR of paracetamol Group (A), which was statistically significant ( $P < 0.05$ ) [Table 4].

In control Group (B) the MAP compared to basal MAP, at induction was  $85.97 \pm 10.19$  ( $P = 0.000$ ); however, 15 min after PNP and after extubation the MAP was high  $101.67 \pm 9.65$  and  $101.07 \pm 5.74$ , respectively, which was statistically significant ( $P = 0.000$ ) [Table 5 and Figure 2].

In paracetamol group, there was no statistically significant change in MAP compared to basal MAP intraoperatively, except the MAP at induction is  $89.07 \pm 12.10$  ( $P = 0.000$ ) and 75 min after PNP is  $89.03 \pm 7.35$  ( $P = 0.026$ ) which was statistically significant [Table 6].

In control Group (B), the MAP was increased compared to paracetamol Group (A) intraoperatively, and it

**Table 6: Intraoperative comparison of MAP in mmHg changes in response to laryngoscopy and intubation and PNP in paracetamol Group (A) compared to basal MAP**

Time interval	MAP (mmHg)	P value
Basal (M1)	94.43±10.86	
At induction (M2)	89.07±12.10	0.000
Intubation (M3)	94.13±11.30	0.845
PNP (M4)	94.03±10.83	0.827
15 min after PNP (M5)	97.53±11.28	0.172
30 min after PNP (M6)	95.67±15.40	0.689
45 min after PNP (M7)	90.80±11.00	0.158
60 min after PNP (M8)	91.50±10.30	0.280
75 min after PNP (M9)	89.03±7.35	0.026
90 min after PNP (M10)	88.52±7.58	0.062
105 min after PNP (M11)	88.95±7.73	0.074
After abdomen deflation (M12)	91.33±6.53	0.211
After extubation (N1)	95.80±6.35	0.551

MPA: Mean arterial pressure, PNP: Pneumoperitoneum

**Table 7: The intergroup comparison of mean MAP in mmHg changes in response to laryngoscopy and intubation and PNP between control (B) group and paracetamol (A) group**

Time interval	Group A	Group B	P value
Basal (M1)	94.43	93.67±10.41	0.781
At induction (M2)	89.07	85.97±10.19	0.288
Intubation (M3)	94.13	90.37±7.94	0.141
PNP (M4)	94.03	93.77±9.28	0.919
15 min after PNP (M5)	97.53	101.67±9.65	0.133
30 min after PNP (M6)	95.67	99.20±8.66	0.278
45 min after PNP (M7)	90.80	95.07±6.01	0.067
60 min after PNP (M8)	91.50	93.57±5.62	0.339
75 min after PNP (M9)	89.03	92.80±5.53	0.029
90 min after PNP (M10)	88.52	93.13±5.18	0.021
105 min after PNP (M11)	88.95	95.25±7.70	0.009
After abdomen deflation (M12)	91.33	95.60±6.81	0.016
After extubation (N1)	95.80	101.07±5.74	0.001

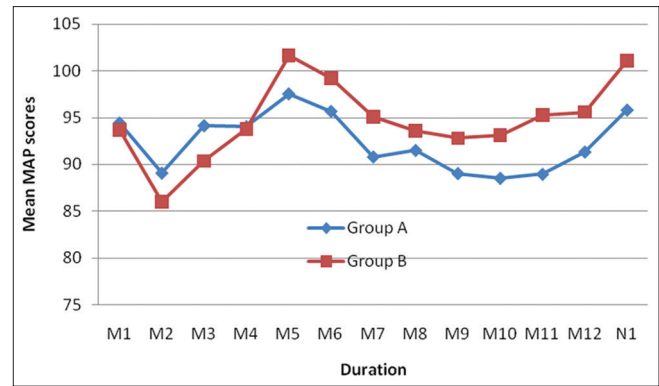
MPA: Mean arterial pressure, PNP: Pneumoperitoneum

**Table 8: Requirement of intraoperative dose of IV fentanyl in both groups**

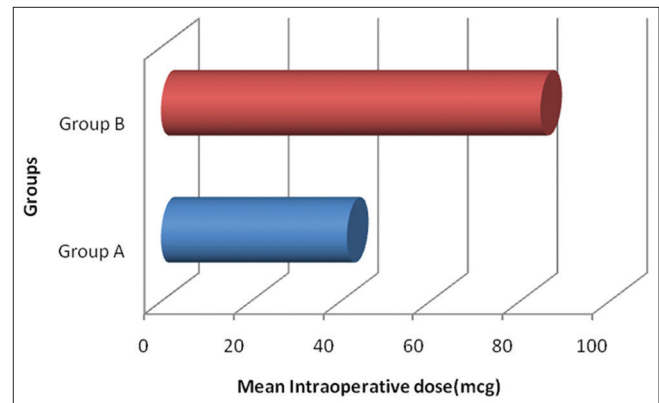
Intra-operative dose	Group A	Group B	P value
Intraoperative dose			
Mean (mcg)	41.50±32.40	84.66±32.32	0.000

was statistically significant after 60 min of PNP and subsequently until after extubation ( $P < 0.05$ ). However, in paracetamol group, there was no significant variation in MAP compared to basal MAP [Table 7 and Figure 3].

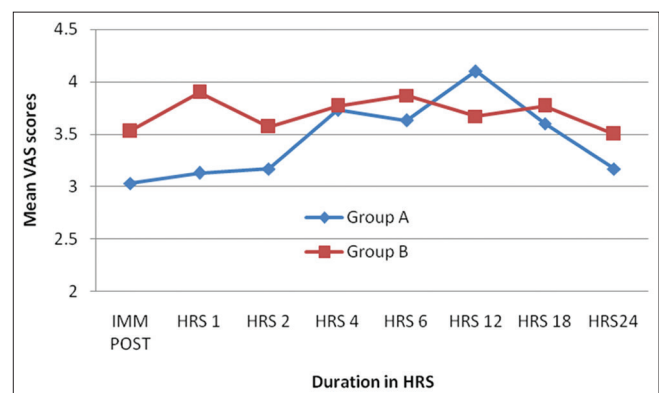
We found the intraoperative requirement of a mean dose of IV fentanyl was  $41.50 \pm 32.40$  in paracetamol Group (A) and  $84.66 \pm 32.32$  in control Group (B) which is statistically significant ( $P = 0.000$ ) [Table 8 and Figure 4].



**Figure 3: The intergroup comparison of mean arterial blood pressure (MAP in mmHg) changes in response to laryngoscopy and intubation and pneumoperitoneum between control (B) Group and paracetamol (A) Group**



**Figure 4: Requirement of intraoperative dose of IV fentanyl in both groups**



**Figure 5: Comparison of visual analog scale score at different hours postoperatively between control and paracetamol group. IMM POST - immediate post-operative, HRS - hours, and VAS - visual analog scale**

The mean VAS score immediate postoperatively and after 1 h was lower in the paracetamol group with statistically significant  $P = 0.018$  and  $P = 0.003$ , respectively [Table 9 and Figure 5].

The Ramsay sedation score in paracetamol group was less as compared to control group at 1 h ( $P = 0.023$ ), 6 h



**Table 9: Comparison of VAS scores at different hours postoperatively between control and paracetamol group**

VAS score	Group A	Group B	P value
Immediate postoperative	3.03±0.41	3.53±1.04	0.018
1 HR	3.13±0.57	3.90±1.21	0.003
2 HR	3.17±0.59	3.57±1.00	0.066
4 HR	3.73±1.08	3.77±1.16	0.909
6 HR	3.63±1.15	3.87±1.22	0.452
12 HR	4.10±1.34	3.67±0.95	0.157
18 HR	3.60±0.89	3.77±0.85	0.464
24 HR	3.17±0.46	3.50±0.93	0.086

HR: Heart rate, VAS: Visual analog scale

**Table 10: Comparison of Ramsay sedation score at different hours postoperatively between control (B) and paracetamol (A) group**

Ramsay sedation score	Group A	Group B	P value
1 HR	1.433±0.678	1.833±0.647	0.023
2 HR	1.500±0.572	1.566±0.568	0.652
4 HR	1.700±0.702	1.500±0.682	0.268
6 HR	1.200±0.406	1.566±0.727	0.019
12 HR	1.100±0.305	1.433±0.504	0.003

**Table 11: Requirement of first dose of rescue analgesia in both groups**

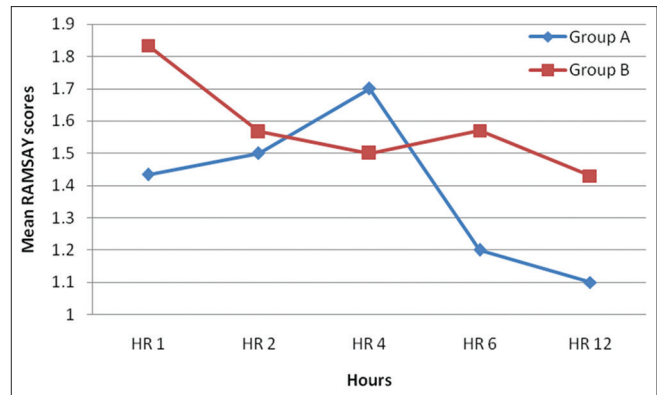
Requirement of dose	Group A	Group B	P value
First dose - rescue analgesia			
Received	26	24	0.000
Not received	4	6	
Mean (hours)	5.84±4.44	1.83±1.09	

**Table 12: Frequency (number of doses) of rescue analgesia**

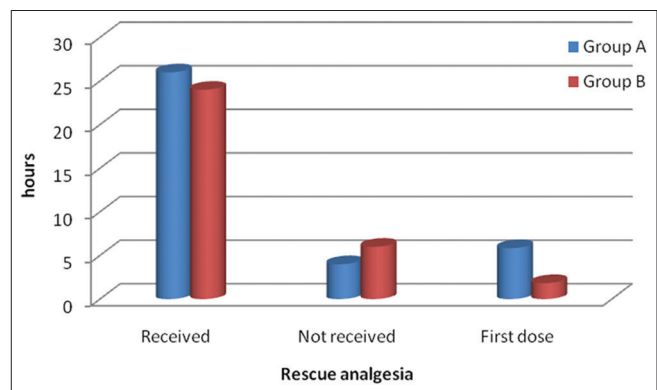
NO of doses	Group A	Group B	P value
Frequency -rescue analgesia			
Mean	1.81±1.0	2.80±0.55	0.000

( $P = 0.019$ ), and at 12 h ( $P = 0.003$ ) postoperatively which was statistically significant [Table 10 and Figure 6].

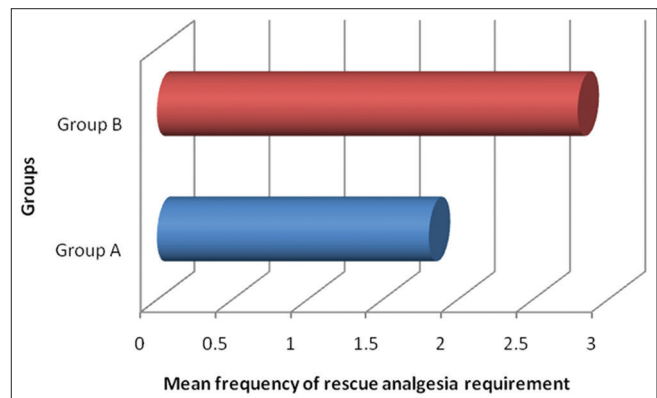
The requirement of the first dose of rescue analgesia in Group (B) was in early hours postoperatively as compared to paracetamol Group (A). The mean hours was 5.83 in Group A and 1.83 in Group B which was statistically highly significant ( $P = 0.000$ ). The 4 patient out of ( $n = 30$ ) did not require rescue analgesia (13.3%) in Group A whereas 6 patient out of ( $n = 30$ ) did not required rescue analgesia (20%) in Group B [Table 11 and Figure 7].



**Figure 6: Comparison of Ramsay sedation score at different hours postoperatively between control (B) and paracetamol (A) Group**



**Figure 7: Requirement of first dose of rescue analgesia in both groups**



**Figure 8: Frequency of rescue analgesia**

The mean frequency (no of doses) of rescue analgesia in paracetamol Group (A) was lower as compared to control Group (B) which was  $1.81 \pm 1.00$  and  $2.80 \pm 0.55$ , respectively, and was statistically highly significant with  $P = 0.000$  [Table 12 and Figure 8].

There was no significant difference found in the incidence of PONV and pruritus in both groups [Tables 13 and 14].

**Table 13: Incidence of PONV between control (B) and Paracetamol group (A)**

PONV	Group A n (%)	Group B n (%)
1 h		
No	28 (93.3)	27 (90)
Yes	2 (6.7)	3 (10)
2 h		
No	28 (93.3)	30 (100)
Yes	2 (6.7)	0 (0.0)
4 h		
No	30 (100)	28 (93.3)
Yes	0 (0.0)	2 (6.7)
6 h		
No	29 (96.7)	30 (100)
Yes	1 (3.3)	0 (0.0)
12 h		
No	29 (96.7)	30 (100)
Yes	1 (3.3)	0 (0.0)
18 h		
No	30 (100)	30 (100)
Yes	0 (0.0)	0 (0.0)

PONV: Post-operative nausea and vomiting

**Table 14: Incidence of pruritus**

Symptom	Group A (%)	Group B (%)	P value
Pruritus			
No	29 (96.7)	28 (93.3)	0.554
Yes	1 (3.3)	2 (6.7)	

## DISCUSSION

The overall pain after laparoscopic cholecystectomy shows individual variation in intensity and duration. Adequate pain control is the mainstay during the post-operative period. Poor pain control may lead to short-term or long-term complications. The complications such as atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism, and myocardial ischemia are related to inadequate pain control.<sup>[12]</sup> The present study was conducted in the Department of Anaesthesiology, CSI Holdsworth Memorial Hospital, Mysuru - 21 during the period of May 2012–May 2013. The study population consisted of 60 patients divided randomly by using computer-generated randomization numbers into two groups with 30 patients in each group. Both the groups were comparable, and there was no statistically significant difference with regard to mean age, weight, and DOS. In this study, efforts have been taken to evaluate the efficacy of IV Paracetamol for post-operative analgesia. Opioids are most commonly used as post-operative analgesics, but the side effects of opioids such as PONV, sedation, and respiratory depression are frequently encountered. Recent studies show opioid-sparing effect of IV paracetamol; therefore, we studied the effects of IV paracetamol.

**Table 15: Studies showing different doses of paracetamol with opioids**

Author and year	Dose of paracetamol	Opioids used
Arici. S <sup>[17]</sup> 2009	1 g 30 min before induction (Group I) and 1 gm before skin closure (Group II)	Morphine
Memis <i>et al.</i> <sup>[19]</sup> 2010	1 g every 6 hourly	Meperidine
Altun <i>et al.</i> <sup>[20]</sup> 2010	1 g - Group I 2 g - Group II	Tramadol
Chaudhury <i>et al.</i> <sup>[21]</sup> 2011	1 g paracetamol just before induction	Fentanyl
Present study	1 g paracetamol 10 min before induction	Fentanyl

**Table 16: Intraoperative hemodynamic observation**

Author and year	Observation
Semih <i>et al.</i> <sup>[13]</sup> 2009	No intraoperative and post-operative change in hemodynamic
Turan <i>et al.</i> <sup>[14]</sup> 2012	No intra-operative change in MAP, HR
Present study	Intraoperative hemodynamic MAP, HR was stable with paracetamol group

## Dose of Paracetamol

In this study, we used single dose IV paracetamol (1 g) as a preemptive analgesic 10 min before induction. Various studies used paracetamol dose of 1 g or 2 g for comparison with different opioids [Table 15].

## Intraoperative Hemodynamics

In laparoscopic cholecystectomy intraoperative hemodynamic alteration is known to occur due to PNP and pain. In this study, we used 1 g (100 mL) IV paracetamol 10 min before induction as a part of the multimodal analgesic regime. Intraoperatively we assessed heart rate, MAP during induction, intubation, PNP, and every 15 min subsequently until extubation. We found there was a significant change in heart rate and MAP with fentanyl group, however, with paracetamol hemodynamic were stable. However, there was no significant change found in intraoperative hemodynamics with paracetamol in studies done by Semih *et al.*<sup>[13]</sup> and Turan *et al.*<sup>[14]</sup> [Table 16].

## Fentanyl Requirement

In this study, as we found there was a significant change in HR and MAP in control Group (B) compared to paracetamol Group (A) from the baseline value; hence, the requirement of fentanyl was more in control group. It may be due to the short-acting nature of fentanyl and significant hemodynamic variation related to different stages of laparoscopy with the control group. Intraoperative consumption of a mean dose of fentanyl was  $41.50 \pm 32.40$  in paracetamol Group (A) as compared

to the control Group (B) which was  $84.66 \pm 32.32$  with statistically significant  $P$  value ( $P = 0.000$ ). Similar results found in a study done by Salihoglu *et al.*,<sup>[15]</sup> there was less opioid consumption intraoperatively inpatient received IV paracetamol [Table 17].

### Rescue Analgesia and Opioid Consumption (Post-operative)

Adequacy of analgesia was assessed postoperatively by Visual Analogue Scale score. We found a significant difference ( $P = 0.012$ ) in mean VAS score between two groups. The mean VAS score immediate postoperatively and after 1 h was lower in paracetamol group  $3.9 \pm 1.21$  and  $3.13 \pm 0.57$  whereas in control group it was  $3.53 \pm 1.04$  with significance  $P = 0.018$  and  $0.003$ , respectively. There was the significant efficacy of paracetamol plus fentanyl for post-operative analgesia. A comparison was made in regard with rescue anaesthesia and opioid consumption in the present study with studies by various authors<sup>[15,18-21]</sup> and found that, Longer time for first rescue analgesia and less opioid consumption in paracetamol group with mean  $5.84 \pm 4.44$  (h) and  $1.83 \pm 1.09$  (h) in fentanyl group ( $P=0.000$ ) was observed, [Table 18]. Overall, the VAS score was lower in the paracetamol group compare with other groups. In this study, the VAS score immediate post-operative and at 1<sup>st</sup> h was significantly lower in the paracetamol group. This may be because of an initial loading dose of paracetamol before induction which provides higher plasma concentration.

### Sedation Score

In the present study, we found the mean time required in hours for first rescue analgesia was  $5.84 \pm 4.44$  in paracetamol group as compared to  $1.83 \pm 1.09$  in control group, respectively, and post-operative fentanyl consumption in terms of a number of doses (frequency) was less in paracetamol group with statistical significance. Our study is comparable with a study done by various studies [Table 19]. Wininger *et al.*<sup>[18]</sup> and Salihoglu *et al.*<sup>[15]</sup> observed there was the longer time required for first rescue analgesia in paracetamol group with less opioid consumption in post-operative period. Choudhery *et al.*<sup>[21]</sup> observed prolonged time required for the first dose of rescue analgesia in paracetamol group with a mean of  $76.0 \pm 24.7$  and  $48.0 \pm 15.8$  (min) in fentanyl group.

In this, it was observed that the sedation score in paracetamol group was less as compared to fentanyl group at 1, 6, and 12 h postoperatively with significant  $P = 0.023$ ,  $0.019$ , and  $0.003$ , respectively. Memis *et al.*<sup>[19]</sup> also noted less sedation score in paracetamol group compared to placebo with significant  $P$  value ( $P < 0.05$ ). Hong *et al.*<sup>[22]</sup> found the sedation score was significantly lower ( $P = 0.019$ ) in the paracetamol group.

**Table 17: Pain intensity score or VAS score observation**

Author and year	VAS score in different group observed
Goroc <i>et al.</i> , <sup>[16]</sup> 2009	Majority of patient VAS score $< 3$ cm at 15 min at the end of surgery in paracetamol group
Semih <i>et al.</i> , <sup>[17]</sup> 2009	VAS score in the control group at rest and movement was higher than the paracetamol group
Wininger <i>et al.</i> , <sup>[18]</sup> 2010	VAS over 24 h more favorable for paracetamol group than placebo. Group with $P < 0.007$ with 1 g IV paracetamol and $P < 0.019$ with 650 mg IV paracetamol, respectively
Memis <i>et al.</i> , <sup>[19]</sup> 2011	VAS score significantly lower in the paracetamol group than placebo group
Choudhury <i>et al.</i> , <sup>[20]</sup> 2011	VAS (mean) score at 1 h was $5.2 \pm 0.9$ and $3.3 \pm 0.4$ ; 2 h was $4.3 \pm 0.3$ and $3.1 \pm 0.4$ in fentanyl group and paracetamol group, respectively
Present study	VAS mean score at the immediate post-operative period and 1 <sup>st</sup> h was $3.53 \pm 1.04$ and $3.03 \pm 0.41$ , and 1 h was $3.9 \pm 1.21$ and $3.13 \pm 0.57$ in fentanyl (control) group and paracetamol group, respectively

**Table 18: Requirement of rescue analgesia and opioid consumption**

Author and year	Rescue analgesia observation
Salihoglu <i>et al.</i> , <sup>[15]</sup> 2009	Longer time for first rescue with paracetamol
Wininger <i>et al.</i> , <sup>[18]</sup> 2010	Longer median time to first rescue, less proportion of requirement of rescue analgesia in paracetamol group
Memis <i>et al.</i> , <sup>[19]</sup> 2011	Significant lower postoperative opioid consumption ( $P < 0.005$ )
Choudhury <i>et al.</i> , <sup>[21]</sup> 2011	Prolonged time of first rescue analgesia in paracetamol group with mean of $76.0 \pm 24.7$ (min) and $48.0 \pm 15.8$ (min) in fentanyl group
Present study	Longer time for first rescue analgesia and less opioid consumption in paracetamol group with mean $5.84 \pm 4.44$ (h) and $1.83 \pm 1.09$ (h) in fentanyl group ( $P=0.000$ )

**Table 19: Sedation score**

Author and year	Sedation score observed
Memis <i>et al.</i> , <sup>[19]</sup> 2011	Less sedation in paracetamol group with significant $P < 0.05$
Hong <i>et al.</i> , <sup>[22]</sup> 2012	Sedation score was significantly lower in paracetamol group with $P=0.019$
Present study	Sedation score was lower in paracetamol group postoperatively with significant $P=0.023$ , $0.019$ , and $0.003$ at 1 <sup>st</sup> , 6 <sup>th</sup> , and 12 <sup>th</sup> h, respectively

### Post-operative Side Effects

There was no significant difference found in the incidence of PONV and pruritus between two groups in our study. This was in agreement with the study done by Petterson *et al.*<sup>[23]</sup> and Choudhury *et al.*<sup>[21]</sup> they found that there was no significant difference in PONV in two comparable groups.

### SUMMARY

The present study entitled “A prospective randomized double-blind study comparing IV paracetamol plus fentanyl and IV fentanyl alone for post-operative analgesia during Laparoscopic cholecystectomy” was conducted in the Department of Anaesthesiology, CSI Holdsworth Memorial Hospital, Mysuru - 21 during the period of May 2012–May 2013. 60 patients, scheduled for elective laparoscopic cholecystectomy belonging to ASA Class I and II, age group 18–65 years were included in the study. Patients with known hypersensitivity to paracetamol and fentanyl, abnormal coagulation profile, hepatic or renal insufficiency, and open cholecystectomy were excluded from the study. Based on the computer-generated randomization numbers, patients were randomly divided into two groups with 30 patients in each group. Group A (paracetamol + fentanyl group): Received 100 mL of paracetamol IV (1 g) 10 min before induction. Group B (fentanyl alone group): Received 100 mL of normal saline 10 min before induction. After the preoxygenation for 3 min, patients in both the groups were induced with injection fentanyl 2 µg/kg, injection propofol 2 mg/kg, and injection rocuronium 0.6 mg/kg. Laryngoscopy and endotracheal intubation were done, and lungs were mechanically ventilated. Anesthesia was maintained with O<sub>2</sub> in N<sub>2</sub>O (66%:33%), isoflurane 1%, and intermittent bolus dose of rocuronium. Fentanyl was repeated in a dose of 1 µg/kg intraoperatively if both HR and MAP increased >15–20% from baseline despite maintaining adequate depth of anaesthesia. The intraoperative hemodynamic monitoring such as SBP, DBP, MAP, and HR was done after induction of the patient in every 15 min interval, and intraoperative requirement of IV fentanyl was noted and recorded. There was better intraoperative hemodynamic stability with paracetamol group compared to fentanyl group. There was a significant reduction in pain intensity score (VAS) immediate postoperatively and at 1 h with IV paracetamol. The intraoperative and post-operative requirement of opioid was less with patients receiving IV paracetamol and IV fentanyl than the IV fentanyl alone. The sedation score was lesser with IV paracetamol as the number of doses opioid requirement was lesser compared to fentanyl group. There was no difference found in PONV, pruritus, and other opioid-related side effects such as bradycardia, hypotension, and respiratory depression in

both the groups.

### CONCLUSION

The use of IV paracetamol 1 g for preemptive analgesia as an adjunct to IV fentanyl in patients undergoing laparoscopic cholecystectomy had better intraoperative hemodynamic parameters, good quality post-operative analgesia, reduced consumption of fentanyl doses and lesser sedation in post-operative period. Therefore, we recommend preemptively administered IV paracetamol 1gm can be safely administered for postoperative analgesia in laparoscopic cholecystectomy.

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# A Prospective, Double Blind, Randomized Study to Compare the Analgesic Effect of Oral Clonidine and Oral Pregabalin for Perioperative Pain in Lower Abdominal Surgeries

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## Abstract

**Background and Aims:** The aim of this study is to compare the post-operative analgesic properties of oral clonidine versus oral pregabalin used preemptively.

**Materials and Methods:** Our study included 64 patients of both sex, aged between 18 and 50 years of ASA Grade I and II, scheduled for lower abdominal surgeries. Group A patients were provided with oral clonidine in a dose of 200 mcg 45 min before the scheduled operation. Group B patients were given oral pregabalin in a dose of 150 mg 45 min before the schedule time of operation. Various parameters were recorded such as intra- and post-operative hemodynamics, post-operative visual analog scale scores, time to first rescue analgesic, and mean doses of analgesic required in the post-operative period and the associated side effects of the drugs used in the study.

**Results:** Group A had least intraoperative cardiovascular stability and Group B had best intraoperative and post-operative cardiovascular stability. Group B patients showed maximum post-operative analgesia requirement. Overall, side effects were highest in Group B.

**Conclusion:** It could be concluded that the use of preemptive pregabalin provides excellent hemodynamic stability while superior analgesia, less post-operative analgesic requirement was observed with the preemptive use of oral clonidine.

**Key words:** Clonidine, Post-operative analgesia, Pregabalin

## INTRODUCTION

Perioperative pain management is one of the major topics of interest for anesthesiologists. Post-operative pain has a direct relation with hospital stay that leads to more morbid complications and extra hospital costs. The cutting of the skin stimulates nerve fibers (myelinated A-delta and unmyelinated C fibers) which signal pain to the brain

through the spinal cord. As the body begins to heal or the noxious stimulus is withdrawn, pain should decrease and eventually stop. Steps can be taken to minimize or eliminate pain.

A person's self-report is considered the most reliable measure of pain.<sup>[1]</sup> Many pain scoring systems have been formed for assessment of pain such as visual analog scale (VAS), verbal numerical scale, and word scale which employ scale from 0 (no pain at all) to 10 (worst pain ever felt).

Many drugs are used for pain management in perioperative period such as opioids (most commonly used), nonsteroidal anti-inflammatory drugs, selective cyclo-oxygenase-2 inhibitors, local anesthetics, alpha-2 adrenergic agonists, alpha-2 delta receptor modulators, N-methyl-D-aspartate

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antagonists, and glucocorticoids.<sup>[2]</sup> Due to their side effects (when used alone or in higher doses), anesthesiologists are more inclined these days to employ multimodal analgesia technique using combination of different classes of analgesics with different mechanism of action and acting at different sites in the nervous system either central or peripheral, resulting in additive/synergistic analgesia with lowered side effects.<sup>[3]</sup> There had been a continuous search for newer and better drugs for the benefit and safety of the patient, surgeon, and anesthesiologist.

Clonidine is an imidazoline derivative having predominantly alpha-2 adrenergic activity. It is commonly used for its: (a) Anti-hypertensive and negative chronotropic effects, (b) sedative and anxiolytic properties, and (c) anesthetic and analgesic effects.<sup>[4]</sup>

### Mechanism of Action

Drug being highly lipid soluble penetrates blood–brain barrier. Binding of the drug to the receptors is highest in the rostral ventrolateral medulla in the brain stem, which is the final common pathway for the sympathetic outflow, where it activates inhibitory neurons. The antihypertensive action is exhibited by binding of the drug to imidazoline receptors (non-adrenergic) in brain. Analgesic effect is mediated by blocking nociceptive transmission through pre- and post-synaptic alpha-2 adrenergic receptors. Overall effect (a) decreased sympathetic activity, (b) enhanced parasympathetic tone, and (c) reduced circulating catecholamines.<sup>[5]</sup>

Clonidine is available in various forms for oral, intramuscular, intravenous, intrathecal, epidural, and transdermal patch use. Oral dose: 3–5 µg/kg, onset: 30–60 min, duration of action: 8–12 h, bioavailability: 95%, urinary excretion: 62%, and plasma bound: 20%.<sup>[6]</sup>

### Side Effects

- A. More common: Sedation, dizziness, bradycardia, dry mouth, and hypotension.
- B. Less common: Anxiety, nausea/vomiting, diarrhea, erectile dysfunction, weight gain/loss, and rash.
- C. Uncommon: Hallucination, paraesthesia, itching, and nightmares.
- D. Rare: Gynecomastia, alopecia, and hyperglycemia.

It is known to cross the placenta and has been kept in pregnancy category C. Caution has been warranted in breastfeeding women as it can pass into breast milk.<sup>[7]</sup>

Pregabalin is a lipophilic gamma aminobutyric acid (GABA) analog substituted at the 3'-position to facilitate diffusion across the blood–brain barrier. It was invented by medicinal

chemist Richard Bruce Silverman at Northwestern University in the United States.<sup>[8]</sup>

Pregabalin is commonly used: (a) As an adjunct to the treatment of partial seizures, (b) for neuropathic pain management (diabetic peripheral neuropathy and postherpetic neuralgia), and (c) for anxiolysis and sleep modulation.

### Mechanism of Action

It does not directly act on GABA receptors but modifies the synaptic and non-synaptic release of GABA by binding avidly to alpha-2 delta sub-unit of pre-synaptic voltage-gated Ca<sup>++</sup> channels. Hence, it does not alter GABA uptake and degradation. This binding results in a reduction of the release of several neurotransmitters including glutamate, noradrenaline, serotonin, dopamine, and substance P.<sup>[9]</sup>

Pregabalin is not metabolized and is not bound to plasma proteins. Hence, virtually there is no drug–drug interaction. It is almost entirely (98%) excreted unchanged in urine. Pregabalin elimination is nearly proportional to creatinine clearance.

Oral dose: 150–600 mg/day in 2–3 divided doses, onset: 45–60 min, duration of action: 4.5–7.0 h, bioavailability: >90%, urinary excretion: 98%, plasma bound: Nil.<sup>[10]</sup>

Side effects: (a) Very common: Somnolence and dizziness, (b) common: Dry mouth, blurred vision/diplopia, peripheral edema, weight gain/increased appetite, and abnormal thinking, (c) in-frequent: Depression, lethargy, tachycardia, myoclonus, anorgasmia, agitation, and hallucinations, and (d) rare: Neutropenia, hypotension, and dysphagia.

It has been categorized as Schedule V controlled substance in the United States.<sup>[11]</sup>

The aims and objective of this study were to compare the analgesic effect of oral clonidine and oral pregabalin for perioperative pain in lower abdominal surgeries with the assessment of hemodynamic effects and compare the side effects of both the drugs.

## MATERIALS AND METHODS

### Study Design

This was a hospital-based, cross-sectional, and observational (comparative) study.

### Study Area

The study is conducted in a tertiary care level institute in Peoples College of Medical Sciences and Research Centre (PCMS and RC), Bhopal.

### Study Population

Patients posted for lower abdominal surgeries admitted at PCMS and RC, Bhopal.

### Sample Size and Group Division

Sample size includes all the patients coming in the defined period and fulfilling the inclusion criteria ( $n = 64$ ). Subjects are equally divided into 2 groups, i.e., Group A (clonidine) and Group B (pregabalin).

### Inclusion Criteria

The following criteria were included in the study:

- All cases of ASA Grade 1 and 2.
- Age group 18–60 years.
- Weight 40–65 kg.
- Patients undergoing lower abdomen surgeries under spinal anesthesia.

### Exclusion Criteria

The following criteria were excluded from the study:

- All cases of ASA Grades 3-6 and E.
- All patients who have contra-indication(s) to spinal anesthesia.
- Patients undergoing upper abdominal surgeries.
- Pregnant patients.
- Renal insufficiency patients.
- Surgeries performed under general anesthesia.

### Premedication and Anesthetic Procedure

After complete pre-anesthetic check-up and obtaining valid written informed consent, the subjects went through the following.

#### In the Pre-operative Room

Recording the baseline vitals (pulse rate, blood pressure, respiratory rate, oxygen saturation, and cardiac rhythm).

Given oral drug with a sip of water 45 min before the commencement of surgery.

- Group A (pregabalin) received Cap. pregabalin 150 mg.
- Group B (clonidine) received Tab. clonidine 0.2 mg.

Pre-loading is done with 500 mL of ringer lactate after taking the vitals and giving the drug.

#### In the Operative Room

For pre-medication, injection ranitidine 50 mg and injection ondansetron 4 mg are given.

Undertaking all aseptic precautions, lumbar puncture is performed at L<sub>3</sub>–L<sub>4</sub> level space using 25 G Quincke's needle, with the subject in sitting position. 3.5 mL injection bupivacaine (0.5%, hyperbaric) is injected intrathecally, and then the subject is turned supine for fixation of the drug.

No intraoperative sedative or analgesic was given.

Intraoperative monitoring of pulse rate, blood pressure, electrocardiogram, and SPO<sub>2</sub> is done. For the first 15 min, the vitals are recorded after every 3 min, and after that, vitals are recorded after every 5 min until the surgery is over.

### In the Surgical Intensive Care Unit

Post-operative on demand analgesia requirement is calculated in 24 h.

Injection diclofenac 75 mg (intravenous in 100 mL of normal saline) to be given on pain of grade more than 3 on VAS.

### VAS Scale

- Grade 0: No pain
- Grade 1–3: Mild pain (can be ignored)
- Grade 3–5: Moderate pain (interferes with tasks)
- Grade 5–7: Moderate pain (interferes with concentration)
- Grade 7–9: Severe pain (interferes with basic needs)
- Grade 9–10: Worst pain possible (bed rest required).

Any side effects such as hypotension, bradycardia, nausea, vomiting, sedation, dry mouth and pruritis are noted.

Hypotension (fall in mean arterial pressure of more than 20% of pre-induction value) is treated by pushing intravenous fluids, and with an intravenous bolus of vasopressor drug (injection mephentermine 6 mg) if not manageable with fluids alone.

Any episode of bradycardia (heart rate <60/min) is treated with increments of 0.02 mg/kg of I.V. atropine.

All the drugs used in the study are sourced from the same manufacturer.

### Statistical Analysis

Statistical analysis was performed using Statistical Package of the Social Sciences (SPSS Version 20.0; Chicago Inc., USA). Data comparison was done by applying specific statistical tests to find out the statistical significance of the comparisons. Quantitative variables were compared using mean values and qualitative variables using proportions. The significance level was fixed at  $P \leq 0.05$ .

## RESULTS

Table 1 shows the demographic distribution of study subjects according to age and gender. The mean age in Group A is 34.25 years and Group B is 41.75 years. The average age of study group is 38 years.



Table 2 shows the distribution of study subjects according to type of surgery and mean duration of surgery in minutes. The subjects were distributed according to the type of surgery and crudely categorized into three types (Types 1–3) according to the pain felt in the surgery. In Type 1, mild pain surgeries such as hydrocoele and sinus tract surgeries were considered. Type 2 included moderate pain surgeries such as hernia, hemorrhoids, and fistula while Type 3 included severe pain surgeries such as hysterectomy, orchidectomy, and appendicectomy.

Type 1 surgery included 22 (34.4%) subjects among which 16 (50.0%) subjects were from Group A and the rest of the 6 (18.8%) subjects were from Group B. Similarly, Type 2 surgery included 26 (40.6%) subjects, 8 (25.0%) subjects from Group A, and 18 (56.2%) subjects from Group B. Type 3 surgery constituted 16 (25.0%) subjects in total and equal number of subjects from Groups A and B, i.e., 8 (25.0%) subjects each. On applying Chi-square test, value came out to be 8.392. The derived  $P = 0.015$ , which is significant.

Mean duration of surgery in Group A was  $97.81 \pm 41.23$  min and Group B was  $102.1 \pm 40.99$  min. The

calculated  $t$  value came out to be 0.426. The calculated  $P$  value comes out to be 0.672 which is not significant.

Table 3 shows the demographic distribution of subjects under study according to type of pain and analgesic requirement. The pain intensity was assessed using a 10-cm VAS. VAS = 1–3 denoting mild pain, VAS = 3–5 denoting moderate pain (interferes with task), and VAS = 5–7 denoting moderate pain (interferes with concentration). In a total of 64, 16 (25%) subjects experienced mild pain, 40 (62.5%) subjects experienced moderate pain (interferes with task) while only 8 (12.5%) subjects experienced severe pain (interferes with concentration). It is observed that the moderate pain (interferes with task) was experienced by the highest number of subjects followed by the subjects who experienced mild pain while moderate pain (interferes with concentration) was observed in the least number of subjects.

Among the 50% subjects of Group A 12 subjects experienced mild pain, 18 subjects experienced moderate pain (interferes with task) and only 2 subjects experienced moderate pain (interferes with concentration) while in

**Table 1: Demographic distribution of study subjects according to age and gender**

Gender	Group A clonidine $n$ (%)	Group B pregabalin $n$ (%)	Total $n$ (%)	Chi-square value	$P$ value
Male	22 (68.8)	16 (50.0)	38 (59.4)	2.332	0.127 (NS)
Female	10 (31.2)	16 (50.0)	26 (40.6)		
Age (year)				6.926	0.008 (S)
18–40 years	26 (81.2)	16 (50.0)	42 (65.6)		
41–60 years	6 (18.8)	16 (50.0)	22 (34.4)		
Total	32	32			
Mean age	34.25 years	41.75 years			
Total mean age	38.0 years				

**Table 2: Distribution of study subjects according to type of surgery and mean duration of surgery in minutes**

Type of surgery	Group A clonidine $n$ (%)	Group B pregabalin $n$ (%)	Total $n$ (%)	Chi-square value	$P$ value
Type 1	16 (50.0)	6 (18.8)	22 (34.4)	8.392	0.015(S)
Type 2	8 (25.0)	18 (56.2)	26 (40.6)		
Type 3	8 (25.0)	8 (25.0)	16 (25.0)		
Duration of surgery (minutes)					
Mean $\pm$ SD	97.81 $\pm$ 41.23	102.1 $\pm$ 40.99			
Student $t$ -test	0.426				
$P$ value	0.672 (NS)				

**Table 3: Type of pain and analgesic requirement among Group A and B**

Type of pain	Group A clonidine $n$ (%)	Group B pregabalin $n$ (%)	Total $n$ (%)	Chi-square value	$P$ value
Mild pain (VAS=1–3)	12 (37.5)	4 (12.5)	16 (25.0)	6.400	0.041 (S)
Moderate pain (VAS=3–5)	18 (56.2)	22 (68.8)	40 (62.5)		
Severe pain (VAS=5–7)	2 (6.2)	6 (18.8)	8 (12.5)		
Analgesic requirement				5.333	0.021 (S)
Yes	20 (62.5)	28 (87.5)	48 (75.0)		
No	12 (37.5)	4 (12.5)	16 (25.0)		

VAS: Visual analog scale

the Group B there were only 4 subjects who experienced mild pain, 22 subjects who experienced moderate pain (interferes with task) and 6 subjects experienced moderate pain (interferes with concentration).

The calculated Chi-square value is 6.400 and *P* value came out to be 0.041 which significant.

Out of total 64 subjects, the analgesia was given in only 48 (75%) subjects while no requirement of analgesia was found in the remaining 16 (25%) subjects. The cumulative analgesic requirement was statistically significantly less for Group A than Group B. From Group A; there were 20 subjects who were given analgesia while 28 subjects were given analgesia in Group B. Furthermore, the subjects with analgesic requirement are far more than those without it. In Group A, there is no significant difference in the subjects with and without analgesic request. On the contrary, major portion of the population from Group B required analgesia leaving just 4 subjects in which no analgesia was given. It can be said that the requirement of analgesia is high in pregabalin group. The calculated Chi-square value is 5.333 and *P* value came out to be 0.021 which is highly significant.

Table 4 shows mean VAS, mean time to 1<sup>st</sup> dose of analgesic, and mean required total dose of analgesic among Groups A and B. It was observed that the mean VAS score for Group A was  $4.13 \pm 1.008$  and the mean time to 1<sup>st</sup> dose analgesic was  $375 \pm 233.84$  min with required  $84.38 \pm 80.25$  mg total dose of analgesic. On the other hand, the mean VAS score for Group B was  $4.81 \pm 0.089$ . The mean time to 1<sup>st</sup> dose of analgesic with  $117.19 \pm 71.11$  mg required a total dose of analgesic was  $316.25 \pm 285.33$  min.

### Demographic Distribution of Subjects Under Study According to Side Effects in Perioperative Period among Groups A and B

The side effects such as bradycardia, hypotension, sedation, and dry mouth were observed in the perioperative period. Among 64 subjects, bradycardia was observed in 22 (20%) subjects, hypotension was observed in 28 (25%) subjects, sedation was observed in 38 (35%) subjects, and dry mouth was observed in 22 (20%) subjects. It is clear that the overall incidence of sedation is highest, followed by hypotension, whereas the incidence of bradycardia and dry mouth is least.

It can be seen that the incidence of side effects is more in Group A as compared to Group B. Among Group A, bradycardia was observed in 20 subjects, hypotension was observed in 22 subjects, sedation was observed in 18 subjects, and dry mouth was observed in 6 subjects. Furthermore, the incidence of hypotension was highest in Group A, followed by bradycardia, sedation, and incidence of dry mouth was least in Group A. On the other hand, 2, 6, 20, and 16 subjects from Group B had side effects of bradycardia, hypotension, sedation, and dry mouth, respectively. It was observed that the incidence of bradycardia was least, followed by hypotension, dry mouth, and sedation. The incidence of sedation was highest in Group B [Table 5].

The incidence of bradycardia was observed in 20 (62.5%) subjects from Group A and 2 (6.2%) subjects from Group B. Among Group A, mean baseline heart rate was  $74.56 \pm 7.474$  and mean last heart rate was  $60.31 \pm 5.025$ . For Group B, the noted value of mean baseline heart rate was  $78.69 \pm 8.014$  and that of mean last heart rate was  $70.00 \pm 7.397$ . The calculated Chi-square value is 22.442 and the calculated *P* = 0.001 which is highly significant [Table 6].

**Table 4: Mean VAS, mean time to 1<sup>st</sup> dose of analgesic and mean required total dose of analgesic among Groups A and B**

Group	VAS (0–10)	Time to 1 <sup>st</sup> dose of analgesic (min)	Required total dose of analgesic (mg)
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A clonidine	4.13 $\pm$ 1.008	375.00 $\pm$ 233.84	84.38 $\pm$ 80.25
Group B pregabalin	4.81 $\pm$ 0.896	316.25 $\pm$ 285.33	117.19 $\pm$ 71.11
Student <i>t</i> -test	2.884	0.901	1.731
<i>P</i> value	0.005 (HS)	0.371 (NS)	0.058 (S)

VAS: Visual analog scale

**Table 5: Bradycardia among Groups A and B**

Group	Baseline heart rate	Last heart rate	Bradycardia <i>n</i> (%)		Chi-square value	<i>P</i> value
	Mean $\pm$ SD	Mean $\pm$ SD	Yes	No		
Group A clonidine	74.56 $\pm$ 7.474	60.31 $\pm$ 5.025	20 (62.5)	12 (37.5)	22.442	0.001 (HS)
Group B pregabalin	78.69 $\pm$ 8.014	70.00 $\pm$ 7.397	2 (6.2)	30 (93.8)		
Student <i>t</i> -test	2.129	6.128				
<i>P</i> value	0.037 (S)	0.001 (HS)				

**Table 6: Mean systolic and diastolic blood pressure among Group A and B**

Group	Baseline systolic BP	Last systolic BP	Baseline diastolic BP	Last diastolic BP
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Group A clonidine	115.13 $\pm$ 6.84	101.31 $\pm$ 7.315	73.94 $\pm$ 5.886	62.25 $\pm$ 4.745
Group B pregabalin	125.50 $\pm$ 11.37	111.31 $\pm$ 8.775	81.75 $\pm$ 8.948	68.94 $\pm$ 7.286
Student <i>t</i> -test	4.422	4.952	4.126	4.351
<i>P</i> value	0.001 (HS)	0.001 (HS)	0.001 (HS)	0.001 (HS)

**Table 7: Hypotension and bradycardia among Groups A and B**

Group	Hypotension <i>n</i> (%)		Bradycardia <i>n</i> (%)	
	Yes	No	Yes	No
Group A clonidine	22 (68.8)	10 (31.2)	20 (62.5)	12 (37.5)
Group B pregabalin	6 (18.8)	26 (81.2)	2 (6.2)	30 (93.8)
Total	28 (43.8)	36 (56.2)	22 (34.37)	42 (65.63)
Chi-square value	16.254		22.442	
<i>P</i> value	0.001 (HS)		0.001 (HS)	

**Table 8: Sedation and dry mouth in perioperative period among Groups A and B**

Group	Sedation <i>n</i> (%)		Dry mouth <i>n</i> (%)	
	Yes	No	Yes	No
Group A clonidine	18 (56.2)	14 (43.8)	6 (18.8)	26 (81.2)
Group B pregabalin	20 (62.5)	12 (37.5)	16 (50.0)	16 (50.0)
Total	38 (59.4)	26 (40.6)		
Chi-square value	0.259		6.926	
<i>P</i> value	0.611 (NS)		0.008 (S)	

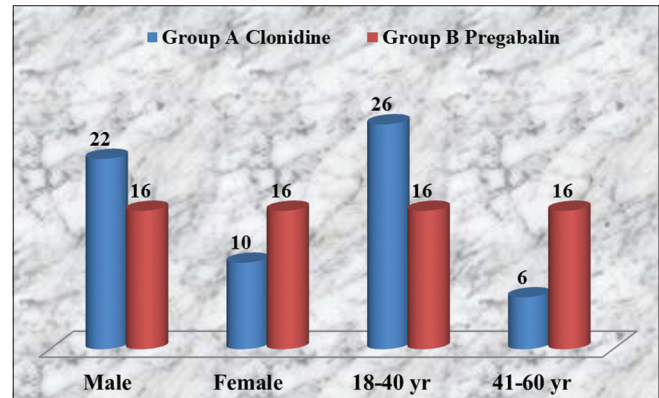
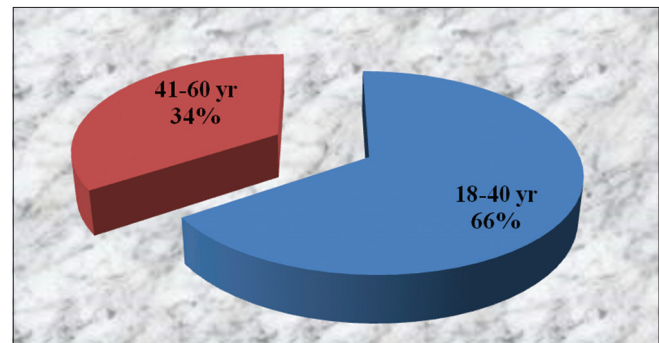
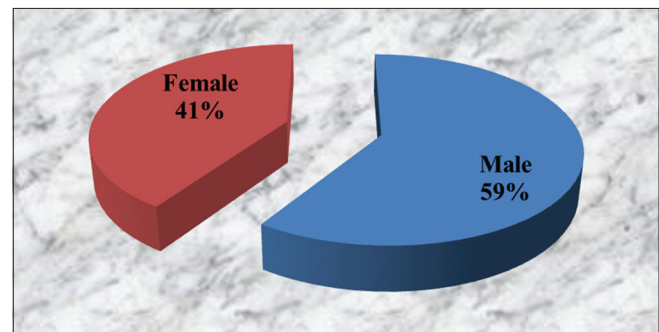
The incidence of hypotension was observed in 25% subjects. The values for BP are high for Group B in comparison to Group A. The calculated *P* value in all the cases was 0.001 which is highly significant [Table 7].

On comparing the occurrence of bradycardia and hypotension, it was observed that the incidence of both is high in Group A than Group B. Among Group A, both the incidences are approximately same but in Group B, the incidence of bradycardia is more than hypotension [Table 8].

The remaining side effects with the equal incidence of 20% were sedation and dry mouth. The incidence of both the side effects is high in Group B with 20 (62.5%) subjects suffering sedation and 16 (50.0%) subjects having problem of dry mouth. It can also be observed that there is no significant difference in the number of subjects with sedation among both the groups [Figures 1-11].

## DISCUSSION

Clonidine is an  $\alpha_2$  adrenergic agonist that produces dose-dependent analgesia at spinal and supraspinal sites. Oral

**Figure 1: Demographic distribution of study subjects according to age and gender****Figure 2: Demographic distribution of study subjects according to age****Figure 3: Demographic distribution of study subjects according to gender**

clonidine is almost completely absorbed, and peak plasma concentration is reached after 1–3 h of administration. It is highly lipid soluble and crosses the blood–brain barrier



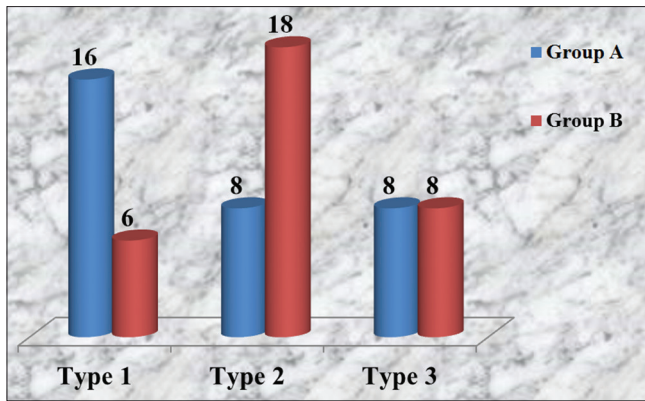


Figure 4: Distribution of study subjects according to type of surgery

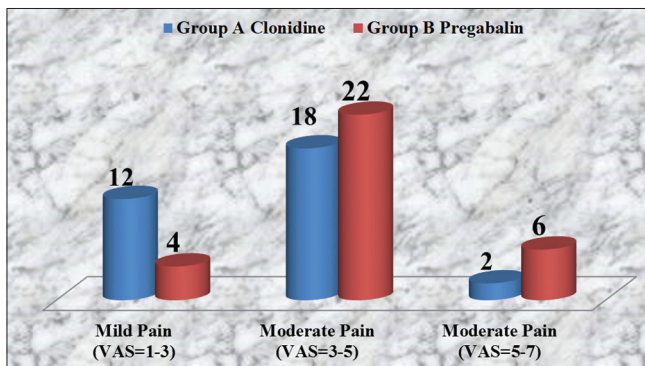


Figure 5: Distribution according to type of pain

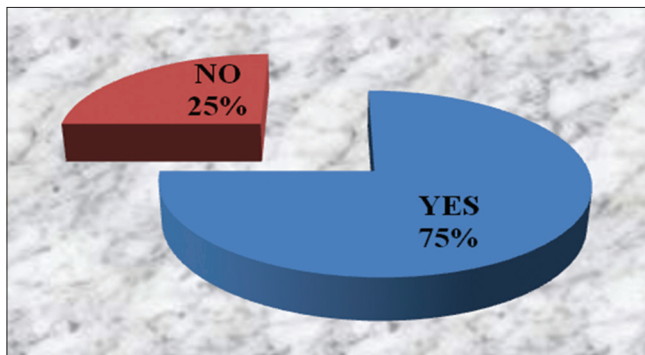


Figure 6: Analgesic requirement among Groups A and B

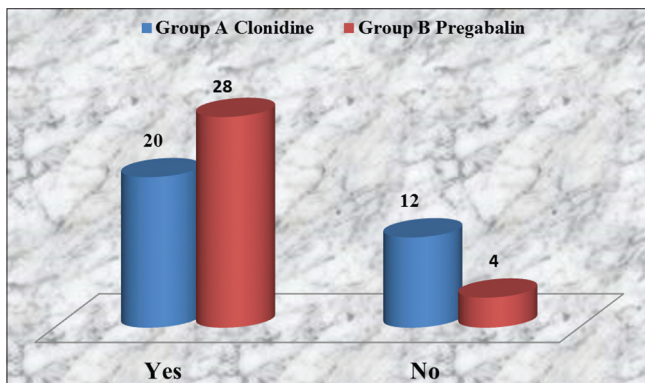


Figure 7: Analgesic requirement among Groups A and B

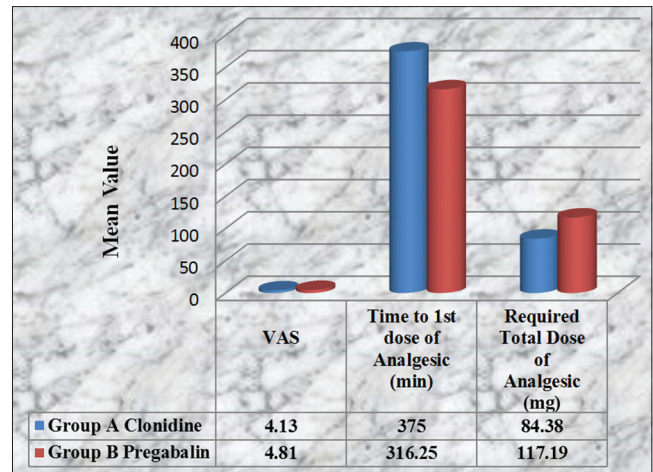


Figure 8: Mean visual analog scale, mean time to 1<sup>st</sup> dose of analgesic and mean required total dose of analgesic among Groups A and B

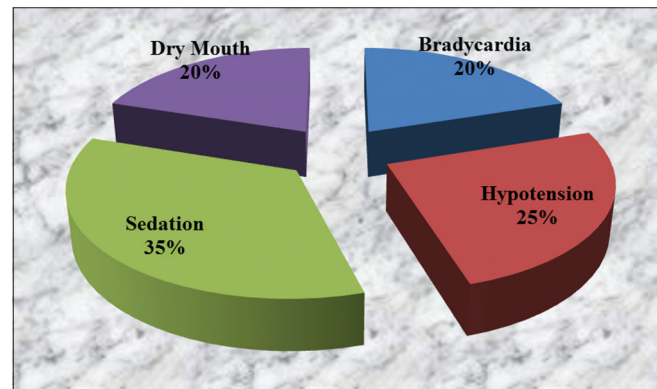


Figure 9: Incidence of side effects in peri-operative period

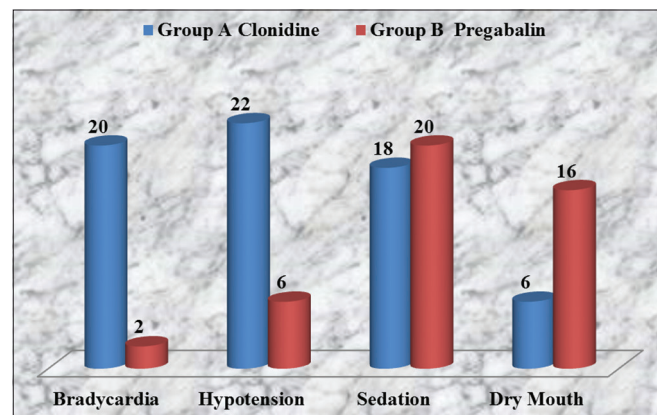
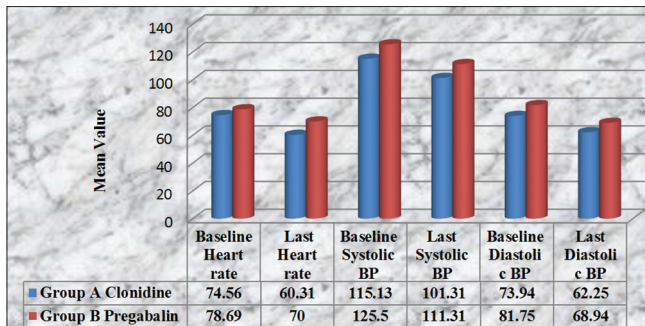


Figure 10: Side effects in perioperative period among Groups A and B

easily. It is an imidazoline derivative commonly used as antihypertensive, sedative, anxiolytic, and analgesic. Clonidine is licensed for the treatment of hypertension, migraine, and menopausal flushing.<sup>[12]</sup> Analgesic effect of clonidine is mediated by blocking nociceptive transmission through pre- and post-synaptic  $\alpha_2$  adrenergic receptors. It is





**Figure 11: Mean systolic and diastolic blood pressure among Groups A and B**

metabolized in the liver and excreted by kidneys. Clonidine used in the study was through the oral route with dose 0.2 mg (200 µg).

Pregabalin is a lipophilic GABA analog substituted at the 3'-position to facilitate diffusion across the blood-brain barrier. Pregabalin is used for partial seizures and as an anxiolytic. Pregabalin was shown to be effective in neuropathic pain, incisional injury, and inflammatory injury.[13] It modifies the synaptic and non-synaptic release of GABA by binding to  $\alpha_2 \delta$  subunit of pre-synaptic voltage-gated  $Ca^{++}$  channels. It is almost entirely excreted unchanged in urine. The oral dose used is 150–600 mg.

The rationale for the dose selection (150 mg for pregabalin and 0.2 mg for clonidine) is that it adequately sedates the patient and the hemodynamic stability is maintained. When individually concerned, pregabalin attenuates the pressor response to tracheal intubation in adults if given 1 h before surgery.[14] Clonidine at its low dose results in less bradycardia and hypotension during spinal anesthesia. A test dose of 150 mg of oral pregabalin was based on the studies where such a dose produced no acute hemodynamic alterations as well as sedation.[15]

In our study, 0.2 mg of oral clonidine and 150 mg of oral pregabalin were given 45 min before the commencement of surgery which prolonged the duration of analgesia. On pain of VAS >3, rescue analgesia (injection diclofenac 75 mg i.v. in 100 mL of normal saline) was given.

This study was a prospective study where total 64 subjects were divided into two groups, i.e., Group A where oral clonidine was used and Group B in which oral pregabalin was used in the subjects.

There was no significant difference found in the demographic distribution of study subjects according to age and gender. However, there was statistically significant result in analgesic requirement and side effects of the drug in the mentioned study groups.

### Analgesic Effect of the Drug on Subjects in Both the Groups

In this study, as far as the analgesic effect of oral clonidine and pregabalin taken to an account,  $P$  value came out as 0.015 which is significant. In a study conducted by Bafna *et al.*<sup>[16]</sup> where oral pregabalin was used for post-operative analgesia in gynecological surgeries, the results came as significant with  $P < 0.001$  hence, showing longer mean duration and effective analgesic property of both the drugs.

### Additional Analgesic Requirement

In the study Group A, 48 (75.0%) required whereas 16 (25.0%) do not required any additional analgesia. In the study conducted by Kolarkar *et al.*, it was concluded that pregabalin proved to have a better analgesic effect, reducing the total consumption of post-operative analgesia as compared to the placebo group.<sup>[17]</sup> There was a meta-analysis evaluating the addition of  $\alpha_2$  agonist on post-operative pain following surgery by Blaudszun *et al.* This review concluded that perioperative clonidine use decreases the post-operative opioid consumption, pain intensity, and nausea without prolonging the recovery times.<sup>[18]</sup> In our study, the requirement of post-operative analgesia is slightly more in pregabalin group which may explain as it was used in low dose and its better effect on mild pain as compared to moderate or severe pain on VAS.

### Drugs Side Effects

On observing both drug groups, the study came out with the result that side effects such as sedation found in (35%) followed by hypotension (25%) and dry mouth, and bradycardia (20%) each with maximum subjects included in the Group A, i.e., in clonidine group. In Group A (clonidine), bradycardia and hypotension were observed in the majority of subjects while side effects such as sedation and dry mouth in Group B (pregabalin) subjects. Common side effects of both the drugs include dizziness and dry mouth. Sedation and bradycardia are usually more seen with clonidine while somnolence and disturbed vision is with pregabalin. Gupta *et al.*<sup>[14]</sup> studied the side effects of oral pregabalin and oral clonidine where she concluded that there is an increased incidence of intra- and post-operative bradycardia with oral clonidine. However, clonidine is still considered superior to pregabalin for attenuation of hemodynamic responses. Prasad *et al.* concluded in her study that oral pregabalin 150 mg prolong the post-operative pain relief after spinal anesthesia but produces less sedation as compared with oral clonidine.<sup>[15]</sup>

### Hemodynamic Response of the Drug

As far as blood pressure was concerned, clonidine group showed 22 cases of hypotension and pregabalin with 6 cases which proved that oral clonidine causes more decrease in blood pressure as compared to oral pregabalin. In the study conducted by Gupta *et al.* where 150 mg of

oral pregabalin and 0.2 mg of oral clonidine were used, it concluded that clonidine was superior to pregabalin for attenuation of the hemodynamic responses to surgery, without prolongation of recovery times and side effects.

Thus, overall; oral clonidine and oral pregabalin prolong the time period for the first dose of analgesic requirement, in lower abdominal surgeries conducted under the subarachnoid block.

## CONCLUSION

This study was a hospital-based, cross-sectional, and observational (comparative) study. 64 subjects of ASA physical status 1 and 2, between the age of 18 and 60 years were divided into two groups of 32 subjects each. Group A (clonidine) received tab. Clonidine 200 µg and Group B (pregabalin) received cap. Pregabalin 150 mg orally, with a sip of water, approximately 45 min before the surgery (after recording the baseline vitals). Time for the first dose of analgesia and total analgesic requirement in the 24 h was recorded, and hemodynamic stability and side effects of the drugs were also observed.

Both groups were comparable with respect to the demographic distribution of age and gender. Type and duration of surgery, type of pain (based on VAS), analgesic requirement, and adverse effects of the drugs were also comparable.

On the basis of age, the subjects recruited in our study were of age between 18 and 60 years. The mean age of total, Group A and B subjects came out to be 38.0, 34.25, and 41.75 years, respectively, which is highly significant for age in two study groups. There was no statistical significance of gender in both the study groups.

Mean duration of surgery in the two study groups was slightly prolonged in Group B (approximately 4 min) but not statistically significant.

Out of total 64 subjects, rescue analgesia was required in 48 subjects. The cumulative analgesic requirement was statistically significantly less for Group A (20 subjects) than Group B (28 subjects). The requirement of analgesia was high in Group B as major portion of the population required analgesia leaving just 4 subjects in which no analgesia was given, which is highly significant.

The pain intensity was assessed using a 10-cm VAS. The statistical data suggest that pain felt by subjects of Group A was of lower intensity as compared to that of Group B and total requirement of analgesia was more in the latter.

The side effects such as bradycardia, hypotension, sedation, and dry mouth were observed in the perioperative period. It is clear that the overall incidence of sedation is highest, followed by hypotension, whereas the incidence of bradycardia and dry mouth is least. It can be seen that the incidence of side effects is more in Group A as compared to Group B. The incidence of hypotension was highest in Group A, followed by bradycardia, sedation, and incidence of dry mouth was least in Group A. On the other hand, incidence of bradycardia was least, followed by hypotension, dry mouth, and sedation. The incidence of sedation was highest in Group B.

To conclude, both drugs lowered the analgesic requirement in the perioperative period in lower abdominal surgeries conducted under the subarachnoid block, oral pregabalin providing better hemodynamic stability with lesser side effects but with more sedation.

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# The Study of Seizure Disorder in Women

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## Abstract

**Introduction:** Despite the increasing interest in sex differences in disease manifestations and responses to treatment, very few data are available on sex differences in seizure types and semiology. Both experimental and clinical evidence indicate that ovarian hormones exert a profound effect on neuronal excitability, though in a complex manner.

**Aim:** The aim was to study seizure disorder in 50 adult women.

**Methods:** A total of 50 adult women admitted with seizure were taken up for the study. Pseudoseizure, syncope, and movement disorder are excluded. Clinical history and physical examination were done in all patients.

**Result:** In this study, seizure occurred during the childbearing age in 78% compared to postmenopausal state which is 32%. The seizure occurred in 32% in the age group of 21–29 years. More common is the generalized seizure. 46% is idiopathic, and 28% is post stroke seizure.

**Conclusion:** Seizure occurrence is more common during childbearing age than the postmenopausal state. The idiopathic seizure occurs at a younger age. The generalized seizure is more common than partial seizure in this study. Stroke is the most common cause of seizure in elderly women.

**Key words:** Hormones, Seizure, Women's health

## INTRODUCTION

The seizure is a paroxysmal event due to abnormal, excessive, hypersynchronous electrical discharge from an aggregate of central nervous system neurons. The seizure is not a disease in themselves. Instead, they are the symptoms of a much different disorders affecting the brain. If an underlying chronic process leads to recurrent seizures, it is called epilepsy. Epilepsy affects ~50 million people worldwide and has a lifetime risk of ~3%.<sup>[1,2]</sup> The incidence and prevalence of unprovoked seizures are higher in men than women,<sup>[3]</sup> and status epilepticus is more frequent in men than women.<sup>[4]</sup> However, some idiopathic generalized epilepsies are more common in women, particularly juvenile myoclonic epilepsy and absence epilepsy.<sup>[5]</sup> There are no sex differences for patients with hippocampal

sclerosis on magnetic resonance imaging (MRI). Sex disparities after epilepsy surgery are reported with more favorable outcomes in women as well as men.<sup>[6]</sup> Men are 1–2.4 times more likely to have epilepsy than women. Epilepsy has a special implication for women health, and specific management strategies are required to solve the problem.

## Aim

The aim is to study seizure disorder in 50 adult women.

## MATERIALS AND METHODS

A prospective study was conducted in Thoothukudi Medical College Hospital for 6 months. A total of 50 adult women admitted with seizure in the intensive care unit were randomly included in this study. Pseudoseizure, syncope, and movement disorder are excluded. Clinical history and physical examination were performed in all patients. All patients underwent routine blood investigation electroencephalograph (EEG), and computed tomography (CT) scan brain/MRI brain were done in all patients.

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## RESULTS

In this study, age varied from 13 years of age to 70 years of age. Eight patients were in 13–19 years of age accounting for 16%. In 21–29 years of age, 16 patients had seizure. Seven patients were in 30–39 years of age. In 40–49 years of age, six patients had seizure. Nine patients are in 50–59 years of age accounting for 18%. In 60–69 years of age, three patients had seizure. One patient had seizure at the age of 70 [Table 1].

Of 8 patients in the teenage group, 7 had generalized tonic-clonic seizure with irregular menstrual cycle and 1 had seizure with regular menstrual cycle. In this group, 2 had family history of seizure. EEG was abnormal in 6 patients and CT scan brain was normal in all of these 8 patients. Of 16 patients in 20–29 years of age, 8 had eclampsia. All eclampsia patients are primigravida. 1 of the 16 had postpartum cerebral venous thrombosis. CT scan brain and MRI brain with venogram showed evidence of cerebral venous thrombosis. Two of 16 had complex partial seizure and 4 of 16 had generalized tonic-clonic seizure during pregnancy. One patient at 24 years of age had late onset post-traumatic seizure. 2 of 7 patients in the age group of 30–39 had neurocysticercosis. 5 of 7 had seizure in already known idiopathic epilepsy. Of 6 patients in the age group of 40–49, 1 had hypoglycemia and other 1 had electrolyte imbalance. 4 of 6 in the age group of 40–49 had idiopathic epilepsy. Nine patients in the age group of 50–59, three patients in the age group 60–69, and one in 70 years of age had cerebrovascular accident with seizure. All cerebrovascular accident is of ischemic type. Patient in 70 years of age had right middle cerebral artery infarct with uremia [Table 2].

**Table 1: Frequency of age-wise seizure occurrence in 50 woman patients**

Age	Number of patients (out of 50) (%)
13–19	8 (16)
21–29	16 (32)
30–39	7 (14)
40–49	6 (12)
50–59	9 (18)
60–69	3 (6)
70	1 (2)

**Table 2: Etiology of seizure in 50 woman patients**

Etiology	Number of patients (out of 50) (%)
Idiopathic	23 (46)
Cerebrovascular accident	14 (28)
Eclampsia	8 (16)
Neurocysticercosis	2 (4)
Electrolyte imbalance	1 (2)
Hypoglycemia	1 (2)
Post-traumatic	1 (2)

Of 50 patients in the group, 33 patients had generalized seizure, 8 had simple partial seizure, 2 had complex partial seizure, and 7 had mixed seizure disorder [Table 3].

Of 50 patients in this group, 34 were reproductive period and 16 were postmenopausal state [Table 4].

## DISCUSSION

In our study, of 50 women patients, 34 were in reproductive age group, and 16 were in postmenopausal state. Seven patients in the age group of 13–19 in our study had seizure with irregular menstrual cycle and delayed periods. 1 of 7 patients in the teenage group had seizure with regular menstrual cycle. Cumming *et al.* reported over one-third of women with temporal lobe seizure as having an anovulatory cycle over a time frame of three cycles compared with <10% of control women or women with primary generalized epilepsy.<sup>[7]</sup>

Approximately 50% of women with epilepsy have an increased frequency of seizure during pregnancy. Only a small percentage of women with epilepsy have a decrease in the frequency of seizure during pregnancy. In our study, 16 patients of 50 women with epilepsy in the age group of 20–29, and 6 patients had increased seizure occurrence during pregnancy. This increase in frequency may be due to hormonal change, body fluid change, and salt retention. Absorption, distribution, and elimination of antiepileptic drug also vary during pregnancy. Poor sleep during third trimester may increase the seizure frequency. Women with epilepsy who are pregnant are considered as high-risk pregnancy which indicates high risk to mother and fetus. The study shows an increase in maternal seizure during pregnancy.<sup>[8]</sup>

In our study, 8 patients had eclampsia and all are primigravida in 20–29 age group. All these patients managed with magnesium sulfate, labetalol, and diuretic. Eclampsia is

**Table 3: Seizure type in 50 woman patients**

Seizure type	Number of patients (out of 50) (%)
Generalized seizure	33 (66)
Complex partial seizure	2 (4)
Simple partial seizure	8 (16)
Mixed seizure	7 (14)

**Table 4: Period of seizure occurrence in 50 women patients**

Period	Number of patients (out of 50) (%)
Reproductive period	34 (68)
Postmenopausal state	16 (32)

a vascular disorder, most common in young primigravida in the last trimester of pregnancy. The International Society for the Study of Hypertension in Pregnancy defines eclampsia as the occurrence of generalized convulsion associated with signs of preeclampsia during pregnancy, labor, or within 7 days of delivery not caused by epilepsy or other convulsive disorder. Unfortunately, 30–35% of cases of eclampsia remain unpreventable.<sup>[9-11]</sup>

In our study, one patient at 24 years of age had late onset post-traumatic seizure. Her CT scan brain showed post-operative bone defect with gliosis in left frontal lobe. Head trauma is associated with an increased susceptibility to seizure. Post-traumatic seizure may be earlier if seizure occurs <1 week of head trauma or late if seizure occurs >1 week of injury.<sup>[12]</sup>

One patient of 50 women with epilepsy in the age group of 40–49 had hyponatremia-induced seizure. Hyponatremia is associated with muscle cramps, weakness, confusion, and seizure.<sup>[13]</sup>

In our study, 14 patients 50 adult women with epilepsy had cerebrovascular accident. 13 patients had ischemic stroke, and all patients were >50 years of age. In our study, 1 of 50 women with epilepsy at the age of 24 had cerebral venous thrombosis. Impact of post stroke seizure on stroke outcome is unclear. 43% of stroke patients experienced a seizure within 24 h after stroke.<sup>[14]</sup> In patients with ischemic stroke, epilepsy developed in 35% of patients with early onset seizure and in 90% of patients with late onset seizure.<sup>[15]</sup> The risk for epilepsy was comparable in patients with hemorrhagic stroke: Epilepsy developed in 29% of patients with early onset seizure versus 93% with late onset seizure.<sup>[16]</sup>

## CONCLUSION

Seizure is more common in women of childbearing age than postmenopausal state. Eclampsia is seen in young primigravida in this study. Majority of seizure in our study

is idiopathic, followed by post stroke seizure. Generalized seizure is more common than partial seizure. Stroke is the most common cause of seizure in elderly women.

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# Voice Handicap Index and Voice-related Quality of Life after Botulinum Toxin Injection for Spasmodic Dysphonia Patients

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## Abstract

**Background:** Spasmodic dysphonia (SD) is not an uncommon voice disorder defined as a condition of uncertain etiology with uncontrolled, intermittent, and speech induced spasms of intrinsic muscles of the larynx resulting in strangled, strained, and breathy voice commonly seen in women. Botulinum injection into the thyroarytenoid muscle is the standard treatment in controlling the disorder. Surgical procedures include unilateral sectioning of recurrent laryngeal nerve and partial thyroarytenoid resection. Speech therapy is good in mild cases but not in moderate and severe cases.

**Aim of the Study:** The aim of the study was to determine the effect of botulinum toxin type A injections for adductor type of SD on the duration of benefit, perceived voice-related quality of life (V-RQOL).

**Materials and Methods:** A total of 46 patients treated with botulinum Toxin A injected into thyroarytenoid muscles on both sides were selected. Pre- and post-treatment subjective assessment was done by V-RQOL scoring and during the follow-up for 18 months done.

**Observations and Results:** There was an improvement after injection in the quality of life as indicated by the V-RQOL evaluation. The mean period of remission from dysphonia was  $9.30 \pm 1.75$ .

**Conclusions:** Botulinum is effective in giving a 65–100% VRQOL to the patients with SD. Percutaneous route of injection showed statistically significant results and better acceptance than intraoral route. Results suggested significant effects on participants' perceived quality of life and acoustic variables, over time, for all participants.

**Key words:** Abductor spasmodic dysphonia, Adductor spasmodic dysphonia (ADDSD), Botulinum toxin, Spasm, Spasmodic dysphonia, Voice handicap index, Voice-related quality of life

## INTRODUCTION

Spasmodic dysphonia (SD) is a voice disorder of unknown etiology. Many authors consider it as a psychogenic disorder because it is worse under emotional stress and better in the morning hours and under alcoholic effect.<sup>[1]</sup> The term SD is coined by Traube 1871. It is a disorder of voluntary muscles

of larynx that manifests during speech and four types are described Adductor type, Abductor type, mixed type and Adductor Laryngeal breathing type, and Adductor type accounts for 80% of all types. The patient tries to overcome excessive spasm of adductors causing closure of vocal cords during speech.<sup>[2]</sup> Typically, the patients have strained voice with short outbursts with sudden initiation and cessation of speech. The diagnosis usually made by hearing to the speech, aided by fiber-optic laryngoscopy. The findings are normal, but few patients show hyperadduction of false vocal cords. Treatment is aimed at reducing the tension in the vocal cords without affecting the vibration. Voice therapy is part of surgical and medical treatments in SD which helps the patients to relax the laryngeal muscles with the help of breathe support, inverse phonation, altering one's pitch level,

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and range and biofeedback technique. Treatment consists of Botox injection into intrinsic muscles of larynx, anterior laryngoplasty, and selective denervation of adductors of larynx and using implantable stimulator. The prevalence rate of SD varies from 3 to 732 per 1, 00, 000 population worldwide.<sup>[3-5]</sup> In India a crude prevalence rate is placed as 43.9 per 1, 00, 000 population. In an Indian study by Das *et al.* shows that writer's cramp and blepharospasms are the most common focal dystonia.<sup>[6]</sup> Even though SD does not reduce the life expectancy, it may be responsible for considerable morbidity in terms of pain, low self-esteem, depression, embarrassment, and poor social interaction. Health-related quality of life is a multi-dimensional concept that encompasses the subjective assessment of the impact of illness or treatment across the physical, psychological, and social and somatic domains of functioning and the well-being.<sup>[7]</sup> At present, chemodenervation of thyroarytenoid muscle with the help of Botox is the Gold standard care of Adductor type of SD.<sup>[8]</sup> Similar to other pharmaceutical agents Botox also gets washed out of the muscle after sometime requiring ongoing re-injection to maintain the patient's improvement in voice production.<sup>[9]</sup> The expected duration of benefit ranges from 3 to 12 months and the subjects requiring ongoing re-injections to maintain an easy, efficient manner of phonation.<sup>[10]</sup> Usually, the patients decide when it is time to seek reinjection, but the criteria for their decision remain unclear.<sup>[11]</sup> SD is commonly seen in women around the age of 30 years.<sup>[12]</sup> There is no universal index of vocal function to quantify the degree of dysphonia, and the decision to intensify the treatment is usually based on the magnitude of the voice-related problems experienced by the patients and its importance in his life. That is expressed as voice-related quality of life (V-RQOL). Similarly, post-treatment assessment is also not standardized and hence is measured in terms of patient's perception of improvement related to the quality of his life.<sup>[13]</sup> Studies in literature have employed voice handicap index (VHI) and V-RQOL score as standard methods of assessing patient's subjective perception of the condition. The present study was a prospective study on the effect of botulinum type A toxin injected into the intrinsic muscle of larynx of patients with SD. The patient's perception of improvement in speech and VRQOL score following treatment was analyzed. The clinical significance of using two different routes of administration of the toxin is reviewed in the face available literature.

### Type of Study

This was a prospective, random cross-sectional analytical study.

### Institute of Study

This study was conducted at the Department of Ear, Nose, and Throat (ENT) and Head and Neck Surgery, Kakatiya Medical College and MGM Hospital, Warangal, Telangana.

### Period of Study

This study was from August 2013 to July 2015.

## MATERIALS AND METHODS

A total of 46 patients with SD were included in this study for evaluation. After obtaining approval by the Ethical Committee of the institute as no life-threatening events were predicted during the procedure, the patients were informed, and due consent was taken. 46 patients presenting with hoarseness of voice, at the ENT Department of Kakatiya Medical College and MGM Hospital Warangal Telangana, between August 2013 and July 2015 were included in the present study.

### Inclusion Criteria

1. Patients aged >37 years and <60 years were included.
2. Patients belonging to both the genders were included.
3. Patients with signs and symptoms of SD for >6 months were included.
4. Patients with previous treatment with botulinum toxin injections were also included.
5. Patients with dissatisfaction with voice therapy were included.

### Exclusion Criteria

1. Patients aged <37 years and >60 years were excluded.
2. Patients with history of upper respiratory infection were excluded.
3. Patients with surgical procedures on larynx, thyroid were excluded.

Patient's demographic details were recorded and patients were subjected to ENT examination including voice recording of the speech. Diagnosis was made on history taking, hearing to the speech, and video-laryngoscopy examination. Only adductor type of SD was included. 10 questions of VHI of Jacobson<sup>[13]</sup> were used to assess pre-treatment voice status. First six questions were related to the physical functioning in the production of speech and the past four questions were related to effect of voice on social-emotional aspects of life as shown in Annexure I. After the treatment the response expressed as V-RQOL score (Annexure II) was used. Freshly constituted commercially available botulinum toxin type A was used. Botulinum toxin type A 1.5 units were used initially for the injection and the dose was titrated by increasing or decreasing the dose by 1 unit depending on the period of remission and development of aspiration. 26 patients were administered botulinum toxin into the vocal cords bilaterally visualizing the larynx through fiber-optic nasopharyngoscope under local anesthesia and Alprazolam sedation. 20 patients were administered Botox injection through a percutaneous route by point touch technique described by Morzaria and



Damrose.<sup>[14]</sup> Each cycle of injection was supplemented by another injection depending on the patient's perception of difficulty in speech. All the patients were cautioned about the possibility of aspiration of liquids and difficulty in breathing. 11 patients received single injection, 16 patients received two injections (3 within 1 week 7 after 6 months). 19 patients received 3 injections at 6 months interval. Follow-up was at 6 months interval for 18 months. All the data were analyzed using standard statistical methods using single sample *t*-test, Z score for single sample, and student *t*-test for two-independent means.

### Observations

A total of 46 patients attending the ENT outpatient department with complaints of hoarseness of voice were included in the study. Patients belonged to the age group of 37–60 years. The youngest patient was a female aged 37 years, and the eldest patient was aged 58 years male. The overall mean age was  $45.35 \pm 4.10$  years. The mean age in males was  $46.20 \pm 3.80$  years and  $41.95 \pm 4.70$  years in females. There were 29 (63.04%) female patients and 15 (32.60%) male patients with a female to male ratio of 1.93:1. 22/46 (47.82%) patients belonged to the age group between 45 and 52 years [Table 1]. The duration of symptoms ranged between 9 months and 7 years, and the mean duration was 5.68 years with standard deviation of 1.56. 16/46 (34.78%) patients belonged to the lower middle class, 19 (41.30%) were from middle class, and 11 (23.91%) were from the upper middle class of socioeconomic groups. 33/46 (71.73%) of the 46 patients belonged to the responsible position either in the family or at workplace. 36/46 (78.26%) patients belonged to the habitual voice users; hawkers. 24 (52.17%) of the patients showed emotional stress during the past 3 years. 16 (34.78%) patients showed signs of mood swings. The ENT examination and video laryngoscopy showed no

demonstrable organic changes in the vocal cord or their movement.

Patients were assessed with VHI score and VRQOL scores. 26/46 patients (56.52%) had their VHI score at 40 with VRQOL score at 25%, 11/46 patients (23.91%) had their VHI score at 50 with VRQOL score at 0% and 09/46 (19.56%) with 30 VHI and 50% VRQOL score before treatment. Assessment after 6 weeks showed 07/46 patients (15.21%) showing complete relief from dysphonia and these patients had their VRQOL score of 0%. 21/46 patients (45.65%) showed VRQOL score at 75% and 18 patients (39.13%) showed 50% VRQOL score [Table 2]. Even though the patients participated in the study at different points of time, the calculation of scores was done at fixed time intervals to observe the significance of the injection Botulinum in our institute. After 18 months of follow up 07/46 (15.21%), patients continued to show no recurrence in dysphonia, 16/46 (34.78%) patients showed VRQOL score at 75%, and 13/46 (28.26%) patients had 50% response on VRQOL score. 08/46 (17.39%) patients showed 25% VRQOL score and 02/46 patients (04.34%) showed 0% VRQOL scores in this study [Table 2]. The overall efficacy of treatment was seen in 36/46 (78.26%) patients who had at the end of 18 months a VRQOL of 50% and above, which was statistically significant ( $P = 0.018$ ;  $P$  taken significant at  $<0.05$ ), [Table 2].

Out of 11 patients who were given single injection 05 did not require further injections in 18 months, and 06/46 (13.04%) showed VRQOL 100% recovery. Out of 16 patients who received two injections 13/46 (28.26%) patients had their VRQOL between 75 and 50% and all the 19 patients who received three injections 16/46 (34.78%) showed 75–50% VRQOL. The remaining 04 (08.69%) patients showed little (25%) or no 0% VRQOL score [Table 3].

The mean value of VHI score before treatment was  $42.13 \pm 6.15$  with VRQOL score of 25% in the sample studied. The same values calculated at the end of 6 weeks, 12 weeks, 6 months, 12 months, and 18 months of follow-up was observed is shown in Table 4.

**Table 1: The age incidence and sex incidence (n=46)**

Age group	Male -15 (32.60%)	Female - 29 (63.04%)	Percentage
37 to 44–11	03	08	23.13
45 to 52–22	08	14	41.37
53 to 60–13	04	07	23.13

**Table 2: The response to treatment during follow-up and related VBI and VRQOL scores (n=46)**

VHI score	VRQOL score%	Pre-treatment patients	Post-treatment patients					Total	P value
			6 Weeks	12 weeks	6 months	12 months	18 months		
0	100	Nil	07	07	07	07	07	36	0.018
20	75	Nil	21	19	17	16	16		
30	50	09	18	16	15	13	13		
40	25	26	Nil	Nil	03	04	08	10	
50	0	11	Nil	Nil	01	01	02		

VHI: Voice handicap index, VRQOL: Voice-related quality of life

To know the significance of the study Z test for single sample was used and the Z score was -30.77. *P*-value was 0, and hence the result was significant at *P* < 0.05.

A student *t*-test for two-independent means was used to calculate *t*-value and *P*-value to know the significance between the two routes of administration of the drug. *t*-value was 2.8521 and *P*-value was 0.004. The test was significant at *P*-value < 0.05 [Table 5].

## DISCUSSION

SD is a disease of uncertain etiology. It is commonly seen in the females;<sup>[1,3,4]</sup> present study shows the incidence to be common in the females. 63.04% of the present sample was of females with a female to male ratio of 1:1.93. SD is characterized by irregular, intermittent and uncontrollable spasms within the laryngeal muscles as the person starts to speak. It is exaggerated by emotional stress, fatigue, and absent after a good sleep. Few authors support that it can be treated by itself on the psychogenic basis<sup>[13]</sup> The present study showed 24 (52.17%) of the patients showed emotional stress during the past 3 years and 16 (34.78%) patients showed signs of mood swings. In a similar study by Liu *et al.* showed the incidence of anxiety, depression, and somatization among the patients of SD in a higher level.<sup>[10]</sup> Recently few authors have hypothesized that SD is a dysfunction of the basal ganglia resulting in focal laryngeal dystonias and similar to blepharospasms and torticollis.<sup>[15]</sup> Demonstration of electromyographic tracings recorded from 90% of the 10 patients with SD by Behlau Robe in 1990 changed the concept of the disease pointing toward its neurological nature.<sup>[16]</sup> Murray *et al.* concluded that there is no evidence to show the effectiveness of speech therapy in SD treatment; it only improves the effectiveness of other treatments to minimize the hyperfunctional state of the larynx.<sup>[17]</sup> Speech therapy was not given to the patients in the study. Since 1988 Botulinum toxin injection has become

the mainstay of treatment of SD following the use and demonstration of Botulinum toxin by Blitzer *et al.*<sup>[18]</sup> The mode of action of botulinum toxin is to reduce the release of acetylcholine at the neuromuscular junctions. This has an effect to reduce the paralysis of adductor spasm and in speech production. The effect may last for 3–4 months and requires repeat administration of the toxin.<sup>[19]</sup> In the present study patients had improved VRQOL from 50 to 75% lasting at an average of 24.5 weeks per cycle. The present study with a follow up of 18 months duration, 16/46 patients (34.78%) required two injections, 19/46 patients (41.30%) of them required three injections, and the remaining 11/46 (23.91%) patients required one injection of the botulinum toxin. 07/46 (15.21%) of the patients showed VRQOL 100% improvement of voice during the period. Subjective assessment of the improvement in voice and quality of life is an appropriate mode of assessment, as the treatment used is only an attempt to achieve symptomatic relief rather than cure.<sup>[20]</sup> Blitzer *et al.*<sup>[21]</sup> published a study of 900 patients over a period of 12 years of follow-up wherein there was 90% improvement in patients with Adductor type of SD with a mean duration of 15.1 weeks (4 and 1/2 months). Effect of botulinum toxin on Abductor type of SD in their study showed an improvement in 66% with a mean duration of normal voice being 10.5 weeks.<sup>[13-15]</sup> The overall efficacy of treatment was seen in 36/46 (78.26%) patients which were statistically significant in the present study with *P* value of 0.018 [Table 2]. Various surgical procedures are attempted to achieve a long-term result from spasms of the larynx but do not offer great advantages than botulinum toxin injections.<sup>[3,16,17]</sup> To know the significance of the present study Z test for the single sample was used and the Z score was 30.77. *P*-value was 0, and hence the result was significant at *P* < 0.05. A student *t*-test for two-independent means was used to calculate *t*-value and *P*-value to know the significance between the two routes of administration of the drug. *t*-value was 2.8521 and *P*-value was 0.004. The test

**Table 3: The total dose of Toxin and its correlation with VRQOL score (n=29)**

Number of injections	Number of patients	Total dose of Botox (units)	VRQOL 100%	VRQOL 75%	VRQOL 50%	VRQOL 25%	VRQOL 0%
1	11	3	06	04	1	-	-
2	16	5	-	09	04	03	-
3	19	7		14	02	02	02

VRQOL: Voice-related quality of life

**Table 4: The mean VBI and VRQOL scores during the follow-up of treatment**

Voice parameter	Pre-treatment	Post-treatment 6 weeks	Post 12 weeks	Post 6 months	Post 12 months	18 months
Mean VHI	42.13	23	28.41	27.20	31.93	32.17
SD	6.15	5.64	5.85	5.75	6.00	6.4
VRQOL score	25	75	50	50	50	50

VHI: Voice handicap index, VRQOL: Voice-related quality of life, SD: Standard deviation

**Table 5: The significance administration of the botulinum toxin by two different routes (n=29)**

Route of Administration	Pre-treatment mean VHI score	Post-treatment mean VRQOL score
Intra laryngeal- 26	41.68	28.70
Percutaneous-20	42.69	18.15

VHI: Voice handicap index, VRQOL: Voice-related quality of life, SD: Standard deviation

was significant at  $P$ -value  $<0.05$ . To know the significance of the study Z test for the single sample was used and the Z score was  $-30.77$ .  $P$ -value was 0, and hence the result was significant at  $P < 0.05$ .

## CONCLUSIONS

Botulinum toxin injection into intrinsic laryngeal muscle in the treatment of SD is effective in giving a 50–100% VRQOL to the patients even though for a short period. The average period of remission is about 24 weeks in the present study. Percutaneous route of injection showed statistically significant results than intraoral route;  $P$  value 0.004.

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## ANNEXURE

### Annexure I

Symptom	1	2	3	4	5
1 I run out of Air when I talk					
2 The sound of my voice varies throughout the day					
3 My voice sounds dry and creaky					
4 I feel that I have to strain to produce speech					
5 I use a great deal of effort to speak					
6 My voice worsens in the evening					
7 People have difficulty in understanding my voice in noisy surroundings					
8 My voice difficulties restrict my personal and social life					
9 I feel tense when talking to people because of my voice					
10 I am losing my income due to my voice					

Table showing the 10 Questions related to voice problem; VHI index. 1 - None, Not a Problem, 2 - A small amount, 3 - A moderate amount (Medium), 4 - A Lot, 5 - Problem is as bad as it can be

### Annexure II

Questionnaire score	VRQOL score
0	100 (excellent)
20	75 (fair to good)
30	50 (poor to fair)
40	25 (poor)
50	0 (worst possible)

Table showing the VRQOL scores and interpretation of the score form Annexure I



# Clinical Presentation and Outcome of c1q Nephropathy - A Single-Centre Prospective Study

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## Abstract

**Background:** C1q nephropathy is a rare glomerular disease with characteristic mesangial c1q deposition noted on immunofluorescence microscopy. It is histologically defined and poorly understood. Light microscopic features are heterogeneous and comprise minimal change disease, focal segmental glomerulosclerosis (FSGS), and proliferative glomerulonephritis (GN).

**Aim:** This study aims to study the clinical presentation, histopathological profile, and outcomes in patients with c1q nephropathy.

**Methods:** A total of 13 patients who satisfied the above criteria were studied. Clinical profile and laboratory parameters including urine analysis, urine spot protein-creatinine ratio, blood biochemistry, serum complement, and histopathological profile were analyzed. Creatinine clearance was estimated using Cockcroft Gault formula. They were followed up for the assessment of response to treatment.

**Results:** Among the 13 patients, 12 were female (92.3%). All (100%) were hypertensive at the time of presentation. Age ranged from 15 to 48 year with the mean of 34 years. Microscopic hematuria was found in all 13 patients (100%). Nephrotic proteinuria was found in 10 patients (77%), and 4 patients (30.7%) had GFR <60 mL/min. The kidney biopsy revealed diffuse proliferative glomerular nephritis (DPGN) in 12 patients (92.3%), one patient had FSGS (7.7%). Cellular crescents were found in 2 patients (15.3%). One patient was lost for follow-up. 3 patients (25%) improved with ACE inhibitors and statins. 9 patients (69.2%) were started on steroids, of which the four patients who had renal failure received cyclophosphamide in addition to steroids. Of the nine patients, complete remission was found in 2 patients (22%), partial remission in 2 patients (22%), and no response to immunosuppressive medication was seen in 5 patients (55.5%) (one patient had FSGS and four patients had DPGN).

**Conclusion:** Of the 13 cases with c1q nephropathy, all patients had hypertension and microscopic hematuria. Nephrotic proteinuria was seen in three-fourths of the patients. The most common histopathological presentation was diffuse proliferative GN. Half of the patients showed poor response to oral steroids.

**Key words:** Antinuclear antibodies, C1q nephropathy, C3, C4, Diffuse proliferative glomerulonephritis, Focal segmental glomerulosclerosis, Immunosuppressive medication, Minimal change disease, Nephrotic proteinuria

## INTRODUCTION

C1q nephropathy, first described by Jennet and Hipp in 1985, as a pattern of glomerulonephritis (GN)

characterized by predominant mesangial c1q deposition but with other histological features resembling lupus nephritis.<sup>[1]</sup> This is a variant of lupus nephritis called seronegative lupus nephritis, yet at the time of presentation of renal disease, there is no past or present clinical or serological evidence of systemic lupus erythematosus (SLE).<sup>[2,3]</sup> It is proposed that if the pattern has renal histology entirely consistent with lupus nephritis, a significant proportion of them will in due course develop overt SLE.<sup>[3]</sup> The prevalence of c1q is 0.2–16.0% and seems to be higher in children.<sup>[3]</sup> C1q nephropathy often manifests as steroid-resistant asymptomatic proteinuria or nephrotic

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syndrome. Light microscopic features are heterogeneous and comprise no glomerular lesion, focal segmental glomerulosclerosis (FSGS), and proliferative GN.<sup>[4-6]</sup> The clinical and microscopic presentations are quite varied, and the diagnosis is based on histopathology. Likewise, outcomes generally depend on clinical and histological factors. Patients presenting with lower level proteinuria, nephritic syndrome, and the histologic variant of minimal change disease (MCD) tend to have favorable outcomes, as opposed to those with nephrotic range proteinuria and FSGS variant having unfavorable outcomes.

### Aim

This study aims to study the clinical presentation, histopathological profile, and outcomes in patients with c1q nephropathy.

## MATERIALS AND METHODS

This is a retrospective case series analysis that was done in Kilpauk Medical College. Inclusion criteria are patients with renal biopsy showing dominant or codominant c1q immune deposits were analyzed for clinical, biochemical, and histopathological profile. Patients with clinical and serological evidence of lupus and hypocomplementemia were excluded from the case series. 13 patients who satisfied the criteria for c1q nephropathy were analyzed. All the patients were examined clinically for the presence of systemic hypertension, pedal edema, and extrarenal manifestations of lupus (malar rash, discoid rash, photosensitivity rash, recurrent oral ulcer, non-erosive arthritis, polyserositis, neuropsychiatric lupus, hemolytic anemia, and thrombocytopenia). Urine analyzed for red blood cells (RBCs) and urine spot protein-creatinine ratio (PCR). Serum creatinine, creatinine clearance (Cockcroft-Gault formula), antinuclear antibodies (ANA), C3, and C4 were done.

## RESULTS

Total of 13 patients, among them 12 were female. Mean age group of our cohort was 34 years. Predominant age was between 20 and 40 years of age.

All 13 patients had systemic hypertension (100%) and pedal edema (100%). Nephrotic proteinuria was found in 10 patients (77%), other 3 patients (23%) had non-nephrotic proteinuria. Average urine spot PCR was 6.5. Microscopic hematuria was found in all patients (100%). Renal failure was found in 4 patients (33%). In all 13 patients, C3 and C4 were in normal range [Table 1].

In accordance with the selection criteria, all 13 cases had positive glomerular staining for c1q in the mesangium, in

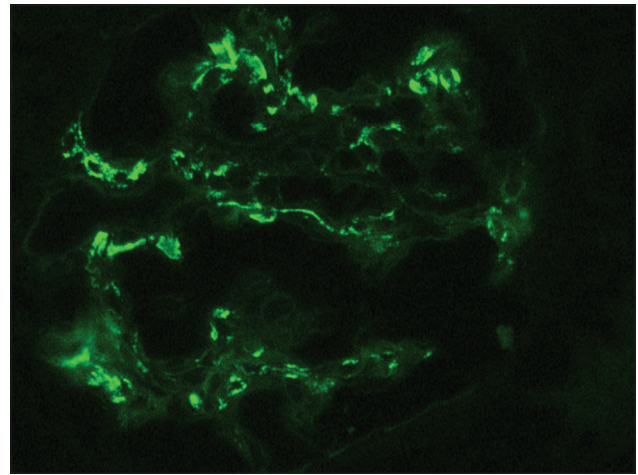


Figure 1: C1q deposits in mesangium

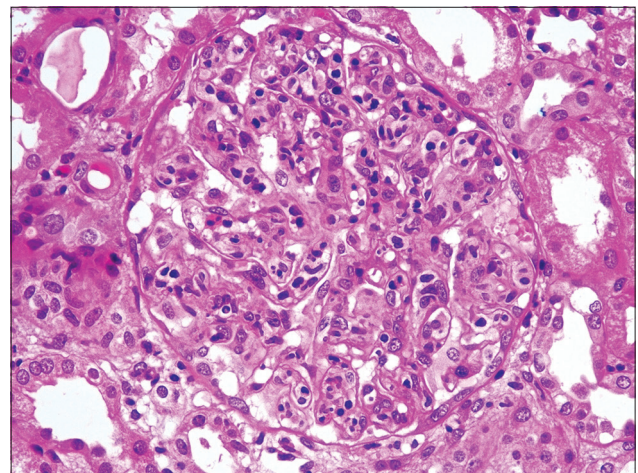


Figure 2: Diffuse endo capillary proliferation

addition to that IgG, IgM, and IgA (full-house pattern) were also found in 12 patients with diffuse proliferative GN. Dense c1q deposit with the intensity of 3+ or 4+ was found in all 13 patients. In all cases, c1q was deposited in mesangial areas, and in some cases, c1q deposits found in peripheral areas of the glomerulus [Figure 1].

Light microscopic examination showed 12 patients had features of diffuse proliferative glomerular nephritis (DPGN) (92.3%). Among them, two patients had fibrocellular crescents. 1 patient (7.7%) showed features of FSGS [Table 2 and Figure 2].

All patients received angiotensin-converting enzyme (ACEI) and statins (100%). 9 patients (69.2%) received immunosuppressive medications. 5 patients (55.5%) were treated with steroids alone. 4 patients (30.7%) with renal failure were treated intensively by following the National Institute of Health protocol of Class IV lupus nephritis. Cellular crescent was found in two patients.

**Table 1: Distribution of clinical presentation**

Date of admission	Age	Sex	BP	U. Alb	U. Dep RBC/hpf	U. Spot PCR	S. creatinine	CR. CL mL/min
12/07	29	F	160/100	3+	5-6	3.2	1.1	89
3/09	24	F	150/90	4+	8-10	2.8	3.1	24
3/09	29	F	160/100	2+	3-4	3.0	1.5	46
7/09	36	F	150/100	2+	6-7	1.5	1.1	74
7/09	48	F	170/100	4+	10-15	3.03	0.9	67
1/10	30	F	150/90	4+	9-10	12.45	0.8	85
2/10	20	M	170/100	3+	9-10	4.7	0.9	79
3/10	33	F	200/120	4+	4-5	6.2	2.7	28
4/10	26	F	160/100	4+	10-11	4.5	1.0	76
5/10	40	F	150/100	4+	4-5	15.4	1.5	59
6/10	14	F	140/100	4+	8-10	12.7	0.9	84
6/10	20	F	150/100	4+	15-18	11.0	1.2	74
10/10	45	F	160/100	4+	4-6	4.0	1.0	73

PCR: Protein-creatinine ratio, RBCs: Red blood cells

**Table 2: Distribution of renal histopathology**

Age	Sex	ANA	C3	C4	LM	IF
29	F	-Ve	132	42.5	Segmental sclerosis-FSGS	C1q4+M
24	F	-Ve	138	31.90	DPGN - partial fibrocellular crescent	C1q4+M
29	F	-Ve	142	25.3	DPGN	C1q4+PM
36	F	-Ve	133	20.1	DPGN	C1q4+PMD
48	F	-Ve	173	21.5	DPGN - ?FSGS	C1q4+M
30	F	-Ve	113	43.4	DPGN	C1q4+PM
20	M	-Ve	136	33.3	DPGN	C1q4+PMD
33	F	-Ve	142	23.6	DPGN - fibrocellular crescent	C1q4+PM
26	F	-Ve	102	28.5	DPGN	C1q4+PMD
40	F	-Ve	155	45.2	DPGN	C1q4+PM
14	F	-Ve	137	38.9	DPGN	C1q4+PMD
20	F	-Ve	129	40.4	DPGN	C1q4+PMD
45	F	-Ve	150	44.7	DPGN	C1q4+PMD

FSGS: Focal segmental glomerulosclerosis, ANA: Antinuclear antibodies, DPGN: Diffuse proliferative glomerulonephritis

2 patients (22%) with crescents and 1 patient (11.1%) with massive proteinuria and renal failure received three daily pulses of injection. Methylprednisolone and 6 monthly pulses of injections Cyclophosphamide and followed with oral prednisolone. 1 patient (11.1%) with renal failure was treated with three daily doses of injections. Methylprednisolone and mycophenolate mofetil and oral prednisolone [Table 3].

One patient with diffuse proliferative GN lost the follow-up. Other 12 patients are on regular follow-up. Mean duration of follow-up was 14.4 months. Apart from ACEI and statins, nine patients who received immunosuppressive medication are on low-dose prednisolone now. Three patients are receiving azathioprine in addition to oral steroids.

Complete remission was defined as urine spot PCR <0.5, absence of microscopic hematuria, and normal glomerular filtration rate. Partial remission was defined as urine spot

PCR between 1.0 and < 3.0, with or without RBC in urine and normal glomerular filtration rate.

3 patients (28%) were remitted with ACEI and statins. Remission with oral steroids was found in 2 patients (22%). Partial remission was found in 2 patients (22%), among them one had fibrocellular crescent, and renal failure was treated with three doses injection Methylprednisolone and 6 monthly pulses of injections Cyclophosphamide. 5 patients (55.5%) showed resistant to immunosuppressive medication, of which on histopathology one had FSGS and four had DPGN. Among the five patients, three had renal failure and one among them had partial fibrocellular crescent. These three patients were treated with injections. Methylprednisolone, injection Cyclophosphamide, and oral prednisolone. None of the patients progressed to chronic kidney disease Stage V.

## DISCUSSION

C1q nephropathy is a controversial and uncommon form of GN characterized by mesangial Ig and complement deposits predominantly c1q with no evidence of SLE. It is a distinct clinicopathological entity of steroid-resistant nephrotic syndrome<sup>1</sup>.

### Diagnostic Criteria for C1q Nephropathy<sup>1,2</sup>

1. Dominant or codominant c1q staining in kidney biopsy
2. Mesangial electron dense deposits
3. No clinical or serological evidence of SLE.

Two predominant clinicopathological subsets of c1q nephropathy are as follows:

1. Podocytopathy with a minimal change lesion or FSGS which typically presents with nephrotic syndrome
2. The typical immune complex glomerular disease that varies from no glomerular lesion to diffuse form of glomerular lesion.



**Table 3: Distribution of treatment and follow-up**

Age	Sex	Immunosuppressive medication	Duration of follow-up (months)	S. Cr	U. Alb	U. spot PCR	Response
29	F	Oral steroids	30	1.2	4+	4.0	NR
24	F	MP - three doses, cyclo six doses, PDN+AZA	22	1.3	3+	2.0	PR
29	F	MP - three doses MMF+PDN	18	1.5	3+	3.0	NR
36	F	ACEI+Statins	14	0.8	+	0.3	SR
48	F	ACEI+Statins	14	0.9	Nil	0.2	SR
30	F	Oral steroids - 4 months	12	1.0	Nil	0.4	R
20	M	No follow-up					
33	F	MP - three doses, four doses of CYCLO Low-dose PDN+AZA	9	2.5	4+	3.5	NR
26	F	ACEI+Statins	9	0.8	Trace	Nil	SR
40	F	MP 3 doses+6 doses of cyclo low-dose PDN	8	1.6	4+	3.0	NR
14	F	Oral steroids	8	0.8	4+	3.5	NR
20	F	Oral steroids+AZA	4	1.1	Nil	1.0	PR
43	F	Oral steroids	3	0.9	Nil	0.2	R

MMF: Mycophenolate mofetil, PCR: Protein-creatinine ratio, ACEI: Angiotensin-converting enzyme

C1q, the first component of the complement cascade, is a pentamer compound consists of single c1q, two c1r, and two c1s. The complement cascade begins with the CH2 domain of IgG molecule binding to c1q, leads to conformational changes that sequentially activate c1r and c1s, and initiates a cascade of downstream events. C1q is a large calcium-dependent glycoprotein had Ig-binding site and controlled triple helical collagen-like domain. C1q results from complement activation by IgG. Hence, IgG is a codeposit along with c1q. C1q fixes the Ig that may become trapped non-specifically in the mesangium due to increased mesangial trafficking and defective clearance of plasma proteins. Ultrastructurally, c1q is located in the paramesangial area. Paramesangial area is a site where small electron dense deposits are not uncommonly seen. In MCD/FSGS, non-specific deposit of IgM and/or C3 can be seen in the paramesangial area. In the absence of the history of autoimmune disease, it is unlikely that the deposits of IgG and c1q can be found in the paramesangial area.<sup>[7-10]</sup>

When c1q nephropathy presented as proliferative GN, it shares some features with IgA nephropathy in renal biopsy. Overlapping with IgA nephropathy can be differentiated by more intense staining of c3 than c1q in IgAN.<sup>[8]</sup> In contrast to lupus nephritis, tubular reticular inclusions and antibody against c1q are usually negative in c1q nephropathy.<sup>[9]</sup>

Iskandar *et al.* reported that a series of 15 children with c1q nephropathy, in their experience c1q nephropathy, appear to fit within the morphology of MCD/FSGS, and the most common presentation is nephrotic or non-nephrotic proteinuria.<sup>[6]</sup>

Markowitz *et al.* reported that the largest series of c1q nephropathy, histologically falls within MCD/FSGS continuum and appears to exhibit the full spectrum of the histological variant of FSGS. Their cohort of 19 patients was predominately African-American females, and the

cohort age group falls between 10 and 30 years of age. Their cohort had full nephrotic range proteinuria in 50% and renal insufficiency in 27.8%. The light microscopic evaluation showed MCD (two cases), FSGS NOS (nine cases), collapsing FSGS (six cases), and cellular FSGS (two cases). The outcome was generally good with 7 of 13 patients entering into partial or complete remission over a mean follow-up of 27.1 months.<sup>[5]</sup>

Davenport *et al.* reported four adult patients with c1q nephropathy, the pattern of glomerular disease was MPGN Type III, DPGN, FSGS, and membranous nephropathy. All had nephrotic proteinuria and renal insufficiency. Hypocomplementemia was reported in three patients, three patients underwent spontaneous remission, and one patient with FSGS had complete remission with steroids and cyclosporine.<sup>[11]</sup>

Sharman *et al.* reported nine cases with c1q nephropathy with the different light microscopic picture of diffuse proliferative GN (three cases) FSGS (two cases), combined membranous and mesangial proliferation (three cases), and crescentic GN (one case). All nine patients had c1q deposit in the mesangial and paramesangial region. In this series, more patients had asymptomatic proteinuria with the fewer nephrotic syndrome when compared with other studies. Ultrastructural evidence of tubule reticular inclusion was absent in all patients. Poor response to corticosteroids with the renal survival of 85% at 3 years was reported.<sup>[10]</sup>

In our cohort, we had predominately female patients (12 of 13 patients), all satisfied the diagnostic criteria of c1q nephropathy as suggested by Jennet and Hipp. In our cohort, DPGN was the dominant histopathological finding with the partial cellular crescent in two patients, nephrotic proteinuria in 10 patients, and renal failure was found in four patients. Steroid unresponsiveness was found in five patients (one FSGS and four DPGN) and none of them



showed the progression of renal failure. In concordance with Davenport *et al.* reported in NDT 1992 and Sharman *et al.* reported in NDT 2004, our cohort was predominantly DPGN. Reanalysis of ANA, C3, and C4 was negative and normal levels, respectively. Our cohort did not undergo assay of anti-c1q antibody and electron microscopy examination for tubuloreticular inclusions.

## CONCLUSION

All of our patients had hypertension and microscopic hematuria. Nephrotic proteinuria was found in three-fourths of the patients. The most frequent histopathological presentation was diffuse proliferative GN. Inadequate response to immunosuppressive medication was found in more than half of the patients.

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# Comparing the Analgesic Efficacy of Parecoxib and Rofecoxib for Post-operative Analgesia Following Lower Abdominal Surgery

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## Abstract

**Background:** This study tested the hypothesis that an intravenous parecoxib 40 mg and deep intragluteal rofecoxib 40 mg will be effective for post-operative pain relief after hysterectomy and well tolerated.

**Materials and Methods:** In this prospective, double-blinded, placebo-controlled study, we included 90 women posted for hysterectomy under spinal anesthesia. Patients were allocated into three groups in Group A (intravenous parecoxib 40 mg), Group B (deep intragluteal rofecoxib 25 mg), and Group C (2 mL normal saline). We administered studied drug preemptively, 15 min before the surgical incision. We measured pain on visual analog scale (VAS) and recorded observations at fixed intervals to investigate the duration of post-operative analgesia. We administered 100 mg tramadol as rescue analgesic once patient complained 25% pain relief on VAS.

**Results:** A total of 90 patients were enrolled. All treatment groups had comparable demographics and baseline pain status. Overall, each rofecoxib dose was superior to each dose of parecoxib and parecoxib is superior to placebo for post-operative pain relief in patient who underwent hysterectomy. In our study, we observed that total duration of analgesia in Groups A-C was  $3.42 \pm 0.52$  h,  $5.23 \pm 0.52$  h, and  $2.31 \pm 0.23$  h, respectively, and average duration of post-operative analgesia in Groups A-C was  $1.21 \pm 0.41$  h,  $3.04 \pm 0.45$  h, and  $10 \pm 0.18$  min, respectively. All treatments were well tolerated.

**Conclusions:** In this study, we found that deep intragluteal rofecoxib 25 mg is more effective than intravenous parecoxib 40 mg and placebo; similarly, intravenous parecoxib 40 mg is more effective than placebo for post-operative pain relief in patients who underwent hysterectomy. Rofecoxib extends post-operative analgesia up to 5 h, parecoxib up to 3 h without any adverse effects. We did not find comparable results with previous studies.

**Key words:** Analgesic, Post-operative, Surgery

## INTRODUCTION

“The word pain comes from the Latin word poena which means punishment (Winston CV Parris).”<sup>[1]</sup> By definition, “pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”<sup>[2]</sup> Therefore, many patients are more afraid and anxious about post-operative

pain than surgery. Pain is very subjective and cannot be defined satisfactorily in medicine for a complete solution since long. Acute post-operative pain has specific characteristic and it is the only pain syndrome that can be predicted before its occurrence; hence, this pain is entirely different from other pain syndromes.<sup>[1]</sup> Many methods have been tried to treat post-operative pain since long back such as parenteral drugs including both narcotic and non-narcotics like anti-inflammatory and other drugs such as N-methyl-D-aspartate receptor blockers, namely ketamine and Mgso<sub>4</sub>, regional techniques such as caudal epidural and peripheral nerve blocks. Nowadays, multimodal analgesic approaches are preferred over any single modality of pain management. Several years ago the concept of preemptive analgesia emerged from the experimental researches and this new approach for the

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world of pain management had been considered promising and convincing but soon became controversial because of the different results.<sup>[3]</sup> Among the different analgesics, non-selective (cyclooxygenase-1 [COX-1] and COX-2) nonsteroidal anti-inflammatory drugs (NSAIDs) have limited use in post-operative pain relief often due to the risk of bleeding.<sup>[4]</sup> Few years, hence, some COX-2 inhibitors had been introduced as analgesics which lack the conventional side effects of non-selective NSAIDs, namely valdecoxib, celecoxib, etoricoxib, parecoxib, and rofecoxib. Many studies had been done to establish the efficacy of these COX-2 inhibitors in post-operative pain.

Parecoxib is the first injectable COX-2 selective inhibitor manufactured for the analgesia. It is a prodrug of valdecoxib and 28,000 more potent against COX-2 than COX-1,<sup>[4]</sup> rofecoxib another COX-2 selective inhibitor and is a methylsulfonyl derivative. It is found that it can selectively inhibit recombination COX-2 if compared with COX-1 selectivity in the ratio of >800.<sup>[5]</sup> Our work been done to study and compare the efficacy of recently introduced COX-2 inhibitors, parecoxib and rofecoxib for post-operative pain management after hysterectomy.

## MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Committee, a prospective, randomized, double-blind study was conducted in female patients which had been scheduled for hysterectomy at Netaji Subhash Chandra Bose Medical College, Jabalpur, M.P., from 2002 to 2005. 90 female patients of ASA Grades I and II of age ranging from 18 to 80 years were selected randomly who were posted for abdominal or vaginal hysterectomy under spinal anesthesia. Exclusion criteria for the present study were any contraindication for spinal anesthesia, known allergy to NSAIDs or any contraindications to NSAIDs, and history of bleeding disorder, patient was on anticoagulants, current pregnancy, breastfeeding, history of known, or suspected drug abuse. If patient was having any central nervous system, cardiovascular disorder, gastrointestinal, hepatic, renal or psychiatric disorder. After taking valid informed written consent, all the patients were examined preoperatively and vitals recorded. All the demographic data such as age, sex, weight, and height were noted. Patients were allocated into the three groups: Group A received intravenous parecoxib 40 mg, Group B patients received deep intragluteal rofecoxib 25 mg, and Group C patients received 2 mL normal saline. Group C was a control group. Under all aseptic precautions, spinal anesthesia had been administered to the study patients. Study drugs iv parecoxib, im rofecoxib, or normal saline were given as a preemptive analgesic to the patients 15 min before surgery. Injection

bupivacaine 0.5% (heavy) 3 mL administered into the intrathecal space at the level of L4-L5 intervertebral space. Vitals recorded every 5 min thereafter. After confirming the adequate level of spinal block. Visual analog scale (VAS) was used to measure the post-operative pain just after surgery and then at every 30 min interval. When the patient was having only 25% pain relief on VAS, this was taken as a cessation of analgesia and rescue analgesic intravenous tramadol 100 mg was given to the patient.

## RESULTS

The total duration of analgesia in Groups A-C was  $3.41 \pm 0.52$  h,  $5.23 \pm 0.50$  h, and  $2.31 \pm 0.23$  h, respectively. As shown in the table, the total duration of pain relief was maximum in Group B, and the difference in means of total duration of analgesia was found to be statistically significant ( $P < 0.0001$ ).

The total duration of post-operative analgesia was measured after the spinal anesthesia worn off completely. The duration of post-operative analgesia after the effect of spinal anesthesia was over in Groups A-C was  $1.21 \pm 0.41$ ,  $3.04 \pm 0.45$ , and  $0.10 \pm 0.18$  min, respectively. The maximum post-operative analgesia was found in Group B which was greater than Groups A and C. This difference in mean duration of post-operative analgesia was significant ( $P < 0.0001$ ).

This table shows the distribution of the groups according to the drugs administered to the patients for post-operative analgesia. All the groups comprised 30 patients each.

Table shows comparison of pre-operative bleeding time with post-operative bleeding time at different intervals. The bleeding time was recorded before the operation, postoperatively immediately after the operation, at 12 h and 24 h. As shown by this table, this difference was found to be statistically insignificant ( $P > 0.05$ ).

The total duration of analgesia was measured by VAS. This table shows the mean post-operative pain relief at every 30 min interval in all the groups [Figures 1-7 and Tables 1-7].

## DISCUSSION

Post-operative pain is a critical factor that hamper recovery from surgery, hence, relief from pain should be the first reason to provide optimum analgesia to all the patients who are suffering from pain including those who underwent surgical procedures.<sup>[6,7]</sup> Various studies suggested that parecoxib sodium and rofecoxib are effective in acute post-operative pain so we have decided to compare the efficacy of parecoxib and rofecoxib with placebo (NS)

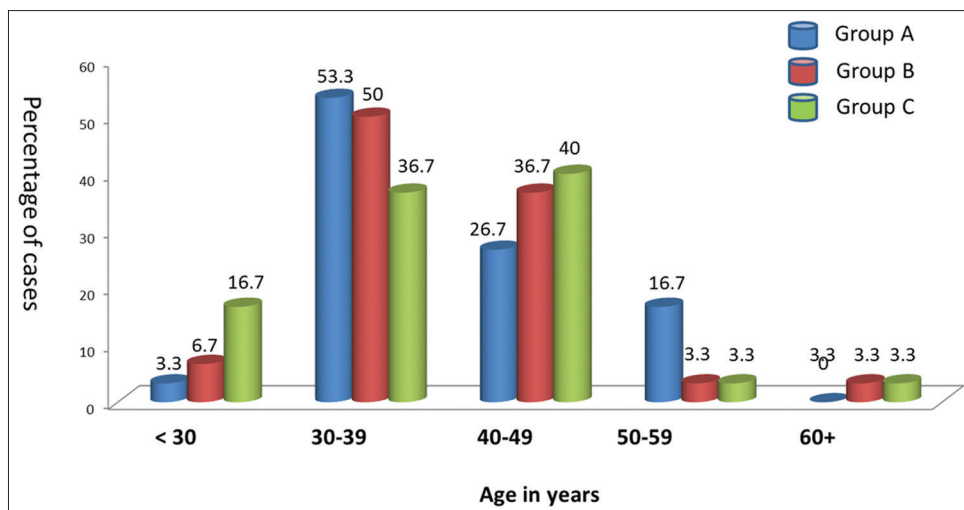


Figure 1: Distribution of the cases according to age in studied groups

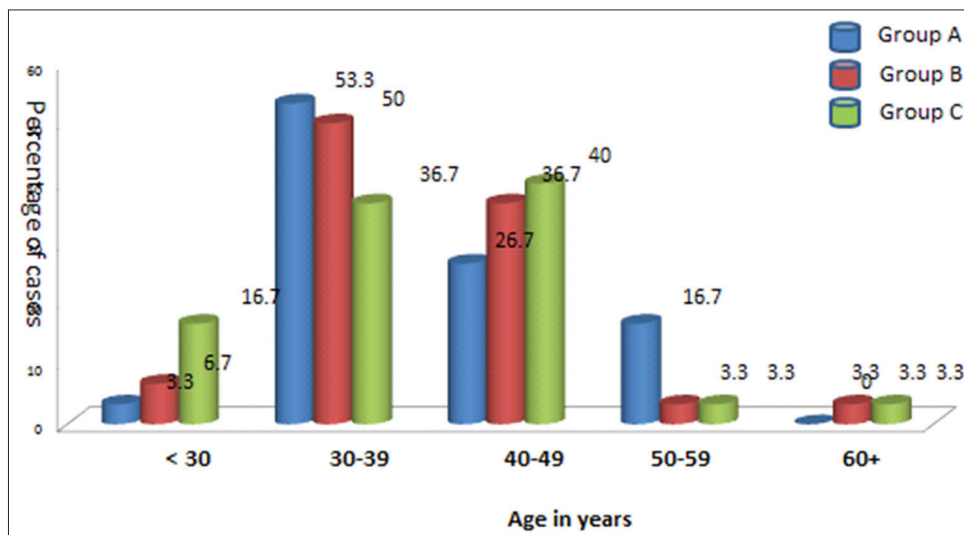


Figure 2: Distribution of the cases according to age in studied groups

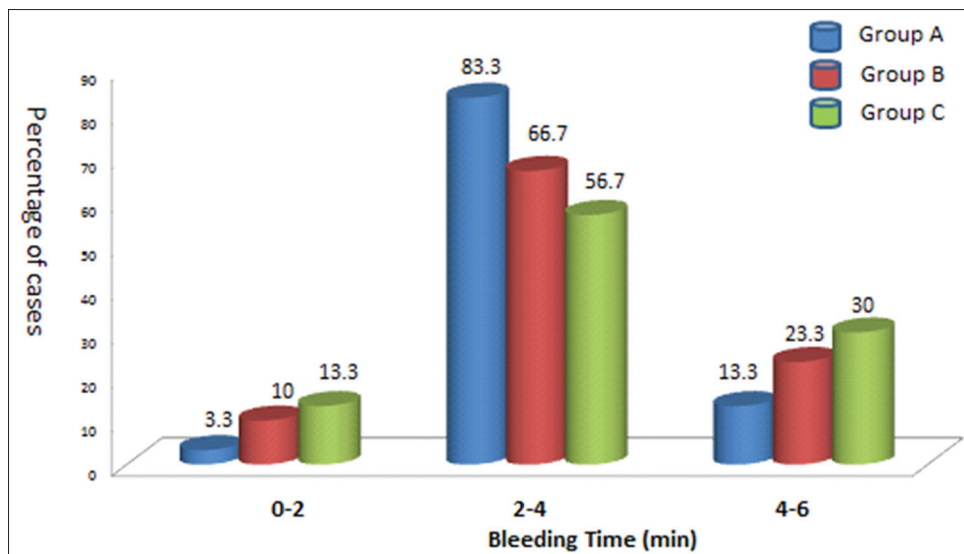


Figure 3: Study of average pre-operative bleeding time



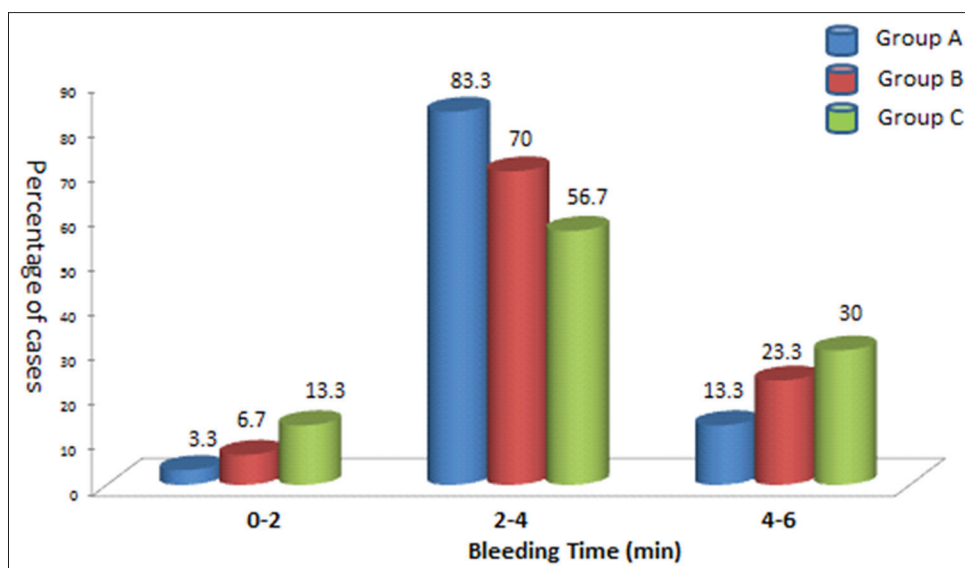


Figure 4: Study of average bleeding time immediately after operation

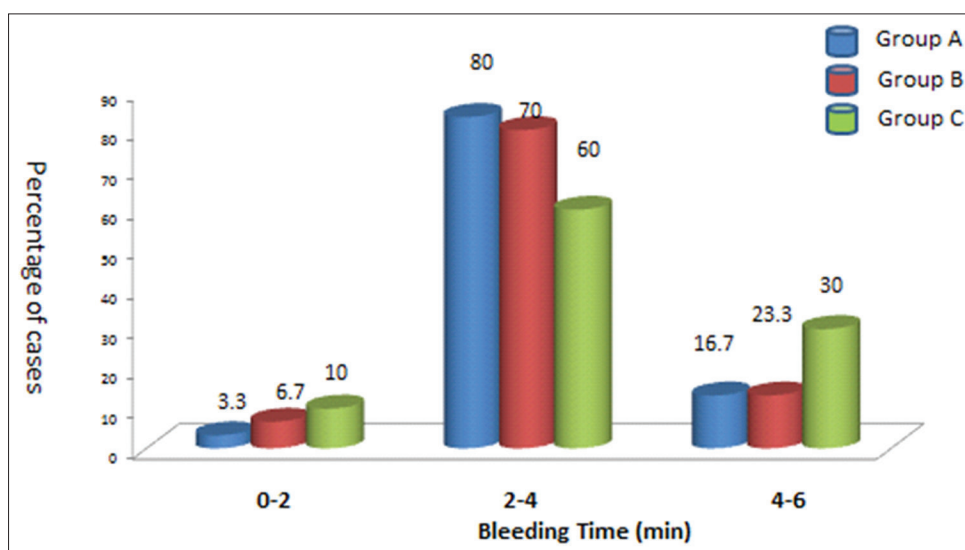


Figure 5: Study of average bleeding time 12 h

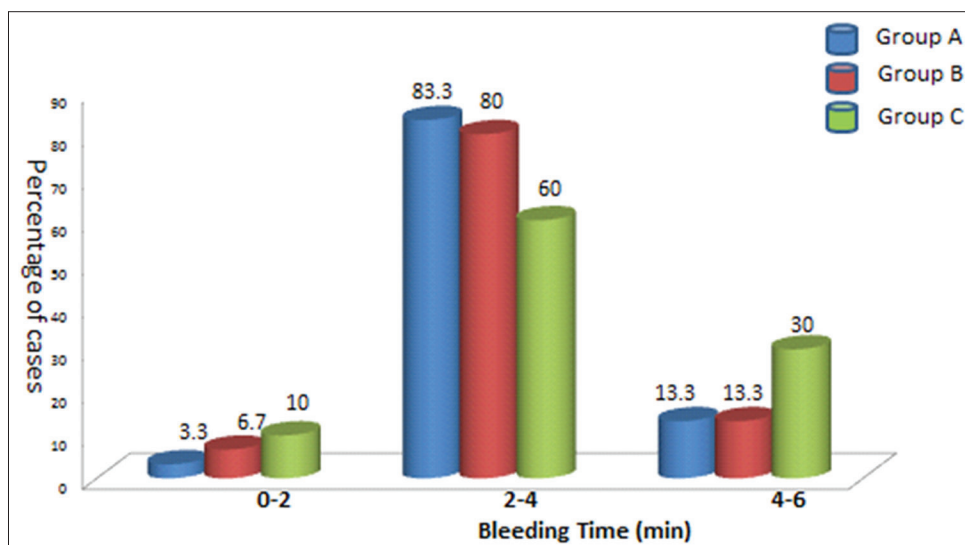


Figure 6: Study of average bleeding time 24 h

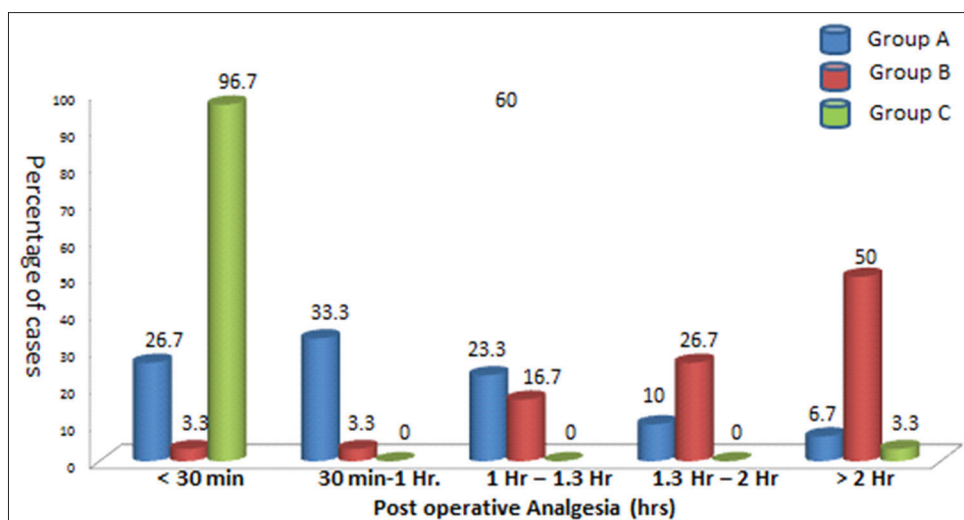


Figure 7: Comparison of post-operative analgesia in studied groups

Table 1: Distribution of the cases according to age

Age in years	Group A (%)	Group B (%)	Group C (%)
<30	1 (3.3)	2 (6.7)	5 (16.7)
30–39	16 (53.3)	15 (50.0)	11 (36.7)
40–49	8 (26.7)	11 (36.7)	12 (40.0)
50–59	5 (16.7)	1 (3.3)	1 (3.3)
60+	0 (0.0)	1 (3.3)	1 (3.3)
Total	30	30	30
Mean±SD	44.00±7.64	43.43±8.82	42.43±9.18

$P > 0.05$ . The age difference among all the groups was found insignificant

Table 2: Weight distribution of the patients in studied groups

Weight (kg)	Group A	Group B	Group C
<30	2	1	1
30–40	10	12	13
41–50	12	14	12
51–60	4	2	3
>60	2	1	1
Mean±SD	43±9.96	41.67±5.02	41.67±8.44

$P > 0.05$ . The weight difference among all the groups was found insignificant

Table 3: Comparison of total duration of analgesia in studies group (from study drug injection to VAS ≥ 25)

Total duration of analgesia in (hours)	Group A n=30 (%)	Group B n=30 (%)	Group C n=30 (%)
<2	1 (3.3)	0 (0.0)	4 (13.3)
2–4	19 (63.3)	1 (3.3)	26 (86.7)
4–6	10 (33.3)	24 (80.0)	0 (0.0)
>6	0 (0.0)	5 (16.7)	0 (0.0)
3.41±mean SD	3.41±0.52	5.23±0.50	2.31±0.23

$P = 0.0001$  significant

for post-operative analgesia. Average age of the patients in Groups A-C was  $44 \pm 7.64$  years,  $43.43 \pm 8.82$  years, and  $47.73 \pm 9.18$  years, respectively. Maximum number of

Table 4: Comparison of post-operative analgesia at the end of spinal anesthesia (from commencement of motor recovery to VAS ≥ 25)

Duration of post-operative analgesia	Group A n=30 (%)	Group B n=30 (%)	Group C n=30 (%)
<0.5 h	4 (13.3)	0 (0.0)	28 (93.3)
0.5–1 h	10 (33.3)	0 (0.0)	2 (6.7)
1–1.5 h	6 (20.0)	1 (3.3)	0 (0.0)
1.5–2 h	9 (30.0)	2 (6.7)	0 (0.0)
>2 h	1 (3.3)	27 (90.0)	0 (0.0)
Mean±SD	1.21±0.41	3.04±0.45	0.10±0.18

$P = 0.0001$  significant

Table 5: Distribution of patient's according to drugs

Group	Drug	Number of patients
A	I/V Parecoxib 40 mg+intrathecal bupivacaine heavy (0.5%) 3 mL	30
B	I/M Rofecoxib 25 mg+intrathecal bupivacaine heavy (0.5%) 3 mL	30
C	I/V normal saline (0.9%) 2 mL+intrathecal bupivacaine heavy (0.5%) 3 mL	30
	Total	90

patients was 30–39 years and the difference was statistically insignificant ( $P > 0.05$ ). The mean weight in Groups A-C was  $43 \pm 9.96$  kg,  $41.67 \pm 5.02$  kg, and  $41.67 \pm 8.44$  kg, respectively, and the difference was not significant ( $P > 0.005$ ).

In this study, all the studied drugs were given preemptively in patients who underwent hysterectomy, and it was comparable to many previous studies as to Desjardins *et al.*, who found that preemptive injection of parecoxib is effective, safe for the management of post-operative

analgesia and well tolerated by the patients as well.<sup>[8]</sup> Karamanlioglu *et al.* investigated that pre-operative use of oral rofecoxib has remarkable analgesic efficacy and opioid-sparing effect as well in patients who underwent abdominal hysterectomies.<sup>[9]</sup> Similarly, the parecoxib dose selected for our study was 40 mg and was also comparable to the previous study which was done by Barton *et al.* for treating acute pain after gynecological laparotomy surgeries.<sup>[10]</sup> Rofecoxib 25 mg dose had been given to the patients in our study which was also comparable to the study conducted by Reicin *et al.*, in their study, they investigated efficacy of single dose and multidose rofecoxib for the management of acute pain after orthopedic surgeries. They administered rofecoxib in 25 mg, 50 mg doses, and placebo and concluded that 25 mg rofecoxib is effective than placebo, but 50 mg once daily dose of rofecoxib was more superior than rofecoxib 25 g in managing post-operative pain ( $P \leq 0.267$ ) and had more opioid-sparing effect.<sup>[11]</sup>

In our, we found that deep intragluteal rofecoxib 40 mg (Group B) has a significantly greater total duration of

post-operative analgesia which was  $5.23 \pm 0.50$  h when compared with intravenous parecoxib 40 mg (Group A) which was  $3.14 \pm 0.52$  h and placebo (Group C)  $2.23 \pm 0.23$  h which was comparable to previous studies.

Reicin *et al.* conducted a double-blind, randomized, placebo- and active comparator-controlled, parallel-group trial in 218 patients enrolled for orthopedic surgery. They compared two doses of rofecoxib 25mg and 50 mg in their study and they concluded that 50 mg rofecoxib is superior for once daily dose than rofecoxib 25 mg for post-operative pain management after orthopedic surgery<sup>[12]</sup> which was not comparable to previous study as we found only  $5.23 \pm 0.50$  h post-operative pain relief after single dose of rofecoxib 40 mg.

Samra *et al.* had done a prospective study in 260 patients undergoing orthopedic, gynecological, dental, and general surgery to investigate the duration of post-operative analgesia after giving intravenous or intramuscular parecoxib 40 mg, and they found a very good pain relief in 89.6% of total cases at the end of 24 h. The mean duration of analgesia was 19.26 h in their study which was not comparable to our study as we found only  $3.41 \pm 0.52$  h of post-operative pain relief after single preemptive dose of parecoxib iv 40 mg.<sup>[6]</sup>

In another study done by Desjardins *et al.*, who investigated the analgesic efficacy of pre-operative parecoxib after unionectomy. In this study, they found that mean duration of analgesia was 4 h 18 min in the placebo group, 7 h 5 min in the 20 mg parecoxib group, and 10 h 43 min in 40 mg parecoxib group<sup>[8]</sup> which was also not comparable to our study because we found only  $3.41 \pm 0.05$  h of analgesia which was significantly lower than the previous studies.

**Table 6: Comparison of bleeding time at different intervals**

Period (minutes)	Group A	Group B	Group C
Baseline (pre-operative)	3.25±0.49	3.09±0.54	3.20±1.01
Immediately after operation	3.14±0.50	3.12±0.52	3.21±1.02
At 12 h	3.17±0.49	3.12±0.53	3.23±1.16
At 24 h	3.17±0.49	3.19±0.52	3.24±1.16
Significance	Z=0.86 P>0.05	Z=0.22 P>0.05	Z=0.04 P>0.05
	Z=0.63 P>0.05	Z=0.22 P>0.05	Z=0.11 P>0.05
	Z=0.63 P>0.05	Z=0.73 P>0.05	Z=0.14 P>0.05
	Z=0.63 P>0.05	Z=0.73 P>0.05	Z=0.14 P>0.05

**Table 7: Comparison of degree of pain relief in studied groups (VAS)**

Time interval	Group A	Group B	Group C	Significance
Initial	77.50±23.99 (n=30)	100.00±0.00 (30)	32.50±14.90 (30)	Z A/B=5.14 P<0.0001 Z A/C=8.73 P<0.0001 Z B/C=24.81 P<0.0001
0.30	62.96±16.07 (n=27)	93.10±11.37 (29)	32.14±12.20 (7)	Z A/B=8.05 P<0.0001 Z A/C=3.36 P<0.0001 Z B/C=6.86 P<0.0001
1.00	42.31±15.44 (n=26)	82.76±16.51 (29)	25.00±0.00 (2)	Z A/B=9.39 P<0.0001 Z A/C=5.72 P<0.0001 Z B/C=18.84 P<0.0001
1.30	40.63±12.50 (n=16)	70.69±16.46 (29)	25.00±0.00	Z A/B=6.86 P<0.0001
2.00	27.50±7.91 (n=10)	58.04±18.07 (28)		Z A/B=7.21 P<0.0001
2.30	50.00±0.00 (n=1)	47.00±18.14 (25)		Z A/B=0.83 P<0.05
3.00	25.00±0.00 (n=1)	43.06±18.80 (18)		Z A/B=4.08 P<0.0001
3.30		35.00±12.91 (10)		NA
4.00		40.00±13.69 (5)		NA

In 2002, Reuben *et al.*<sup>[12]</sup> investigated the effect of rofecoxib as a preemptive analgesic. In this study, they divided total number of patients in three groups in which they administered single dose of 50 mg rofecoxib 1 h before the surgical incision, the post-incisional group had been given 50 mg rofecoxib after the surgery was over, and in placebo group, they administered a placebo tablet before surgery. They found that analgesia was significantly longer in pre-incisional group ( $803 \pm 536$  min) when compared to post-incisional group ( $461 \pm 344$  min) and placebo group ( $318 \pm 180$  min). If we compare their with our study results, these were not comparable as we found the mean duration of analgesia of 5.23 h which was significantly lower than that of the Ruben's study in which they found 13.38 h pain relief after administering 50 mg rofecoxib preemptively, but in our study, we had used 25 mg dose of rofecoxib so dose was also not comparable. This difference in study design also justifies the difference in results between both the studies.

There were wide variations in the mean duration of analgesia observed by different researchers. This discrepancy could be due to multiple factors such as due to different designing of research, race and ethnic variations, different types of surgeries, different doses of studied drugs, different routes of administered drugs, different types of anesthesia techniques used in different studies, and different methods used to measure pain. Some explanations may be offered on the basis of individual reaction to pain, overall psyche of the patients, and intelligence do have a definite influence.

The present study was done under spinal anesthesia in which intrathecal injection of bupivacaine 0.5% heavy 3 mL had been administered to the patients. It was observed that the mean duration of spinal analgesia in Groups A-C was  $2.21 \pm 0.20$  h,  $2.19 \pm 0.18$  h, and  $2.21 \pm 0.22$  h, respectively. These values suggest that the difference between means duration of analgesia was statistically not significant ( $P > 0.05$ ). It means parecoxib, rofecoxib, and placebo do not affect the duration of spinal analgesia.

In our study, all cases were closely observed for any incidence of complications. In this study, we did not find any. None of the patient complaint of nausea, vomiting, headache or any hypersensitivity reaction.

In the present study, bleeding time was estimated preoperatively, immediately after the operation, at 12 h and at 24 h to notice any change in bleeding time and platelet

aggregation. The difference in the bleeding time at different intervals was comparable and statistically insignificant ( $P > 0.05$ ). It was observed that parecoxib, rofecoxib, and placebo all do not affect the bleeding time and platelet aggregation. Greenberg *et al.* found that rofecoxib did not alter the antiplatelet effects of low-dose aspirin. No clinical or laboratory adverse experiences were observed.

## CONCLUSION

In this study, we found that deep intragluteal rofecoxib 25 mg is more effective than intravenous parecoxib 40 mg and placebo; similarly, intravenous parecoxib 40 mg is more effective than placebo for post-operative pain relief in patients who underwent hysterectomy. Rofecoxib extends post-operative analgesia up to 5 h, parecoxib up to 3 h without any adverse effects. We did not find comparable results with previous studies

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# A Comparative Study of Injection Propofol Continuous Infusion and Bolus Doses for Maintenance of Anesthesia in Short Surgical Procedure

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## Abstract

**Introduction:** propofol is an intravenous anesthetic that is being used since years and it is most commonly used induction agent now a days. it has become very popular because of its characteristics of smooth induction and smooth recovery as well. in our study we studied the use of propofol during maintenance of anesthesia and we compared two techniques of propofol administration: continuous infusion and bolus doses of propofol.

**Material and methods:** This was an hospital based randomized control prospective study. After assessing patients and recorded all the vital parameters, patient was induced with iv propofol and in Group I, maintenance of anesthesia was achieved with an infusion of propofol at the dose of 100 µg/kg/min, while in Group II, maintenance of anesthesia was achieved with infusion in IB dose of 0.5 mg/kg on the need basis. Hemodynamic and other monitoring parameters were observed continuously and noted at an interval of 5 min during the operation. Intraoperative depth of sedation was measured by observers assessment of alertness and sedation scale. Score of 1 was considered to be the adequate depth of sedation while score 2 or more was considered to be inadequate depth. CI group patients with inadequate depth were excluded from the study. IB group with inadequate depth was given bolus dose of injection propofol 0.5 mg/kg. Patients were ventilated with 100% oxygen with Bain's Circuit. After surgery was over in IB group, no additional dose was given while in continuous group infusion was stopped immediately.

**Result:** There was no statistical significant differences among demographic parameters such as age, weight and sex. After 30 min of induction, there was a significant reduction of systolic blood pressure in both the groups and the statistically significant difference was there between Groups I and II ( $P=0.05$ ). there was a significant reduction of DBP from the baseline, and statistically, significant difference was there between Groups I and II ( $P=0.033$ ). The mean dose of propofol was required more in CI as compared to IB. There was a statistically highly significant difference between both the group with respect to a dose of propofol ( $P=0.001$ ). 71% of study subjects did not have any side effects. 14% had hypotension and 7% had bradycardia. Apnea was more in group II than group I subjects.

**Conclusion:** In our study, we compared two commonly used methods of dosing regimens, i.e., IB and CI. Both regimens provided comparable hemodynamic stability, depth of sedation, the incidence of adverse effects and recovery time. CI was associated with higher dose requirement and hence higher cost while it was also found to be the more satisfactory mode of anesthesia for both surgeons and patients. Each mode has its own advantage and disadvantage, and hence the method of choice depends on anesthetist's preference, availability of equipment and patients factors.

**Key words:** Propofol, Total intravenous anesthesia, Propofol infusion, Propofol bolus

Propofol was discovered in the year 1977 and gained popularity as an intravenous inducing agent of choice. It is

Intraoperative monitoring during procedures has shown that CI method leads to an adequate depth of anesthesia with less hemodynamic variability in most of the cases. Disadvantages of CI are the complexity of infusion pumps, cost of equipment, high-dose requirements, and delayed recovery. IB dose method is, hence, adopted in most of the scenarios. Although the intermittent dose is associated with more hemodynamic variability and post-operative complications, it is yet very simple and less cumbersome for short procedures. According to our hypothesis, CI

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of propofol might exert a sustained sedative effect by maintaining a constant concentration in the body, which will lead to better intraoperative sedation and hemodynamic stability. However, at the same time, it may lead to drug overdoses, prolong recovery, and side effects.

Development of an ideal drug delivery system has always been an area of interest for clinicians. Drugs used in the practice of anesthesia and critical care are used for a short period of time, but a constant drug concentration is also required. For this reason, different mode of delivering drugs has been studied. Propofol is delivered in form of bolus or CI regimen. Bolus doses are more popular for induction of anesthesia while continuous regimen is frequently used for maintenance of anesthesia and sedation in intensive care unit. For adequate depth of anesthesia, it is important to achieve a constant plasma concentration of the drug. For propofol this concentration is 3–5 µg/ml.<sup>[6]</sup>

This study was planned to compare both drug regimens for intraoperative hemodynamic stability, recovery characteristics, and post-operative complications. We also assessed the satisfaction level among patient and surgeons with both regimens during short surgical procedures. Cost-effectiveness of both regimens is also evaluated. Short surgical cases are very commonly performed in routine practice. Hemodynamic stability is of utmost importance for an anesthetist while quick recovery and less post-operative complications are also important for surgeon and patients. Ideal drug delivery system for short duration of procedures is still a debatable topic, and question remains unanswered. We attempt to find the answer to this query that which one is better method, IB, or CI?

Day surgery is now widely accepted as the default position for the vast majority of patients requiring surgery with inpatient stay chosen only by exclusion. There are very few absolute contraindications.

Day surgery patients have a finite time on the day surgery unit before discharge that same day. Therefore, prompt management of pain and nausea and vomiting and early mobilization are paramount. A more rapid recovery from anesthesia results in quicker turnaround, improved patient experience, and reduced costs.<sup>[7]</sup>

## TIVA

TIVA can be defined as a technique of general anesthesia using a combination of agents given solely by the intravenous route and in the absence of all inhalational agents including nitrous oxide.<sup>[8]</sup> The intravenous route has been used to administer drugs for hundreds of years, and the provision of anesthesia solely by the intravenous route using chloral hydrate was documented as early as the 1870's.<sup>[9]</sup>

Thiopentone was introduced into clinical practice in 1934 and made intravenous induction of anesthesia popular. Propofol was introduced into clinical practice in 1986 and now seems to be taking over that role. It has also become widely used as a component of TIVA.

TIVA has become popular, practical and possible only in relatively recent times. There are two main reasons for this. First, unlike other popular intravenous agents of the past, the pharmacokinetic and pharmacodynamic properties of modern drugs such as propofol and the newer synthetic, and short-acting opioids make them very suitable for administration by CI.<sup>[10]</sup> Second, new concepts in pharmacokinetic modeling and advances in computer technology have allowed the development of sophisticated delivery systems which make control of anesthesia given by the intravenous route as straightforward and user-friendly as conventional inhalational techniques.<sup>[11]</sup>

## Advantages of TIVA

TIVA has many advantages over inhalational anesthesia such as:

- No operating room pollutions
- Minimal cardiac depression
- Lesser neurohumoral response
- Decreased oxygen consumption
- Avoids distension of air-filled spaces within the patient's body, thus producing optimum operating conditions for the surgeon
- Avoids post-operative diffusion hypoxemia
- Decreases the incidence of PONV
- In day care surgery.<sup>[12]</sup>

TIVA can be administered with a variety of equipments. Very simple to operate Syringe Infusion Pumps is easily available. TCI pumps are sophisticated computer derived pumps which maintain steady-state concentration of propofol for adequate depth of sedation.<sup>[13]</sup> Recent advance in this field is in the form of closed-loop anesthesia delivery systems. It incorporates input from the patient's depth of sedation and adjusts the dose of anesthetic agents to maintain the depth of sedation.<sup>[14]</sup>

## MATERIALS AND METHODS

### Study Design

This was a hospital-based randomized interventional analytical study.

### Study Area

This was Peoples College of Medical Sciences and Research Centre, Bhopal.

### Study Population

Patients are coming for short surgical procedures admitted at PCMS and RC, Bhopal during November 14–March 16).

### Sample Size and Group Division

Sample size calculation was based on a pilot study involving 10 patients. A error was fixed at 0.05% with a power of study >80%. Sample size calculated was 100 patients that come in the defined period and fulfilling the inclusion criteria.

### Randomization

Each patient had an equal probability to get selected in either group with the help of randomization. They were randomized into two groups, that is, Group A IV IB and Group B CI.

### Inclusion Criteria

The following criteria were included in the study:

- Elective cases of ASA Grade I and II
- Age group 18–60 years
- Patients undergoing short surgical procedure.

### Exclusion Criteria

The following criteria were excluded from the study:

- Cases of ASA Grade III and above and emergency procedures
- Patients with the cardiovascular and respiratory disease
- Pregnant patients.

### Methodology

With Institutional Review Board Committee approval and written consent from all 100 patients of age group 18–60 years, undergoing elective surgeries of 45 min duration were randomized into two groups, using simple randomization technique, each group receiving either CI or IB doses of propofol.

### Anesthesia Technique

The standard anesthetic technique was used in all the patients. After securing intravenous line, monitoring gadgets were attached which included electrocardiography, SpO<sub>2</sub>, and non-invasive BP cuff. Baseline parameters were observed and recorded. Oxygen was delivered initially by face mask at 4 L/min.

All patients received premedication of injection ranitidine (1 mg/kg), injection ondansetron (0.08 mg/kg), injection midazolam (0.02 mg/kg), injection glycopyrrolate (0.004 mg/kg), and injection pentazocine (0.5 mg/kg).

### Induction of Anesthesia

Induction of anesthesia in patients of both groups was done with propofol 1.0 mg/kg body weight as IV bolus doses.

Hemodynamic and other monitoring parameters were observed continuously and recorded at an interval of 5 min.

### Maintenance of Anesthesia

In Group I, maintenance of anesthesia was achieved with an infusion of propofol at the dose of 100 µg/kg/min, while in Group II, maintenance of anesthesia was achieved with infusion in IB dose of 0.5 mg/kg on the need basis.

Hemodynamic and other monitoring parameters were observed continuously and noted at an interval of 5 min during the operation.

Intraoperative depth of sedation was measured by observers assessment of alertness and sedation scale. Score of 1 was considered to be the adequate depth of sedation while score 2 or more was considered to be inadequate depth. CI group patients with inadequate depth were excluded from the study. IB group with inadequate depth was given boluses dose of injection propofol 0.5 mg/kg.

Patients were ventilated with 100% oxygen with Bains Circuit.

After surgery was over in IB group, no additional dose was given while in continuous group infusion was stopped immediately.

Hemodynamic monitoring was continued until patient regained consciousness. Any complication during the procedure was noted and treated according to the protocol.

### Recovery

Recovery time to assess the shifting to recovery was done by Modified Aldrete score and patient was shifted when the score was >9 surgeons were asked to fill surgeon satisfaction score, and reading was noted. The patient was shifted to post anesthesia care unit (PACU) for monitoring.

Patients were asked to fill patient satisfaction score after 2 h of shifting from PACU and reading was noted. The incidence of PONV was noted in both groups. Post-operative pain score was noted with the help of visual analog scale.

### OAS/S

#### Surgeon's Satisfaction Scale

On scale of 1–5, 1 being least satisfied and 5 being highly satisfied.

- How satisfied are you with depth of anesthesia?
- How satisfied are you with intraoperative hemodynamics?
- How satisfied are you with recovery time?

- How satisfied are you with post-operative complications?
- How satisfied are you with the overall procedure?

### Patient's Satisfaction Scale

On a scale of 1–5, 1 being least satisfied and 5 being highly satisfied.

- How satisfied you are with awareness during procedure?
- How satisfied you are with pain during procedure?
- How satisfied you are with pain in post-operative period?
- How satisfied you are with nausea and vomiting in post-operative period?
- How satisfied you are with the overall experience of anesthesia services?

### Statistical Analysis

The data obtained were subjected to statistical analysis with the consult of a statistician. The data so obtained were compiled systematically. A master table was prepared, and the total data were subdivided and distributed meaningfully and presented as individual Tables 1 and 2 along with graphs.

Statistical procedures were carried out in two steps:

1. Data compilation and presentation
2. Statistical analysis.

Statistical analysis was done using Statistical Package of the Social Sciences (SPSS Version 20; Chicago Inc., USA). Data comparison was done by applying specific statistical tests to find out the statistical significance of the comparisons. Quantitative variables were compared using mean values and qualitative variables using proportions.

**Table 1: Observer's assessment of alertness/sedation scale**

Observation	Score level
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1

**Table 2: Demographic distribution of study subjects according to study groups and gender**

Gender	Group I Continuous infusion n (%)	Group II Intermittent bolus n (%)	Total n (%)
Male	15 (30.0)	21 (42.0)	36 (36.0)
Female	35 (70)	29 (58.0)	64 (64)
Total	50	50	100
Chi-square value	1.563		
P value	0.211 (NS)		

Significance level was fixed at  $P < 0.05$ .

## OBSERVATIONS AND RESULTS

### Demographic Distribution

#### Sex distribution

Table 2 reveals the demographic distribution of study subjects. Out of 100 study subjects, 36% were male and 64% were females. There was no statistically significant difference among both the groups with respect to gender ( $P = 0.211$ ).

#### Case-wise distribution

Table 3 reveals the distribution of study subjects according to respective specialties. Out of 100 subjects, maximum 44% were from gynecology department. There was no statistically significant difference among both the groups with respect to the department ( $P = 0.868$ ).

#### Age and weight wise distribution

Table 4 reveals mean age and weight of study subjects according to groups. There was no statistically significant difference among both the groups with respect to age ( $P = 0.181$ ) and weight ( $P = 0.980$ ).

### Systolic Pressure

Table 5 reveals mean systolic blood pressure (SBP) (mmHg) among the groups at a different time interval. After 30 min of induction, there was a significant reduction of SBP in both the groups and the statistically significant difference was there between Groups I and II ( $P = 0.05$ ).

### Diastolic Pressure

Table 6 reveals mean diastolic blood pressure (DBP) (mmHg) of the groups at different time interval. After 30 min of induction, there was a significant reduction of DBP from the baseline, and statistically, significant difference was there between Groups I and II ( $P = 0.033$ ).

Table 7 reveals mean heart rate (beat/min) among both the group at a different time interval. There was no statistically

**Table 3: Case-wise distribution of study subjects**

Departments	Group I Continuous infusion n (%)	Group II Intermittent bolus n (%)	Total n (%)
Gynecology	22 (44.0)	22 (44.0)	44 (44.0)
Surgery	8 (16.0)	10 (20.0)	18 (18.0)
Orthopedics	15 (30.0)	15 (30.00)	30 (30.0)
Others	5 (10.0)	3 (6.0)	8 (8.0)
Total	50	50	100
Chi-square value	0.722		
P value	0.868 (NS)		



**Table 4: Mean age and weight of study subjects according to groups**

Demographic Parameters	Group I Continuous infusion	Group II Intermittent bolus <i>n</i> (%)	Student's <i>t</i> -test value	<i>P</i> value
Mean age (years)	32.54	29.56	1.349	0.181 (NS)
SD	12.184	9.782		
Range (years)	18–56	18–60		
Mean weight (kg)	65.24	65.20	0.025	0.980 (NS)
SD	8.115	7.843		
Range	48–82	48–82		

**Table 5: Comparison of mean systolic blood pressure (mmHg) among the group at a different time interval**

Groups	Mean systolic blood pressure (mmHg)					
	Baseline		10 min		30 min	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Group I continuous infusion	122.04±12.8	120.50	106.58±10.9	108.0	111.04±10.6	109.0
Group II intermittent bolus	120.68±12.3	119.0	109.00±10.9	109.0	106.38±9.5	106.50
Mann–Whitney U-test value	1188.500		1089.500		967.000	
Significance <i>P</i> value	0.671 (NS)		0.267 (NS)		0.05 (S)	

**Table 6: Comparison of mean diastolic blood pressure (mmHg) among the group at a different time interval**

Group	10 min		30 min	
	Mean±SD	Median	Mean±SD	Median
Group I Continuous infusion	61.64±7.2	60.0	61.84±5.5	62.50
Group II Intermittent bolus	58.50±7.1	58.0	59.52±6.7	58.0
Mann–Whitney U-test value	961.500		942.500	
Significance <i>P</i> value	0.046 (S)		0.033 (S)	

significant difference between the groups with respect to pulse rate ( $P = 0.959$ ).

Table 8 reveals the mean respiratory rate among the group at a different time interval. There was no statistical difference.

Table 9 reveals mean oxygen saturation SpO<sub>2</sub> (%) among the groups at a different time interval. Statistically, no significant difference was observed between both the groups ( $P = 0.676$ ).

Table 10 reveals mean observer assessment of sedation score (OASS) among the group at a different time interval. After 5 min mean, OASS was  $2.60 \pm 0.53$  and  $2.46 \pm 0.57$  in Groups I and II, respectively, and there was no statistically significant difference ( $P = 0.293$ ). At 10 and 20 min, the value significantly reduces to almost zero. After 30 min, it again increased to  $4.10 \pm 1.5$  and  $3.84 \pm 1.8$  in Groups I and II, respectively, and there was again no statistically significant difference between groups ( $P = 0.512$ ).

Table 11 reveals a mean dose of propofol (mg) among both the group. The mean dose of propofol was required more in CI as compared to IB. There was a statistically highly

significant difference between both the group with respect to a dose of propofol ( $P = 0.001$ ).

Table 12 reveals the incidence of side effects among both the group. 71% of study subjects did not have any side effects. 14% had hypotension and 7% had bradycardia. Apnea was more in Group II study subjects as compared to Group I.

Table 13 reveals the surgeon's satisfaction score among the group. Mean surgeon's satisfaction score was  $22.68 \pm 1.30$  and  $21.72 \pm 1.73$  in Groups I and II, respectively, and there was the statistically significant difference between both the group ( $P = 0.008$ ).

Table 14 reveals recovery time among the group. It was more in IB as compared to CI group study subjects, and there was no statistically significant difference between both the group ( $P = 0.450$ ).

## DISCUSSION

Daycare surgery is an evolving concept among surgeons and anesthetists. In the current practice of health-care services, it

**Table 7: Comparison of mean heart rate (beat/min) among the group at a different time interval**

Groups	Mean heart rate (beat/min)					
	Baseline		10 min		30 min	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Group I Continuous infusion)	77.62±11.1	78.0	71.08±11.5	70.50	71.70±10.2	71.0
Group II Intermittent bolus	77.44±9.8	79.0	71.88±13.7	76.0	71.98±10.5	72.0
Mann–Whitney U-test value	1230.000		1157.000		1242.500	
Significance <i>P</i> value	0.890 (NS)		0.521 (NS)		0.959 (NS)	

**Table 8: Comparison of mean respiratory rate among the group at a different time interval**

Groups	Mean respiratory rate/min					
	Baseline		10 min		30 min	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Group I Continuous infusion	11.80±1.8	12.0	10.32±2.7	11.0	11.96±1.5	12.0
Group II intermittent bolus	11.32±1.8	11.0	10.24±2.8	11.0	11.40±1.9	11.5
Mann–Whitney U-test value	1032.000		1239.500		1078.000	
Significance <i>P</i> value	0.126 (NS)		0.942 (NS)		0.228 (NS)	

**Table 9: Comparison of mean SpO<sub>2</sub> (%) among both the group at a different time interval.**

Groups	Mean SpO <sub>2</sub> (%)					
	Baseline		10 min		30 min	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Group I Continuous infusion	98.58±0.60	99.0	97.84±1.8	98.0	98.28±0.83	98.0
Group II Intermittent bolus	98.70±0.58	99.0	97.16±2.8	98.0	97.96±1.5	98.0
Mann–Whitney U-test value	1109.000		1110.500		1194.000	
Significance <i>P</i> value	0.225 (NS)		0.308 (NS)		0.676 (NS)	

**Table 10: Comparison of mean observer assessment of sedation score among both the group at a different time interval**

Groups	Mean OASS							
	5 min		10 min		20 min		30 min	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Group I Continuous infusion	2.60±0.53	3.0	0.06±0.24	0.0	0.16±0.42	0.0	4.10±1.5	5.0
Group II Intermittent bolus	2.46±0.57	2.5	0.24±0.43	0.0	0.16±0.37	0.0	3.84±1.8	5.0
Mann–Whitney U-test value	1116.500		1025.000		1229.000		1173.000	
Significance <i>P</i> value	0.293 (NS)		0.012 (S)		0.815 (NS)		0.512 (NS)	

**Table 11: Comparison of mean dose of propofol (mg) among both the group**

Groups	Mean±SD	Median	Range
Group I Continuous infusion	250.30± 29.76	245	180–320
Group II Intermittent bolus	198.60± 19.51	195.0	160–260
Mann–Whitney U-test value	167.000		
Significance <i>P</i> value	0.001 (HS)		

is important to consider the length of hospital stay, patient's safety and comfort to improvise the health-care system.

Daycare surgeries which comprise 10–40% of total surgeries in the western world have an important economic

**Table 12: Incidence of side effects among both the group**

Departments	Group I Continuous infusion <i>n</i> (%)	Group II Intermittent bolus <i>n</i> (%)	Total <i>n</i> (%)
No side effects	38 (76.0)	33 (66.0)	71 (71.0)
Hypotension	7 (14.0)	7 (14.0)	14 (14.0)
Apnea	2 (4.0)	6 (12.0)	8 (8.0)
Bradycardia	3 (6.0)	4 (8.0)	7 (7.0)

impact. Many procedures can be performed under the definition of daycare surgery. Hence, a comprehensive and scientific approach is required to conduct these surgeries.

**Table 13: Comparison of mean surgeon's satisfaction score among the group**

Groups	Surgeon's satisfaction score		
	Mean±SD	Median	Range
Group I Continuous infusion	22.68±1.30	23.0	20–25
Group II Intermittent bolus)	21.72±1.73	22.0	18–24
Mann–Whitney U-test value	872.000		
Significance P value	0.008 (S)		

**Table 14: Comparison of mean recovery time among the group**

Groups	Mean recovery time (min)		
	Mean±SD	Median	Range
Group I Continuous infusion	4.96±1.71	5.0	2–9
Group II Intermittent bolus	5.20±1.78	5.0	2–9
Mann–Whitney U-test value	1142.000		
Significance P value	0.450 (NS)		

Patient selection is important criteria for success of the surgeries, and it needs to be stressed on that not all patients are fit for the daycare surgeries. Likewise not all but many surgeries qualifies for daycare surgeries. Among all techniques available for anesthesia, TIVA has gained popularity and trust.

TIVA has evolved from very simple methods of drug administration by peripheral intravenous line to highly sophisticated closed-loop anesthesia delivery devices.

All these dosing regimens have been developed to achieve an appropriate and constant concentration of drugs in plasma. This, in turn, will lead to better hemodynamic characteristics, constant depth of sedation and hence better outcome of anesthesia.

TIVA in day surgery is advantageous due to rapid recovery without agitation and behavioral disorders. It is simple to use without the need for sophisticated gas delivery systems and scavenger equipment. It avoids the risks of failure of regional blocks, residual paralysis and less chance of side effects like PONV. It also avoids environmental pollution and also avoids the possibility of malignant hyperthermia. The disadvantages include pump failure, disconnection, and awareness.<sup>[15]</sup> The use of N<sub>2</sub>O is associated with increased risk of PONV.

Sevoflurane and desflurane are associated with rapid emergence than propofol. Desflurane emergence is faster than sevoflurane even in prolonged procedures, especially in obese patients.<sup>[8]</sup>

In this study, we compared two dosing regimen of injection propofol for patient posted for short surgical procedures (<40 min) under TIVA. In IB group, after induction with

injection propofol and IB of injection propofol was used to maintain the depth of anesthesia until the end of the procedure. In CI group, after induction with injection propofol, CI of injection propofol was started with the help of syringe infusion pump until the end of the procedure to maintain adequate depth of anesthesia.

We compared the hemodynamic parameters, depth of sedation, the incidence of side effects, total doses required, patients and surgeons satisfaction with anesthesia services, recovery time, and post-operative pain score in two dosing regimens. 100 patients of ASA Grade I and II of both gender were enrolled for the study. Among 100 patients, 36 were male and 64 were females. 84 belonged to ASA I and 16 were of ASA II. Patients with higher ASA grading were excluded from the study. There was no statistically significant difference between two groups ( $P = 0.211$ ). Written informed consent was obtained from all the patients. The patients were randomized into two groups, namely Group CI, i.e., CI and Group IB, i.e., IB.

Two groups were comparable with regard to their demographic variables. Wide range of surgeries was performed such as Dilatation and Curettage, Resuturing, Incision and Drainage, Implant removal, endoscopy, and foreign body removal. Gynecological procedures comprised 44% of total cases, 30% were from orthopedics and 18% were from surgery. Patients were preloaded with lactated ringers solution at the rate of 20 ml/kg/h. Standard monitoring equipment were attached, and baseline parameters such as Pulse, Blood Pressure, Respiratory Rate, SpO<sub>2</sub>, and level of consciousness were recorded and noted.

Induction of anesthesia was done by propofol 1.5 mg/kg over 60 s in both the groups. In CI group after induction propofol was administered with syringe infusion pump connected with PMO line. Dose was 100 µg/kg/min. In IB group, propofol was given as Boluses of 0.5 mg/kg as required. The requirement was determined with the help of hemodynamic parameters. Increase in HR and BP and the presence of muscle movement was considered to be the point of IB dose.

Klein *et al.*, in 2003, studied intermittent and CI of propofol in pediatric oncology and found that both methods were equal in terms of hemodynamic stability and satisfaction among patient and physician, although CI was associated with higher doses and more reduction in blood pressure.<sup>[16,17]</sup> We had similar findings in our study.

Riphaeus *et al.*, in 2012, studied both regimens for deep sedation in interventional endoscopy. They found both regimens were equally good in terms of hemodynamic stability and depth of sedation. Infusion group was associated with less recovery time and more hypotension.<sup>[18]</sup>

González-Santiago *et al.*, in 2013, studied IB versus continuous, and they found both methods to be equally satisfactory.<sup>[5]</sup>

In our study, we used the standard anesthetic technique so that the groups were as comparable as possible except the study intervention. Baseline OAS/S score before premedication was noted in both the groups. After induction, all patients had OAS/S of 0 which was acceptable to start the procedure.

Changes in SBP, DBP, and mean arterial pressure were noted every 10 min during the procedure. Total 7(14%) patients in Group CI and 7(14%) in Group IB developed hypotension, i.e., 20% less than the baseline and were treated. Changes in heart rate were noted every 10 min during the procedure. Total 3 (6%) patients in Group CI while 4 (8%) in Group IB developed bradycardia, i.e., <50 BPM and were treated. Changes in respiratory rate was noted every 10 min during the procedure. Total 3 (6%) patients in Group CI while 4(8%) in Group IB developed apnea, i.e., temporary cessation of breathing. Bag and mask ventilation was done in these patients until respiration is regained.

Depth of sedation was noted every 10 min during the procedure. In Group CI adequate depth of sedation was maintained during the procedure and no additional boluses were required. Both groups had the comparable depth of sedation.

Recovery time was noted in both groups. Recovery was assessed with a modified Aldrete Score. Score of 9 was considered to be fit for discharge. In Group CI mean recovery time was 4.96 min while in Group IB mean recovery time was 5.2 min. There was no statistically significant difference between both groups in terms of recovery time.

Total doses of propofol were noted after each procedure. Total dose includes induction and maintenance by infusion or by IB. Dose required ranges from 180 to 320 mg in the CI group and mean of  $250 \pm 29.76$ . In Group IB dose ranged from 160 to 260 mg with a mean of  $198.60 \pm 19.51$ . This difference was statistically significant ( $P = 0.001$ ), and Group CI was associated with higher doses of propofol and hence higher cost of the procedure.

Immediately after the procedure, the operating surgeon was asked to fill a 5 point questionnaire. The response was noted and evaluated. In CI group score was ranged from 20 to 25, with a mean score of  $22.68 \pm 1.30$  and median of 23.0 In IB group score ranged from 18 to 24, with a mean score of  $21.72 \pm 1.73$  and median of 22.0. Mann-Whitney U-test

value was 872.000. There was the statistically significant difference between both groups ( $P = 0.008$ ), and CI group was associated with more satisfaction among the surgeons.

The primary objective of the study was to compare hemodynamic parameters, depth of sedation, incidence of side effects, total doses required, patients and surgeons satisfaction with anesthesia services, recovery time, and post-operative pain score of IB, and CI of propofol for maintenance of anesthesia in short surgical cases.

We observed that there was no significant difference in the context of hemodynamic stability, depth of sedation, incidence of side effects, recovery time, and post-operative pain score. IB group was found to be more cost effective due to low doses of propofol required to maintain the adequate depth of anesthesia ( $P < 0.05$ ). In CI group satisfaction among patients and surgeons both with the anesthesia services was higher than IB group ( $P < 0.05$ ).

## SUMMARY AND CONCLUSION

Propofol has been used by anesthetists since its discovery for induction and maintenance of anesthesia. It is an agent of choice for TIVA due to its favorable pharmacokinetic and dynamic profile. Propofol can be administered to patients by various methods including IB, CI, TCIs, and Closed Loop Pumps. Each mode has its own advantage and disadvantage, and hence the method of choice depends on anesthetist's preference, availability of equipments and patients factors.

In our study, we compared two commonly used methods of dosing regimens, i.e., IB and CI. Both regimens provided comparable hemodynamic stability, depth of sedation, the incidence of adverse effects and recovery time. CI was associated with higher dose requirement and hence higher cost while it was also found to be the more satisfactory mode of anesthesia for both surgeons and patients.

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# To Assess Rapid Shallow Breathing Index as a Predictor for Weaning in Intensive Care Unit Patients

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## Abstract

**Background:** Weaning from mechanical ventilation (MV) is a major concern for the intensivist and has disastrous results when not accomplished as per the protocols. The preweaning assessment of the patient, address of the underlying condition for which the ventilation was initiated, for recognition of difficult to wean in advance is the best method of preventing damage caused by the inability to maintain the airway.

**Aim:** This study was carried out to evaluate the efficacy of clinical test rapid shallow breathing index (RSBI) which can predict the successful weaning in patients undergoing elective or mandatory MV.

**Materials and Methods:** A total of 120 adult patients of age group 18–70 years of either sex of ASA Class I and II, undergoing MV for various procedures, were included in this study. Preweaning evaluation is carried out by measuring demographic variables, hemodynamic variables, arterial blood gas (ABG), and calculation of RSBI. These variables were then correlated with the success of weaning, successful extubation, need for reintubation, requirement of non-invasive support, and validation of pre-existing RSBI values. Data are presented as the mean  $\pm$  standard deviation. Results having  $P < 0.05$  were considered statistically significant.

**Results:** Sensitivity, specificity, positive predictive value, and negative predictive value of RSBI  $< 105$  as an index for successful weaning were 86.4%, 69.85%, 56.1, and 92.1, respectively. No method either individually or in combination with other identifies all cases of successful weaning. Overall failure to wean rate was 30.43% which was comparable with most of the other studies. There was a weak positive correlation between age and weaning failure, but it was not statistically significant. Correlation between weight and weaning failure was not established. There was a weak negative correlation between the duration of intubation and weaning failure. Patients who were intubated for longer period of time were associated with more incidence of weaning failure, but it was not statistically significant. The higher  $\text{PaO}_2/\text{FiO}_2$  ratio was associated with successful weaning, and there was a statistical significant difference among both groups. Bipap support was required in 15.8% patients in 48 h.

**Key words:** Mechanical ventilation, Reintubation, Rapid shallow breathing index, Weaning

## INTRODUCTION

Mechanical ventilation (MV) is a common life support modality in intensive care unit (ICUs). The process of ventilatory support follows a continuum of care, beginning with the patient requiring initial support and hopefully ending

with the ability to sustain spontaneous breathing. Some patients move through the process quickly, while others require a longer period, and some do not make it through at all. Throughout the process, many patient assessments are made and ventilator adjustments executed to accomplish the therapeutic goals of improving oxygenation and ventilation, increasing patient comfort, and minimizing the likelihood of causing secondary injuries such as ventilator-induced lung injury, ventilator-associated diaphragmatic dysfunction, or ventilator-associated pneumonia (VAP).

Airway management and respiratory support are of great importance in ICU.<sup>[1]</sup> Weaning is a transmission process

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through which patients resume spontaneous breathing after MV.<sup>[1,2]</sup> Accurate weaning time is critically important in ICU. Any delay in ventilation removal may lead to ventilator acquired pneumonia and other possible side effects.<sup>[3,4]</sup> It is also associated with an increase in the cost of the treatment. Premature removal may increase the length of ICU stay or result in patient's death.<sup>[5]</sup> On the other hand, increase in a number of patients who need ICU hospitalization, and high relevant expenses have resulted in using a variety of indices including maximal inspiration pressure (P<sub>I</sub>max), minute ventilation, and vital capacity for successful weaning. These indices have different specificity and sensitivities.<sup>[6]</sup> All these criteria have their shortcomings. The clinical challenge then is to balance aggressiveness with safety. A common quality indicator addressing this balance is the reintubation rate (i.e., patients needing reintubation out of a total number of patients extubated). A value too low suggests unnecessary delays in ventilator removal; a value too high suggests inappropriate aggressiveness in support removal. Reported reintubation rates range from 4% to 23% for different ICU populations and may be as high as 33% in patients with mental status changes and neurologic impairment.<sup>[7,8]</sup>

Rapid shallow breathing index (RSBI) is one of the most commonly used indices which was first introduced by Yang and Tobin.<sup>[8]</sup> RSBI is calculated by this formula:

$$\frac{\text{Respiratory rate}}{\text{Tidal volume (liters)}}$$

Several medical centers perform weaning if RSBI is <105.<sup>[9]</sup> A variety of studies have defined different specificities and sensitivities for RSBI.<sup>[10,11]</sup> Our main objective of this study was to predict the success and failure of extubation based on clinical assessment and RSBI criteria. We wish to find sensitivity, specificity, positive predictive, and negative predictive value of RSBI. We also want to find the newer threshold of RSBI in Indian population, if it exists. Secondary objectives of our study are to find a correlation between age, sex, weight, duration of intubation, and PaO<sub>2</sub>/FiO<sub>2</sub> with success of weaning.

## Aims and Objectives

### Aims

This study is aimed to address the issue of assessing RSBI as an indicator for successful weaning from MV.

### Objectives

The objectives are as follows:

1. To evaluate sensitivity, specificity, positive predictive value, and negative predictive value of RSBI <105 as an indicator of successful weaning.
2. To redefine different values of RSBI as a better predictor of extubation success.
3. To find a correlation between age, sex, weight, duration of intubation, and PaO<sub>2</sub>/FiO<sub>2</sub> with success of extubation.
4. To find a correlation between RSBI and non-invasive ventilation in extubated patients.
5. To find out overall weaning failure rate in our institution using RSBI as an indicator.

## MATERIALS AND METHODS

This study was conducted after getting due approval from Institutional Ethics Committee and Scientific Committee. Written informed consent was taken from the attendants of the patients after providing them with the patient information sheet.

### Study Design

This was a prospective, observational, hospital-based clinical study.

### Study Site

This study was conducted at the Department of Anaesthesiology, St. Stephen's Hospital.

### Study Duration

This study was from June 2015 to May 2017.

### Study Population

Study was conducted on 120 patients admitted in Surgical ICU coming to St Stephen's Hospital who were intubated for at least 48 h.

### Sample Size

Sample size came out to be 112; we included a total of 120 patients in our study.

### Eligibility Criteria of Patient

#### Inclusion criteria

The following criteria were included in the study:

- Patients who are clinically stable and have the criteria for weaning from the ventilator.
- Patients who are intubated for at least 48 h.
- Age >18 years of either gender.

#### Exclusion criteria

The following criteria were excluded from the study:

- Patients who are clinically unstable.
- Evidence of myocardial ischemia, heart rate (HR) >140 beats/min.
- Patient with fever and significant electrolyte abnormalities.
- High vasopressor requirement (i.e., >5 mcg/min of noradrenaline) for maintaining blood pressure (BP).
- PaO<sub>2</sub>/FiO<sub>2</sub> <150–200 mm Hg with FiO<sub>2</sub> ≥50% and PEEP ≥8 cm of H<sub>2</sub>O.

- Unplanned extubation.
- Patient is unable to initiate an inspiratory effort.

### Study Intervention

All those patients who were intubated because of respiratory failure due to miscellaneous diagnosis for at least 48 h were included in the study.

Readiness for weaning was assessed patients who were hemodynamically stable, conscious, and oriented and having a minimum sign for respiratory distress were subjected to spontaneous breathing trial (SBT). Baseline hemodynamic variables such as HR, BP, and SPO<sub>2</sub> were recorded. Baseline ABG were done to assess PaO<sub>2</sub>/FiO<sub>2</sub> ratio. Baseline respiratory rate and tidal volume were calculated with Wright's Spirometer to calculate RBSI. Patients with RSBI <105 were subjected to 30 min SBT with T-Piece.

After 30 min, hemodynamic variables such as HR, BP, and SPO<sub>2</sub> were recorded. ABG were done to assess PaO<sub>2</sub>/FiO<sub>2</sub> ratio.

Respiratory rate and tidal volume were calculated with Wright's Spirometer to calculate RBSI. Patients with RSBI <105 were considered as a candidate for extubation. Patients were extubated after following standard protocol. After extubation patient was observed for 48 h. Hemodynamic parameters such as HR, BP, and SPO<sub>2</sub> were recorded. RR was also recorded and ABG were obtained for monitoring the period of extubation.

Patients showing signs of clinical deterioration were provided with non-invasive ventilation with Bipap support and then observed for clinical stability. Patients who were not able to maintain the clinical stability were reintubated, and they were considered to be a failure to wean on the basis of RSBI.

### Study Tools

Wright's Spirometer and RSBI.



### Statistical Analysis

The data obtained were subjected to statistical analysis with the consult of a statistician. The data so obtained were compiled systematically. A master table was prepared, and the total data were subdivided and distributed meaningfully and presented as individual tables along with graphs.

Statistical procedures were carried out in two steps:

1. Data compilation and presentation.
2. Statistical analysis.

Statistical analysis was done using (Statistical Package of the Social Sciences Version 20; Chicago Inc., USA). Data comparison was done by applying specific statistical tests to find out the statistical significance of the comparisons. Quantitative variables were compared using mean values and qualitative variables using proportions.

Significance level was fixed at  $P \leq 0.05$ .

## RESULTS AND OBSERVATIONS

Table 1 reveals the demographic distribution of study subjects according to age and gender. Most of the patients were >50 years old. There was the statistically significant difference in the distribution of study subjects according to age and gender ( $P = 0.015$ ).

Tables 2 and 3 reveal the demographic distribution of study subjects according to weight and gender. There was statistically no significant difference in the distribution

**Table 1: Demographic distribution of study subjects according to age and gender**

Age groups (year)	Male n (%)	Female n (%)	Total n (%)
<25	4 (3.3)	8 (6.7)	12 (10.0)
26-50	28 (23.3)	15 (12.5)	43 (35.8)
>50	49 (40.8)	16 (13.3)	65 (54.2)
Total	81 (67.5)	39 (32.5)	120 (100.0)
Mean age (year)	54.38	43.64	50.89
Chi-square value	8.339		
Significance <i>P</i> value	0.015 (S)		

**Table 2: Demographic distribution of study subjects according to weight and gender**

Weight (Kg)	Male n (%)	Female n (%)	Total n (%)
<50	13 (10.8)	6 (5.0)	19 (15.8)
50-70	49 (40.8)	23 (19.2)	72 (60.0)
>70	19 (15.8)	10 (8.3)	29 (24.2)
Total	81 (67.5)	39 (32.5)	120 (100.0)
Mean weight (kg)	61.51	61.59	61.53
Chi-square value	0.069		
Significance " <i>P</i> " value	0.966 (NS)		



of study subjects according to weight and gender ( $P = 0.966$ ).

Table 4 reveals the association of RSBI and Bipap requirement among study subjects. It's shows that mean RSBI of study subjects with the requirement of Bipap was 87.76. It was almost the same among both the groups ( $P = 0.990$ ).

Table 5 reveals the frequency of extubation success among study subjects. Out of 120 subjects, 83 (69.17%) were successfully extubated while 37 (30.83%) failed to extubate successfully.

Table 6 reveals the association of age and extubation success among study subjects. It's shows that the mean age of study subjects with successful extubation was less when compared to study subjects who require reintubation, but the difference was statistically not significant ( $P = 0.064$ ).

Table 7 reveals an association between weight and extubation success among study subjects. It was almost the same among both the groups ( $P = 0.971$ ).

Table 8 reveals extubation success among study subjects. It was less among subjects with successful intubation

as compared to subjects who required reintubation but statistically, it was insignificant ( $P = 0.160$ ).

Table 9 reveals the association of RSBI and extubation success among study subjects at baseline. It's shows that mean RSBI was less among subjects with success intubation as compared to subjects who required reintubation and the difference was statistically significant ( $P = 0.019$ ).

Mean  $\text{PaO}_2/\text{FiO}_2$  ratio was more among subjects with successful intubation but the difference was statistically not significant ( $P = 0.774$ ).

Tables 10 and 11 reveal the association of RSBI and extubation success among study subjects at 30 min. Mean RSBI was less among subjects with successful intubation, and the difference was statistically significant ( $P = 0.001$ ).

Table 12 reveals the association of  $\text{PaO}_2/\text{FiO}_2$  ratio and extubation success among study subjects at 30 min. It was more among subjects with successful intubation as compared to subjects who required reintubation. There was a statistically significant association ( $P = 0.188$ ).

**Table 3: Sensitivity, specificity, positive predictive value, and negative predictive value of RSBI**

Parameter	Values
Area under the ROC curve (AUC)	0.757
Sensitivity	86.4%
Specificity	69.85
Positive predictive value	56.1
Negative predictive value	92.1
Cutoff point using Youden Index	88

RSBI: Rapid shallow breathing index

**Table 4: Correlation of RSBI and requirement of Bipap among study subjects at 30 min**

Bipap required	RSBI		
	Mean±SD	Minimum	Maximum
Yes (n=25)	85.76±13.59	40	105
No (n=95)	85.80±13.88	41	104
Pearson's correlation coefficient	0.001 (no linear relation)		
Student t-test	0.013		
Significance P value	0.990 (NS)		

RSBI: Rapid shallow breathing index, SD: Standard deviation

**Table 5: Frequency of extubation success among study subjects**

Extubation success	n (%)
No	37 (30.83)
Yes	83 (69.17)

**Table 6: Association of age and extubation success among study subjects**

Extubation	Age (year)		
	Mean±SD	Minimum	Maximum
Success (n=83)	48.90±16.990	17	87
Failure (n=37)	55.35±18.379	17	90
Student t-test	1.872		
Significance P value	0.064 (NS)		

SD: Stanadard deviation

**Table 7: Association of weight and extubation success among study subjects**

Extubation	Weight (Kg)		
	Mean±SD	Minimum	Maximum
Success (n=83)	61.55±10.004	39	84
Failure (n=37)	61.49±8.252	48	79
Student t-test	0.036		
Significance P value	0.971 (NS)		

SD: Standard deviation

**Table 8: Intubation and extubation success among study subjects**

Extubation	Duration of intubation (days)		
	Mean±SD	Minimum	Maximum
Success (n=83)	2.99±0.956	2	7
Failure (n=37)	3.27±1.122	2	6
Student t-test	1.415		
Significance P value	0.160 (NS)		

**Table 9: Association of RSBI and extubation success among study subjects at baseline**

Extubation	RSBI		
	Mean±SD	Minimum	Maximum
Success (n=83)	83.88±13.236	44	105
Failure (n=37)	89.76±10.797	61	105
Student t-test	2.371		
Significance P value	0.019(S)		

RSBI: Rapid shallow breathing index, SD: Standard deviation

**Table 10: Association of PaO<sub>2</sub>/FiO<sub>2</sub> ratio and extubation success among study subjects at baseline**

Extubation	PaO <sub>2</sub> /FiO <sub>2</sub> ratio		
	Mean±SD	Minimum	Maximum
Success (n=83)	391.88±119.187	166	696
Failure (n=37)	384.95±128.466	216	633
Student t-test	0.287		
Significance P value	0.774 (NS)		

SD: Standard deviation

Table 13 reveals Bi-level positive airway pressure support needed at 24 h and 48 h. Out of 120 study subjects, 13 (10.8%) needed Bi-level positive airway pressure support at 24 h, and 6 (5%) needed Bi-level positive airway pressure support at 48 h.

Table 14 reveals re-intubation needed at 24 h and 48 h. Out of 120 study subjects, 28 (23.3%) needed re-intubation at 24 h, and 37 (30.83%) needed re-intubation at 48 h.

Tables 15 and 16 reveal Pearson's Correlation of Extubation Success with age, weight, duration of intubation, RSBI, and PaO<sub>2</sub>/FiO<sub>2</sub> ratio. All the parameters showed a negative correlation with extubation success except PaO<sub>2</sub>/FiO<sub>2</sub> ratio which had weak positive correlation ( $P = 0.001$ ) [Figures 1-16].

## DISCUSSION

Assessment of spontaneous breathing is a routine procedure carried out in all mechanically ventilated patients. Many different techniques are used to decide if a patient is able to breathe independently.<sup>[12]</sup> Pre-extubation respiratory parameters (also known as weaning predictors) and weaning strategies have been studied previously, and their relevance has been found to vary according to the center where the studies were carried out.<sup>[13]</sup>

MV can cause complications in several systems that can subsequently extend the amount of time that MV is required. Consequently, MV can lengthen a patient's stay in the ICU and increase the risk of mortality. Both prolonged ventilation support and early withdrawal are associated with

**Table 11: Association of RSBI and extubation success among study subjects at 30 min**

Extubation	RSBI		
	Mean±SD	Minimum	Maximum
Success (n=83)	82.52±14.033	40	105
Failure (n=37)	93.14±9.074	55	105
Student t-test	4.220		
Significance P Value	0.001 (HS)		

RSBI: Rapid shallow breathing index, SD: Standard deviation

**Table 12: Association of PaO<sub>2</sub>/FiO<sub>2</sub> ratio and extubation success among study subjects at 30 min**

Extubation	PaO <sub>2</sub> /FiO <sub>2</sub> ratio		
	Mean±SD	Minimum	Maximum
Success (n=83)	415.88±126.433	142	760
Failure (n=37)	384.22±107.736	220	630
Student t-test	1.323		
Significance P value	0.188 (NS)		

SD: Standard deviation

a number of complications.<sup>[14,15]</sup> Between 25% and 40% of extubated patients can develop respiratory failure,<sup>[16,17]</sup> even when extubation is performed appropriately. Moreover, there are no established objective parameters for identifying patients who are at risk of failure during the MV weaning procedure, and 5–20% of extubated patients require reintubation due to associated complications.<sup>[18,19]</sup> It has been shown that systematic identification protocols can significantly decrease the duration of MV by identifying patients with suitable conditions for the interruption of MV, which serves to reduce the likelihood of VAP, the MV times, the ICU and hospital stay and also the complications associated with prolonged ventilation and early withdrawal.<sup>[20,21]</sup>

Finding the cause of respiratory failure is the first step in the management of patients who are under MV. The second step is to select patients who can have spontaneous respiration and can breathe without the aid of ventilator.<sup>[22]</sup> A standard assessment method for weaning should be simple and safe.<sup>[23]</sup>

For the 1<sup>st</sup> time Yang and Tobin used RSBI for weaning in 1991. They reported RSBI as the most specific and most sensitive index for weaning. For tidal volume measurement, they used a special spirometer which was connected to the trachea.<sup>[8]</sup> Although some studies have considered RSBI as a useless method,<sup>[24,25]</sup> many ICUs use RSBI for weaning.<sup>[23]</sup> Such differences may be attributed to sample size or absence of a global definition for weaning.<sup>[25]</sup>

This study was done to evaluate sensitivity, specificity, positive predictive value, and negative predictive value

of RSBI <105 as an indicator of successful weaning. We also aimed to find a lower threshold of RSBI as a better predictor of successful weaning. With this study, we wanted to find a correlation between age, sex, weight, duration of intubation, and PaO<sub>2</sub>/FiO<sub>2</sub> with successful weaning.

In this prospective, observational and hospital-based clinical study, 120 patients who were admitted in SICU with at least 48 h of intubation were selected. SBT was given for 30 min to the patients who were hemodynamically stable and have RSBI <105. After 30 min, RSBI was recalculated and patients with value <105 were extubated. Extubated patients were observed for 48 h for any sign of hemodynamic compromise and requirement of NIV or reintubation. Patients who were reintubated in 48 h were considered to be a failure to wean.

Demographic parameters such as age distribution and sex distribution were recorded.

**Table 13: Bi-level positive airway pressure support needed at 24 h and 48 h**

Bi-level positive airway pressure	24 h n (%)	48 h n (%)
Yes	13 (10.8)	6 (5)
No	107 (89.2)	114 (95.0)

**Table 14: Re-intubation needed at 24 h and 48 h**

Re-intubation	24 h n (%)	48 h n (%)
Yes	28 (23.3)	37 (30.83)
No	92 (76.7)	83 (69.16)

**Table 15: Success of intubation according to gender**

Success	Male (%)	Female	Total
Success	57 (47.5)	26 (21.7)	83
Failure	24 (20.0)	13 (10.8)	37
Total	81	39	
Chi-square value	0.169		
P value	0.681 (NS)		

**Table 16: Pearson's correlation of extubation success with age, weight, duration of intubation, RSBI, and PaO<sub>2</sub>/FiO<sub>2</sub> ratio**

Parameters	Extubation success		
	Pearson's correlation coefficient (r)	P value	Inference
Age	-0.170	0.064	Weak Negative Correlation
Weight	-0.003	0.971	No Linear Relationship
Duration of intubation	-0.129	0.160	Weak Negative Correlation
RSBI	-0.362**	0.001	Moderate Negative Correlation
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	0.121	0.188	Weak Positive Correlation

RSBI: Rapid shallow breathing index

Mean duration of intubation with successful extubation and failure of extubation was 2.99 ± 0.956 and 3.27 ± 1.12, respectively [Table 8]. With RSBI <105, we extubated all the patients and observed them for 48 h. Failure rate was 30.43% in our clinical study [Table 5]. An investigation by Esteban *et al.*<sup>[26]</sup> is perhaps the best known of the randomized trials. This multicenter study evaluated four methods of weaning patients from MV: Intermittent mandatory ventilation, pressure support ventilation, intermittent SBTs throughout the day, and single SBTs. Failure of extubation occurred in 13.8%, 18.9%, 15.2%, and 22.6% of the patients, respectively.<sup>[26]</sup> More recently, Bien *et al.*<sup>[27]</sup> evaluated the predictive power of three contemporary methods of weaning: T-piece, automatic tube compensation, and pressure support ventilation in 68 consecutive medical ICU patients. The rate of failure of extubation for the cohort was 33.8%.

ROC curve was drawn to estimate the parameter, and we found sensitivity to be 86.4%, specificity was 69.85%, positive predictive value was 56.1, and negative predictive value was found to be 92.1 [Table 3]. Fadaei *et al.*<sup>[28]</sup> found that RSBI <105 breaths/min/L has specificity, sensitivity, negative predictor value, and positive predictor value of 77.8%, 71.4%, 96.1%, and 26.3%, respectively. Yang and Tobin<sup>[29]</sup> in their benchmark study found that RSBI <105 is associated with sensitivity, specificity, positive predictive value, and negative predictive value of 97%, 64%, 78%, and 95%, respectively. These values are comparable with our study.

Mean RSBI for patients with successful extubation was 82.52 while it was 93.14 in patients who failed to wean [Table 11]. Our finding was in agreement with Youssef *et al.*<sup>[30]</sup> who found that RSBI value associated with success and failure was 72.9 and 96.0, respectively. Chao *et al.*<sup>[31]</sup> found in their study that lower threshold for RSBI can be as low as 97.

In our study, most of the patients were more than 50 years old, i.e., 65 (54.2%). Extubation was more successful in patients with lesser age. There was statistically no significant association between age and extubation success ( $P = 0.064$ ) [Table 6]. This observation was in also done by Pilcher

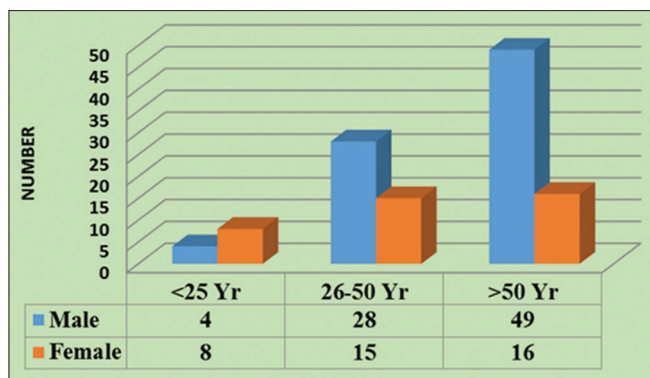


Figure 1: Demographic distribution of study subjects according to age and gender

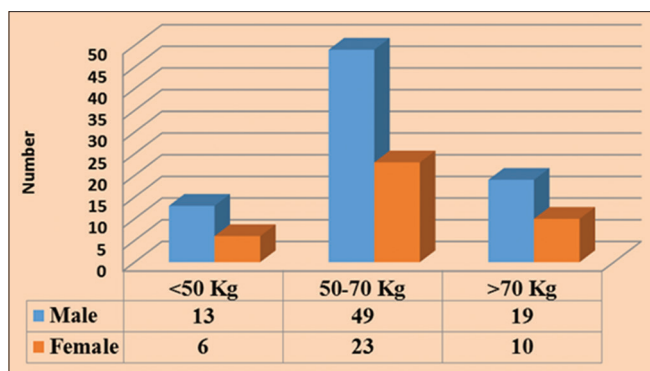


Figure 2: Demographic distribution of study subjects according to weight and gender

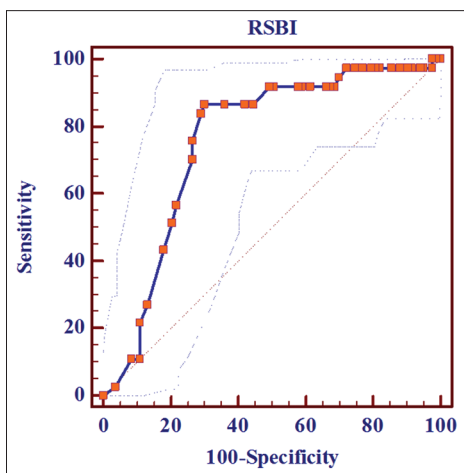


Figure 3: Showing sensitivity and specificity of RSBI

*et al.*<sup>[32]</sup> where they found that though old age patients are associated with more risk of weaning failure but the correlation between age and extubation success is not very strong. Pearson Correlation Coefficient is  $-0.170$  which is weak negative correlation.

In our study, it was observed that the mean weight of study subjects with successful extubation and failure was  $61.55 \pm 10.00$  and  $61.49 \pm 8.25$ , respectively. It was almost the same

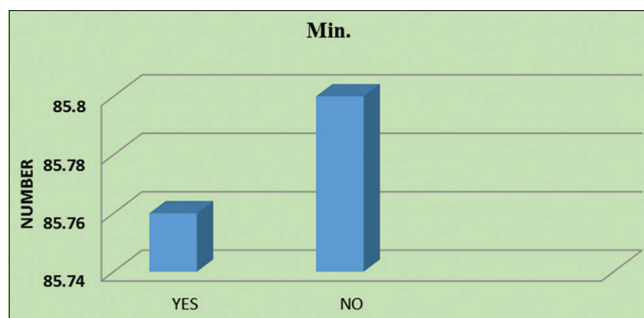


Figure 4: Correlation of rapid shallow breathing index and requirement of Bipap among study subjects at 30 min

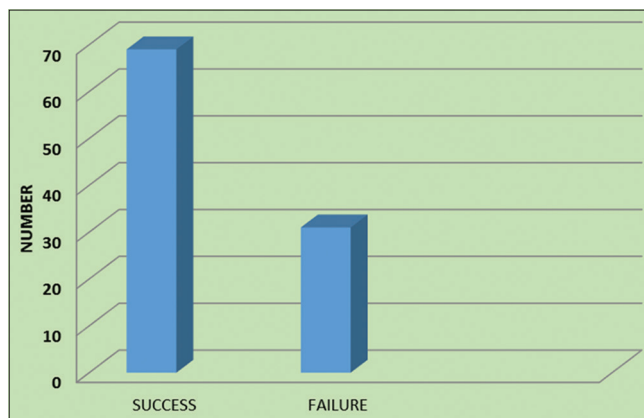


Figure 5: Frequency of extubation success among study subjects

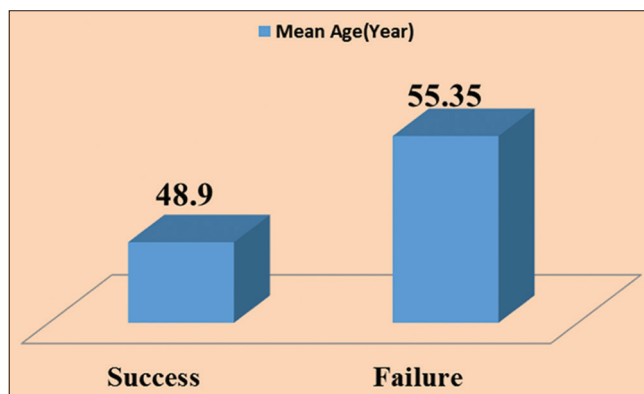


Figure 6: Association of age and extubation success among study subjects

among both the groups ( $P = 0.971$ ) [Table 7]. Association between the weight of patient and extubation success has not been studied in the past. Pearson's Correlation Coefficient is  $-0.003$  with  $P$  value of  $0.9$ , and hence no correlation has been established in our study. Sex also does not affect the weaning success. Utensute *et al.* found that female sex is associated with a higher failure rate than the male ( $97\%$  vs.  $90\%$ ).<sup>[33]</sup>

In our study, the mean duration of intubation with successful extubation and failure was  $2.99 \pm 0.956$  and  $3.27 \pm 1.12$  days, respectively. It was less among subjects with



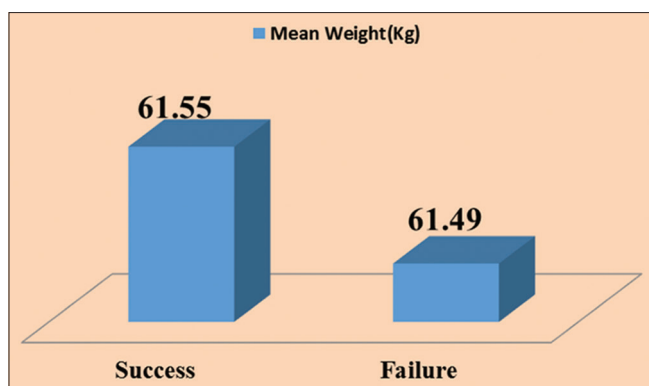


Figure 7: Association of weight and extubation success among study subjects

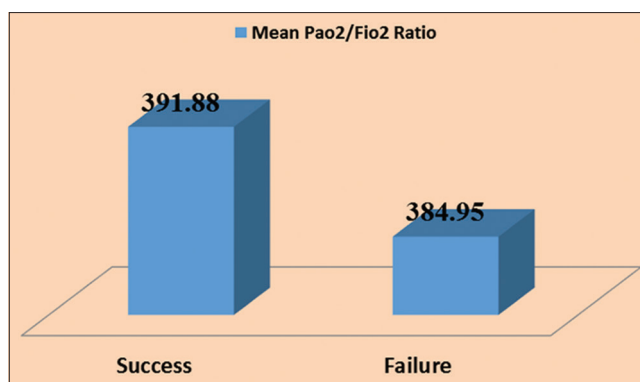


Figure 10: Association of PaO<sub>2</sub>/FiO<sub>2</sub> ratio and extubation success among study subjects at baseline

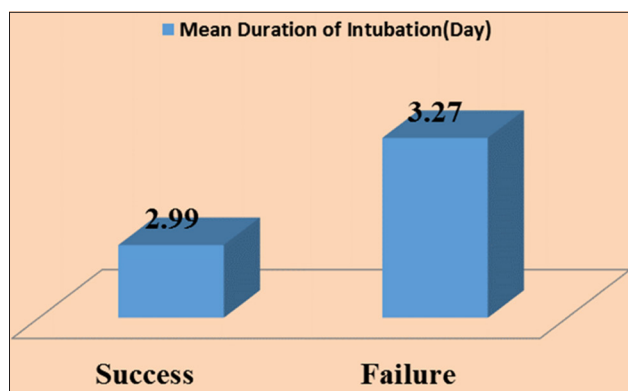


Figure 8: Association of intubation and extubation success among study subjects

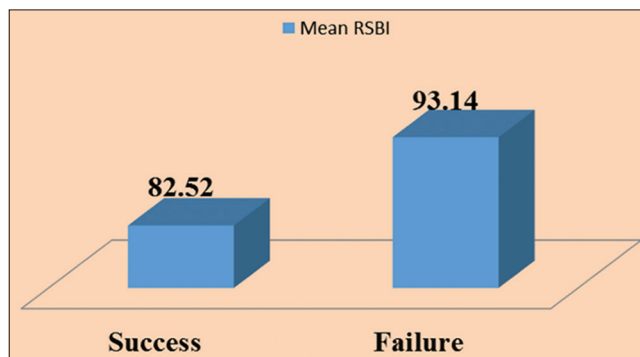


Figure 11: Association of rapid shallow breathing index and extubation success among study subjects at 30 min

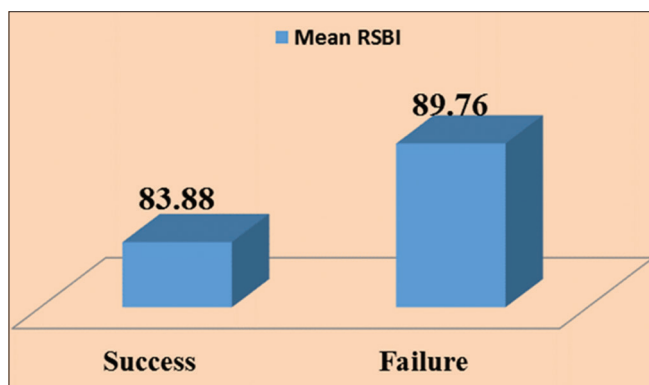


Figure 9: Association of rapid shallow breathing index and extubation success among study subjects at baseline

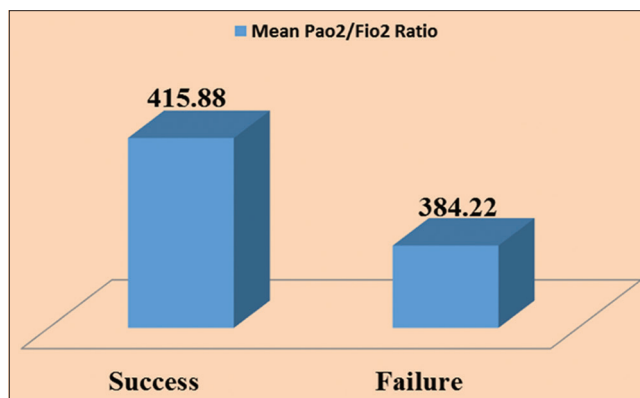


Figure 12: Association of PaO<sub>2</sub>/FiO<sub>2</sub> ratio and extubation success among study subjects at 30 min

successful intubation as compared to subjects who required reintubation ( $P = 0.160$ ) [Table 8]. Pearson's Correlation Coefficient for this association is  $-0.129$  that shows a weak negative correlation. Esteban *et al.* had a similar observation in their systemic review of 2000 mechanically ventilated subjects. They found that there is no correlation between the duration of intubation and success of weaning.<sup>[34]</sup>

PaO<sub>2</sub>/FiO<sub>2</sub> ratio is an index of ventilation and oxygenation adequacy. In our study, mean PaO<sub>2</sub>/FiO<sub>2</sub> ratio with

successful extubation and failure was  $415.88 \pm 126.43$  and  $384.22 \pm 107.73$ , respectively. It was more among subjects with success intubation as compared to subjects who required reintubation ( $P = 0.188$ ) [Table 12]. Pearson Correlation Coefficient is  $0.121$  which signifies a weak positive correlation. This parameter has not been assessed by previous investigators. Salam *et al.* studied ABG analysis in the decision making of extubation. In 83 patients they studied the correlation between PaO<sub>2</sub>/FiO<sub>2</sub> ratio and found a statistically insignificant correlation. In our study, the

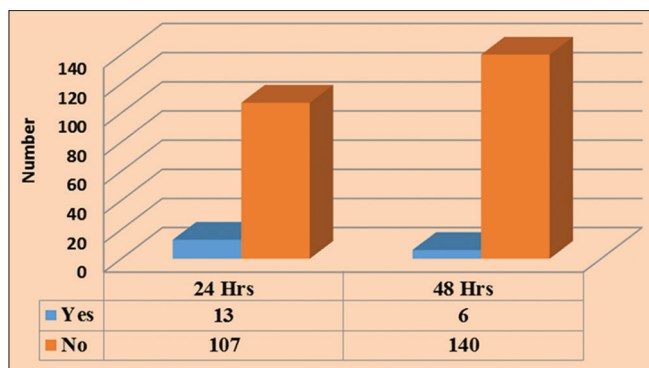


Figure 13: Bi-level positive airway pressure support needed at 24 h and 48 h

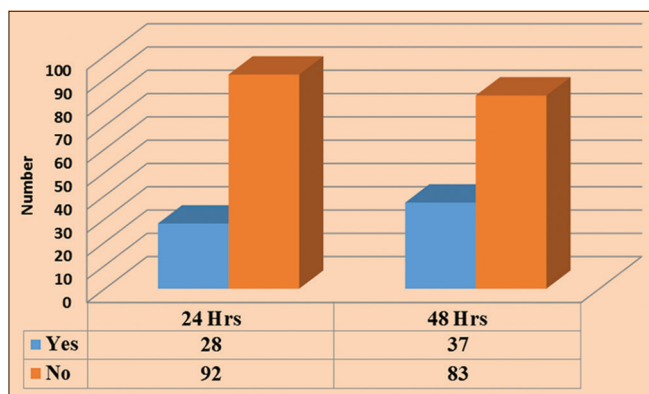


Figure 14: Re-intubation needed at 24 h and 48 h

association between  $\text{PaO}_2/\text{FiO}_2$  and extubation success is statistically significant.<sup>[35]</sup>

### Limitations of the Study

1. This study did not include other clinical parameters such as APACHE Score or systemic involvement. These factors may influence the success of weaning.
2. RSBI calculation was done after 30 min of SBT, but longer duration of SBT is associated with better outcomes.
3. RSBI calculation was done after T piece Trial, many studies have pointed out that SBT with pressure support has been associated with more successful outcomes.<sup>[36]</sup>

### Recommendations

1. We recommend that  $\text{RSBI} < 105$  is an acceptable clinical index for weaning from mechanical ventilation, but a lower threshold value should always be considered to increase the sensitivity and specificity of this index.
2. We recommend that age, weight, and duration of intubation do not seem to be correlated with successful weaning. Further studies should be done to establish an evidence-based recommendation.
3. We recommend that  $\text{PaO}_2/\text{FiO}_2$  ratio should be included in protocols designed to predict weaning success.

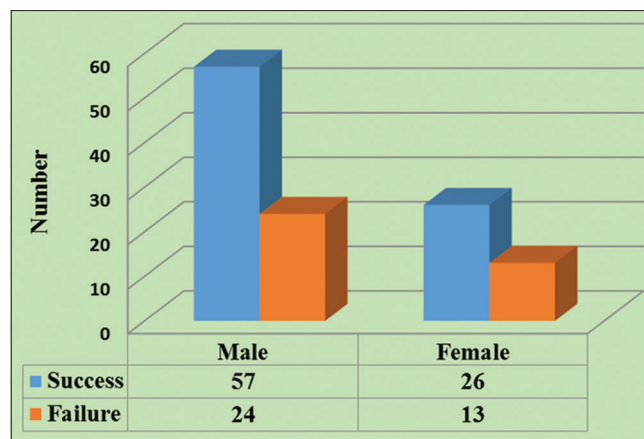


Figure 15: Success of intubation according to gender

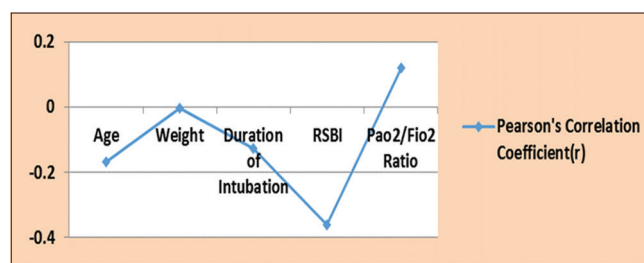


Figure 16: Pearson's correlation of extubation success with age, weight, duration of intubation, rapid shallow breathing index, and  $\text{PaO}_2/\text{FiO}_2$  ratio

4. We recommend that protocol-based extubation should be followed in hospitals to improve the success rate of weaning.

## CONCLUSION

The prospective, observational, hospital-based clinical study was done on 120 patients of age group 18–65 of either gender admitted in SICU and intubated for mechanical ventilation for at least 48 h.

The following conclusions were drawn:

1. Baseline characteristics were comparable in both successful and fail to wean patients.
2. Sensitivity, specificity, positive predictive value, and negative predictive value of  $\text{RSBI} < 105$  as an index for successful weaning were 86.4%, 69.85%, 56.1, and 92.1, respectively, which was comparable with most of the studies.
3. Lower value of RSBI (i.e., 82) was found to be better threshold for successful weaning.
4. Overall failure to wean rate was 30.43% which was comparable with most of other studies.
5. There was a weak positive correlation between age and weaning failure, but it was not statistically significant.
6. Correlation between weight and weaning failure was not established.

7. There was a weak negative correlation between the duration of intubation and weaning failure. Patients who were intubated for longer period of time were associated with more incidence of weaning failure, but it was not statistically significant.
8. The higher PaO<sub>2</sub>/FiO<sub>2</sub> ratio was associated with successful weaning, and there was a statistical significant difference among both groups.
9. Bipap support was required in 15.8% patients in 48 h.

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# A Clinical Study on Incisional Hernia: Anatomical Repair V/S Mesh Repair

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## Abstract

**Background:** The aim of the study is to compare the outcomes of anatomical repair of incisional hernia against open onlay mesh repair of incisional hernia.

**Materials and Methods:** This study is a non-randomized and prospective comparative study with 2 case series (i.e., open anatomical and mesh repair of incisional) hernia repair was conducted in 50 cases of incisional hernia admitted in the Surgical Department of Osmania General Hospital, Afzalgunj, Hyderabad, Telangana, from June 2014 to March 2016 and was randomly selected and subjected to open anatomical repair or by open mesh repair method. Results were analyzed.

**Results:** This study is a comparative study, non-randomized and prospective conducted in Osmania General Hospital, during June 2014–March 2016 Afzalgunj, Hyderabad, Telangana. Total cases in this study are 50 and, 2 patients (8%) out of 25 cases recurred in anatomical repair group and none in mesh repair. Post-operative pain was almost similar (mean analgesic use i.e., 7.52 days in anatomical repair method and 8.20 days in open repair group) in both groups. Wound complications are more in mesh repair group with 40% vs 20% in anatomical repair group.

**Conclusion:** Mesh repair is the almost the gold standard for the incisional hernias. Comparing with other techniques it has an excellent post-operative quality of life and better patient acceptability in terms of recurrence.

**Key words:** Incisional hernia, Mesh repair, Synthetic prosthetic material, Onlay mesh repair, Tension-free repair, Anatomic repair, Ventral hernia

## INTRODUCTION

Post-operative incisional hernia repair is one of the most common surgical procedures being performed in general surgery. The incidence of an incisional hernia, as reported in literature is 3–20%.<sup>[1–6]</sup> It is one of the most frequent long-term complications of abdominal surgery, and it continues to be a significant problem for patients as well as surgeons.

Unfortunately, attempts of repair these hernias have not been uneventful, with high rates of hernia recurrence, and considerable rates of morbidity and mortality, making

many surgeons hesitant to undertake incisional hernia repair.

On the other hand, however, delay in repair may have serious clinical consequences. Apart from discomfort and pain, incisional hernias may predispose to incarceration or strangulation of the primarily small bowel, which is almost certainly fatal if not promptly reduced. Furthermore, as a consequence of the impact on health, incisional hernias have enormous economic consequences.

At this time no consensus has been reached about whether, how, and when to operate on a patient with an incisional hernia. To solve the incisional hernia problem, first of all, methods of prevention are needed. Furthermore, once an incisional hernia has developed, ideally, and methods of repair that does not lead to recurrence or other complications should be available including open mesh and anatomical repair for an incisional hernia and recently laparoscopic repair for it.

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## MATERIALS AND METHODS

This study is a comparative study non-randomized and prospective with 2 case series (i.e., open anatomical and mesh repair of incisional) hernia repair conducted in Osmania General Hospital, Afzalgunj, Hyderabad, Telangana. This study is obtained from patients who consented to get operated for an incisional hernia involving 50 patients that presented in our department during June 2014–March 2016 in our institute and was randomly selected and subjected to open anatomical repair or by open mesh repair method. Patients admitted with incisional hernia are taken up for study with the help of relevant history, doing clinical examination and conducting appropriate investigations.

### Inclusion Criteria

The following criteria were included in the study:

- Age 20 years and above giving written valid consent.
- Medically fit patients to undergo the procedure.

### Exclusion Criteria

The following criteria were excluded from the study:

- Patients age <20 years and 60 years.
- Hernia defect size <1.3 cm and >10 cm.
- Patients with acute or subacute intestinal obstruction.

## Methods

### Pre-operative evaluation

- All the patients are evaluated by proper history and detailed physical examination.
- All the patients underwent relevant hematology and biochemistry investigations.
- Ultrasound abdomen is done for all our patients to know the size of the defect, number of defects, contents and any other abdominal pathology.

### Pre-operative preparation

- Patients were kept NPO for about 6–8 h and were on liquid diet the before the day.
- All patients received antibiotic prophylaxis half an hour before surgery.

### Procedure for anatomical repair

- Almost all the patients were operated under spinal anesthesia.
- Foleys catheterization and nasogastric tube were occasionally used.
- Patients were placed in the supine position. Vertical or transverse incision was taken enclosing the previous scar.
- Abdomen was opened in layers. The hernia sac was identified and dissected.
- Adhesions between the contents and the sac were released. The contents of the sac were reduced after

adhesiolysis. The redundant sac wall was excised hemostasis was achieved. The peritoneum along with the rectus sheath was closed with Prolene No:1.

- A negative suction drain (Romovac) was kept over the rectus sheath and was brought outside through a stab incision in the anterior abdominal wall.
- Excess redundant subcutaneous layer was excised. The subcutaneous layer was closed with Vicryl No. 2.0 in an interrupted manner. The surgical site was painted with povidone-iodine lotion (5% strength).
- Closure of skin was done with Prolene No 2.0 in interrupted sutures. The drainage tubes were secured with purse string sutures.

### Procedure for open mesh repair

- Almost all the patients were operated under spinal anesthesia.
- Foleys catheterization and nasogastric tube were occasionally used.
- Patients were placed in the supine position. Vertical or transverse incision was taken enclosing the previous scar.
- Abdomen was opened in layers. The hernia sac was identified, and dissected adhesions between the contents and the sac were released. The contents of the sac were reduced after adhesiolysis. The redundant sac wall was excised.
- Hemostasis was achieved. The peritoneum along with the rectus sheath was closed with Prolene No:1. Mesh 4–5 cm larger than the size of defect was placed over rectus sheath.
- The mesh is fixed with non-absorbable sutures all over. A negative suction drain (Romovac) was kept over the mesh and was brought outside through a stab incision in the anterior abdominal wall.
- Excess redundant subcutaneous layer was excised. The subcutaneous layer was closed with Vicryl No. 2.0 in an interrupted manner. The surgical site was painted with povidone-iodine lotion (5% strength).
- Closure of skin was done with Prolene No 2.0 in interrupted sutures. The drainage tubes were secured with purse string sutures.

### Post-operative Management

- During post-operative period, all patients received same antibiotics and analgesic injections (injection Diclofenac sodium 75 mg) 12<sup>th</sup> hourly for 1 day unless contraindicated, and thereafter, oral analgesics are given on the patients demand.

### Post-operative Assessment of Pain

The pain experienced by the patients in the post-operative period has been measured according to number of days requiring parenteral analgesics

All the patients are ambulated within 12 h of surgery and are encouraged for oral feeds. Nasogastric tube and Foleys catheter are removed after 12 h. Initially, the feeds were sips of liquids followed by normal diet in a gradual manner after the resolution of post-operative ileus (indicated by passing of flatus and normal bowel sounds on auscultation and return of appetite).

In patients with persistent ileus, they were kept NPO, and whenever required a nasogastric tube is passed only to be removed once the resolution of the ileus. The wounds were inspected for any seroma, hematoma, or any infection. In both groups, drains were removed when the collection was <10 ml for 2 consecutive days.

Patients were discharged after complete ambulation and tolerating normal diet.

All the patients were given abdominal support for 1 month.

### Follow-up Evaluation

After discharge, patients were encouraged to take normal diet and return to their normal activities as early as possible but asked to avoid straining. After the discharge, patients were followed up at 1 week, 1 month, 3 months, and 6 months intervals. In the initial follow-up, the patients were evaluated for short-term complications such as hematoma, wound infection, and wound dehiscence and seroma. During subsequent visits, chronic pain at the operated site, return to normal activity and recurrence were noted.

### End Points of the Study

The endpoints measured in both the groups are duration of surgery, duration of post-operative pain, post-operative local complications, length of hospital stay, and recurrence rates.

## RESULTS

- This study is a comparative study non-randomized and prospective with 2 case series (i.e., anatomical repair and mesh repair of incisional hernia).
- Total number of patients in the study is 50. 25 members in anatomical repair group and 25 in mesh repair group.
- The mean age for anatomical repair group was 42.08 years, for mesh repair group was 45.88 years. The difference is statistically significant among the two groups. The study shows that the majority of the patients are in between 40 and 50 years in both groups.
- Out of the 25 patients in anatomical repair group, 7 (28.0%) are male while 18 (72%) are females whereas in mesh repair group, out of the 25 patients 4 (16%) are males while 21 (84%) are females. Most of the patients in the study 78% were females and 22% were males [Table 1].

**Table 1: Distribution of the previous operation**

Previous operation	Anatomical repair group n (%)	Mesh repair group n (%)
LSCS	6 (24)	6 (24)
Peritonitis	6 (24)	6 (24)
Hysterectomy	6 (24)	7 (28)
Tubectomy	3 (12)	2 (8)
Intestinal obstruction	4 (16)	4 (16)
Recurrent hernia	0 (0)	0 (0)
Total	25 (100)	25 (100)

### Previous Operation

From the above data, it is found that in our study, most of the incisional hernias occurred below the umbilicus in the midline.

### Distribution of Clinical Presentation

According to the study, all the patients presented with swelling, i.e., 100% and 16 patients, i.e., 44.44% presented with pain in addition to swelling.

### Post-operative Stay

The mean duration of stay for anatomical repair group is 7.24 days, while in mesh repair group is 9.52 days.

### Distribution of Post-operative Pain

The pain experienced by the patients in the post-operative period has been measured according to number of days requiring analgesics. In this study, mean number of days requiring analgesics is 7.52 days in anatomical repair group and 8.20 days in mesh repair group.

### Distribution Post-operative Wound Complication

Five out of 25 cases, i.e., (20%), wound got complicated (seroma, infection, and flap necrosis) in the anatomical repair group and 10 out of 25 in the mesh repair group.

### Distribution of Recurrence

All the cases were followed for 6 months for recurrence and reappearance of swelling clinically or radiologically (sonographically).

Two out of 25 cases recurred in anatomical repair group and none in mesh repair.

## DISCUSSION

Incisional hernia is one of the most common long-term complications of abdominal operations, with an overall incidence of 3–20%.<sup>[1]</sup>

Before the introduction of mesh prosthesis for repair of an incisional hernia, only open suture repairs were used for its cure but with an unacceptable rate of recurrence of more than 50%.<sup>[2]</sup>

With the introduction of mesh prosthesis, the rate of recurrence has been brought down.

### Gender Distribution

In the present study which consists of 50 patients (25 patients in anatomical repair group and 25 patients in the open mesh repair group), the overwhelming majority of the patients were females in both the groups. In this study of 50 patients with an incisional hernia, the gynecological causes of laparotomy were most commonly associated with incisional hernia formation, and naturally, the incidence was found to high among females. The development of incisional hernias may also be influenced by factors such as BMI and post-cesarean complications including infection, that is, why it is found to be higher incidence in females. Similar results are observed in other studies.

### Age Distribution

Our study shows that the majority of the patients are in between 40 and 50 years in both groups. The incisional hernia occurrences were most commonly noted between the age group of 40–50 years in this study, which could be explained by a large number of gynecological procedures done at the younger age group.

Most (60%) of the hernias were located in the lower abdomen. This reflects the cesarean section and other gynecological operations as the prime etiology of incisional hernias in the Indian population.

### Previous Operation

- Midline incisions are used more frequently in emergency surgery and are more prone to develop an infection. The incisions, therefore, have a higher recurrence rate than transverse incisions.<sup>[3-5]</sup>
- Cesarean section was noticed as the most common individual operation associated with an incisional hernia (58%). The probable cause, other than the presence of comorbid conditions may be the use of absorbable suture during the fascial closure. Use of non-absorbable suture in the fascial closure of all laparotomy wounds is recommended to reduce the incidence of an incisional hernia.
- The suture material and suture technique used to close the fascia have been shown to affect the risk of an incisional hernia in midline incisions. A suture technique with continuous sutures placed 1 cm apart and 1 cm from the incision using a suture 4 times the length of the incision has been shown to prevent hernias.<sup>[6]</sup>
- Preventive aspects include a proper choice of incision, avoidance of tension on suture line, preservation of nerves, and proper closure of the abdominal wounds.

### Clinical Presentation

All of them presented with swelling over the abdomen and 34% of the patients presented with pain in the swelling site.

### Incisional Hernia Defect Size

- Defect size is one of the important factors that determine the outcome.
- In techniques for the repair of incisional hernias in which sutures are used, the edges of the defect are brought together, which may lead to excessive tension and subsequent wound dehiscence or incisional herniation as a result of tissue ischemia and the cutting of sutures through the tissues.<sup>[7]</sup> With prosthetic mesh, defects of any size can be repaired without tension. Hence, larger defects closed by anatomical repair were having high chances of recurrence.
- However, an expert panel on incisional herniorrhaphy concluded that primary suture repair should be used only for simple small hernia <6 cm diameter in both the axis and the repair is oriented horizontally with non-absorbable suture, monofilament suture with a suture to wound length ratio of 4:1.<sup>[8]</sup>
- Furthermore, the extent of the decrease in laxity of the tissue surrounding the hernia, which is influenced by retraction of muscle and scarification of tissues, may be more important than the actual size of the fascial defect.<sup>[9]</sup>

### Duration of Surgery

Mean operational duration was 84.32 min (range 45–150 min) and 96.4 min (range 45–150 min) in anatomical and mesh repair group, respectively. Operational duration was more in incisional hernia repair with mesh repair technique due to dissection of the abdominal wall to raise flaps and by keeping the mesh on defect so as to extend 2–4 cm beyond the edges of fascia and suturing it to the abdominal wall with interrupted sutures with polypropylene mesh.

In some cases, duration was lengthened due to larger defect size and interloop adhesions of the bowel which increased the duration of surgery to close larger defect and to separate the adhesions.

With respect to intraoperative complications, there were no inadvertent enterotomies in these cases.

### Wound Complications

Due to the amount of tissue dissection needed in open incisional hernia repair group wound-related complications such as seroma, hematoma, flap necrosis, and wound infection are higher than anatomical repair.

In our study, overall wound complications are 20% and 40% in anatomical and mesh repair group, respectively. There was no mortality in our study.

The most common complication noticed was seroma formation. Seroma formation is one of the most common complications associated with onlay mesh hernioplasty due to the wide undermining involved.<sup>[10]</sup> Extensive dissection for mesh placement and premature removal of the subcutaneous drain may contribute to this complication. The cases of seroma in our study were noticed between 3<sup>rd</sup> and 7<sup>th</sup> post-operative day, needed aspiration and resolved within a week with a pressure dressing. No case of wound hematoma was noticed. The incidence of tissue necrosis at the wound edge was 8% in mesh repair. The occurrence of wound edge necrosis is due to disturbance of the blood supply of the tissue at the wound margins due to the large size of skin and subcutaneous flap raised during the repair. This can be prevented by placing moist laparotomy pads over the edge of the wound and meticulous dissection of flaps.<sup>[11]</sup>

In our study, wound infections are significantly higher in mesh repair group 16% as compared to 8% in anatomical repair group. Most of the wound-related infectious complications were superficial and responded to local wound toilet and antibiotics. Control of mesh infection can be problematic though it has been documented that infection of polypropylene mesh can be controlled without removal of the mesh whereas in case of ePTFE mesh removal is usually required.<sup>[12]</sup>

One patient in open mesh repair developed severe prolonged mesh infection which responded to antibiotics and local wound toilet techniques which resulted in longer hospital stay.

The infection did not lead to the removal of mesh in this and most other series<sup>[9,12-15]</sup> but maybe a risk factor for recurrence. Therefore, the administration of broad-spectrum antibiotics at the induction of anesthesia is recommended.<sup>[16]</sup>

The most important point regarding the prevention of mesh-related infections is that foreign body reactions depend on the amount of the prosthesis (mesh) used. For this reason, surgeons should try to minimize the area of mesh that is introduced during the hernia operation, since the inserted foreign material is an ideal medium for bacterial colonization.<sup>[17]</sup>

In addition, four main approaches to the prevention of mesh infection have been used. First, the wound can be rinsed with an antibiotic-containing solution, starting immediately after the dissection of the hernia sac, and then intermittently until the skin is sutured. However, the effectiveness of lavage with solutions containing antimicrobial agents is controversial, since antibiotics

require a defined duration of contact with pathogens, while lavage is usually a more rapid process.

A second approach involves the use of material placed in front of the mesh to slowly deliver an antimicrobial agent locally. In a randomized trial, the use of gentamicin-laced collagen tampons was tested in 301 patients undergoing prosthetic groin hernia repair. The collagen tampons were placed in front of the mesh before the aponeurosis of the external oblique muscle was sutured. This new technique resulted in fewer post-operative infections in comparison with 294 patients undergoing surgical repair for the same hernia without the use of gentamicin-containing collagen tampons.<sup>[16]</sup>

Third, a mesh containing embedded antimicrobial agents can be used. Such a mesh is thought to help prevent bacterial adhesion and colonization when implanted in wounds, with a subsequent reduced likelihood of post-operative infections.

Finally, the traditional intravenous perioperative administration of antimicrobial agents can be used. Although hernia repair operations are classified as clean surgery, the administration of intravenous antibiotics perioperatively has been shown to be beneficial if a prosthetic material (mesh) is involved.<sup>[17,18]</sup>

All of the above-mentioned strategies seem to be beneficial in reducing the incidence of mesh-related infection after hernia repair. However, no definitive recommendation can be made in favor of any particular approach in the absence of comparative outcome data. The current standard preventive strategy for other types of surgery, i.e., the perioperative administration of appropriate intravenous antibiotics, may be used until new data regarding alternative preventive strategies become available.

### Post-operative Pain

In our study, we found that post-operative pain was almost similar (mean analgesic use i.e., 7.52 days in anatomical repair method and 8.20 days in open repair group) in both groups.

Diclofenac sodium, i.e., (100/150 mg) used initially in injectable form and later converted to oral form. Most of our patients in both groups were subjectively more comfortable in the post-operative period and were ambulant on the 1<sup>st</sup> post-operative day.

In our study may be due to increased post-operative complications such as seroma and wound infection in mesh repair which resulted in increased post-operative pain than anatomical repair group. Post-operative pain in mesh repair



group, mainly due to the dull aching pain and induration, which were due to the foreign body reaction to the mesh. A few patients, however, suffered a foreign body sensation following mesh repair which subsided over a couple of months. To our experience, reassurance is more effective than pain-killers in these patients.

### Post-operative Stay

The mean hospital stay was shorter in anatomical repair group (7.24 days) as compared to open mesh repair group (9.52 days) which was significant. Hospital stay was more in mesh repair than anatomical repair due to more wound complications in mesh repair group. In our study, it was found out that patients with suture repair had significant shorter hospital stay compared to mesh repair. This may be due to less complication rate in suture repair.

### Recurrence

At a mean follow-up of 6 months, 2 out of 25 cases recurred in anatomical repair group and none in mesh repair group.

In techniques for the repair of incisional hernias in which sutures are used, the edges of the defect are brought together, which may lead to excessive tension and subsequent wound dehiscence or incisional herniation as a result of tissue ischemia and the cutting of sutures through the tissues. With prosthetic mesh, defects of any size can be repaired without tension. In addition, polypropylene mesh, by inducing an inflammatory response, sets up a scaffolding that, in turn, induces the synthesis of collagen. Our study establishes the superiority of mesh repair over suture repair with regard to the recurrence of the hernia.

Primary suture repair has been widely used but has a reported recurrence rate of 12–54%. The technique is stated to predispose to excessive tension and subsequent wound dehiscence due to tissue ischemia and cutting of the sutures through tissue. Surgical complications such as wound infection, prolonged ileus, and dehiscence are established causative factors for recurrence.<sup>[19]</sup> All 4 patients who had wound infection during the initial suture repair developed recurrence within 1 year.

In our study, mesh repair was found to be significantly better for large defects and multiple defects. There was no mortality in our study. None of the cases showed recurrence. Recent trend is to use the prosthetic mesh judiciously. There was no recurrence in our study through the period of follow-up was not adequate to make a correct assessment of recurrence. In short follow-up, it is difficult to comment on recurrence. However, the short-term results indicate a significant improvement in the repair of an incisional hernia by the use of prosthetic mesh compared with conventional repairs.

In our study, 2 out of 25 cases recurred in anatomical repair group and none in the mesh repair group. Due to wound infection and larger defect size recurrence occurred in cases of anatomical repair of an incisional hernia.

The limitations of this study were as follows:

1. There was no randomization of the patients done in this study.
2. It was limited in its validity due to small sample size and short follow-up period.
3. As it was an unblinded study, there was a chance of observational bias.

The suggestion from this study was the need for a large randomized controlled trial comparing the anatomical technique and onlay technique of mesh placement in incisional hernia repair.

## CONCLUSION

- In a small simple incisional hernia defect <2 cm, onlay mesh repair of an incisional hernia carried a high risk of infections and local wound-related complications and pain in the current study.
- In a small, incisional hernia, suture repair had similar outcomes in terms of recurrence rates. The incidence of other complications was less compared to onlay mesh repair in a small, simple hernia. Hence, in a small, simple incisional hernia, repair by conventional suture repair still has a role if proper technique is used and other factors for recurrences are taken care of.
- In large and complex incisional hernia, the use of synthetic prosthetic material provides the tension-free repair and less rate of recurrence. Good pre- and post-operative antibiotics and wound care are essential.
- Mesh repair is the almost the gold standard for the incisional hernias. Comparing with other techniques, it has an excellent post-operative quality of life and better patient acceptability in terms of recurrence.
- In conclusion, mesh repair with polypropylene mesh is superior to suture repair with regard to the recurrence of the hernia.

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