

# A Prospective Randomised Study to Evaluate the Effects of Clonidine and Fentanyl as Premedication for Intraoperative Haemodynamic Stability in Patients Undergoing Laparoscopic Cholecystectomy.

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## ABSTRACT

**Background:** Laparoscopic surgeries are commonly done in patients suffering from cholelithiasis. However, laparoscopic surgeries are associated with pneumoperitoneum, increased intra-abdominal pressure and insufflation of carbon dioxide leading to altered haemodynamic stability. We conducted a prospective randomised study to evaluate the effects of Clonidine and fentanyl in premedication for intraoperative haemodynamic stability in patients undergoing laparoscopic cholecystectomy. **Methods:** 70 patients of either sex posted for elective laparoscopic cholecystectomy were included for our study. All patients were randomised using computer generated program and divided into two groups; Group F (35 patients): received Inj. Fentanyl (2 µg/kg IV) 5 minutes prior to induction of anaesthesia, whereas Group C (35 patients) received Inj. Clonidine (1 µg/kg IV) at the similar time before induction of anaesthesia. Haemodynamic parameters (heart rate, mean arterial pressure) of all patients were assessed prior to premedication, before induction, following laryngoscopy and intubation and after pneumoperitoneum. **Results:** The baseline mean heart rate and mean arterial pressure between Group C was found to be statistically insignificant on comparing with Group F. However, the mean heart rate after intubation, after creation of pneumoperitoneum and after extubation was observed to be statically significant between Group F and Group C (p=0.001). Similar statistical significance was observed between fentanyl group and Clonidine group after premedication and after intubation. **Conclusion:** Both Clonidine and fentanyl as a premedication had effectively attenuated intraoperative haemodynamic responses but the role of Clonidine was observed to be more appreciable.

**Key Words:** Clonidine, Fentanyl, Laparoscopic Cholecystectomy

## INTRODUCTION

Laparoscopic Cholecystectomy is a widely performed surgery for gall bladder stones. It possesses various advantages than surgical open cholecystectomy. It causes less bleeding, lesser hospital stay and a small scar but the pneumoperitoneum, retention of carbon-dioxide and trendelenberg position are the different causes behind its haemodynamic instability during the intra-operative period.<sup>[1]</sup>

Various pharmacological agents have been widely used for attenuation of haemodynamic response during intra-operative period.<sup>[2,3]</sup> Beta blockers, calcium channel blockers, nitroprusside, lignocaine and opioids had been commonly used for this purpose.<sup>[4-7]</sup>

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However, Clonidine (alpha-receptor agonist) possessing sedative, anxiolytic, sympatholytic and anaesthetic sparing properties has been commonly

advocated for the attenuation of instable haemodynamic responses during laryngoscopy and laparoscopy.<sup>[8]</sup> Its sympatholytic response is due to the fact that it decreases epinephrine and norepinephrine levels in blood. However, baroreceptor reflexes are preserved in normotensive patients with the use of Clonidine.<sup>[9]</sup> Fentanyl (a µ-opioid receptor agonist) possesses a potent analgesic property with a rapid and a short duration of action.<sup>[10]</sup> Fentanyl has been used for blunting the haemodynamic pressor response during laryngoscopy and endotracheal intubation but its use for attenuating the haemodynamic responses during laparoscopy is limited.<sup>[10]</sup> We conducted a prospective randomised double blind study comparing the efficacy of Clonidine and fentanyl in attenuating the haemodynamic responses during laparoscopy in patients with cholelithiasis.

## MATERIALS AND METHODS

After obtaining clearance from the Institutional Ethical Committee and due inform consent from the patients, we conducted a double blind prospective randomised study in our Department of

Anaesthesia from January 2014 to December 2014. 70 patients of either sex, American Society of Anaesthesiologists (ASA) Grade I/II, 25-50 years of age and posted for elective laparoscopic cholecystectomy were included for our study. We excluded the patients with anticipated difficult airway, hypertension, and any drug therapy including anti-hypertensives or methyldopa, psychiatric disorder or any chronic renal/liver/pulmonary disease.

All patients were randomised using computer generated program and divided into two groups; Group F (35 patients): received Inj. Fentanyl (2 µg/kg IV) 5 minutes prior to induction of anaesthesia, whereas Group C (35 patients) received Inj. Clonidine (1 µg/kg IV) at the similar time before induction of anaesthesia. An anaesthesia resident blinded to the study protocol prepared all the drugs and another blinded anaesthetist was involved in monitoring the vital parameters.

Premedication was done with Oral Ranitidine (150 mg) and Oral Alprazolam (0.5 mg) at the night before surgery. On arrival to the operative room, after securing a 20 G intravenous cannula Ringer lactate was started and Inj. Ondansetron (4 mg IV), Inj. Dexamethasone (4 mg IV). Standard monitors for monitoring vital parameters (Non-Invasive Blood Pressure, Heart Rate, SpO<sub>2</sub>, EKG) were applied. Thereafter, Inj. Fentanyl or Inj. Clonidine was administered to the patients as per our study protocol.

The induction of general anaesthesia was done using Inj. Propofol (2 mg/kg IV) and tracheal intubation was facilitated by Inj. Vecuronium (0.1 mg/kg IV). After confirming the tube by bilateral auscultation and waveform capnography, the endotracheal tube was secured. The maintenance of anaesthesia was done using intermittent dosing of Inj. Vecuronium (0.05 mg/kg), nitrous oxide and Isoflurane (1%). Intravenous infusion of Inj. Paracetamol (1.0 gm) was administered for post-operative pain. The patients' ventilation was adjusted to maintain an End tidal CO<sub>2</sub> between 35-40 mm Hg.

Pneumoperitoneum was created and maintained using carbon-dioxide. The intra-abdominal pressure was maintained between 12-15 mm Hg. After completion of the surgery, the gases (nitrous oxide/isoflurane) were discontinued and the residual anaesthesia was antagonised using Inj. Neostigmine (0.05 mg/kg IV) and Inj. Glycopyrrolate (0.01 mg/kg IV). Before extubating the patient, skin infiltration at the incision sites were performed using Inj. Bupivacaine 0.25% (5 ml) diluted to 5 ml of normal saline. Tracheal extubation was performed when respiration was adequate and patient the patient was following commands.

Haemodynamic parameters (heart rate, mean arterial pressure) of all patients were assessed prior to premedication, before induction, following laryngoscopy and intubation and after pneumoperitoneum. Thereafter, parameters were noted at every 5 minutes for the next 30 minutes and then at every 15 minutes till the completion of the surgery and trachea were extubated. Haemodynamic alterations (bradycardia, tachycardia, hypotension or hypertension) were noted as any increase or decrease of 25% from the baseline and managed accordingly. After extubation, the patient was shifted to Post-anaesthesia care unit and after monitoring for the next 2 hours the patient was shifted to the ward.

**Statistical Analysis:** All the parametric data was analysed using Student's t-test and non-parametric data using Chi-Square/Fisher test whichever is applicable. Data was analysed using statistical package for social sciences (SPSS) version 19.0. A p value of <0.05 was considered statistically significant.

## RESULTS

All patients were successfully enrolled in our study. The patients were observed to be comparable with respect to demographic profile. No statistical difference was observed on comparing the age, weight, and height, duration of laryngoscopy and duration of surgery in between the groups [Table 1].

The baseline mean heart rate in Group C was found to be statistically insignificant on comparing with Group F (p=0.36) [Table 2]. Similar comparable results were observed on comparing the mean heart rate after premedication and after induction. However, the mean heart rate after intubation was observed to be significantly higher in Group F (86.63 ± 5.37) than Group C (80.14 ± 6.53) (P=0.001) [Table 2]. After the creation of pneumoperitoneum, the mean heart rate in patients given Clonidine was 82.24 ± 4.84 and 89.03 ± 4.38 in patients given fentanyl (p=0.001). During intra-operative period the mean heart rate was observed to be stable in both the groups. However, again statistically significant difference on mean heart rate was observed in between both the groups after extubation (p=0.001) [Table 2].

The mean arterial blood pressure was comparable in between both the groups before premedication (p=0.14) [Table 3]. However, a significant statistical difference was observed on comparing the mean arterial pressure between the Clonidine and Fentanyl group after premedication (p=0.001). During the further course of observation of arterial blood pressure after intubation, after pneumoperitoneum, intra-operative period and after extubation, the results were observed to be comparable between them and better

haemodynamic stability was observed with either of the drugs [Table 3].

Post-operative adverse events were observed to be insignificant in both the groups. One episode of vomiting was observed in Clonidine group which was successfully managed by Inj. Metaclopramide (10 mg IV) [Table 4]. None of the patients desaturated to less than 94% in any of the study

groups. 4 patients in Clonidine group and 6 patients in fentanyl group experienced bradycardia and were successfully managed by oxygen supplementation and Inj. Atropine (0.5 mg IV) [Table 4]. 6 patients in Group C and 8 patients in Group F complaint of shivering which was managed successfully by warm fluids, blankets and Inj. Tramadol (50 mg IV) [Table 4].

**Table 1:** Demographic Characteristics (Mean ± SD)

Variables	Group C	Group F	P value
Age (years)	38.87 ± 5.39	39.42 ± 6.57	0.70
Weight (kg)	65.52 ± 4.61	66.35 ± 5.29	0.49
Height (cm)	157.41 ± 6.58	158.93 ± 6.14	0.32
M:F	13:22	10:25	-
Duration of laryngoscopy (sec)	18.32 ± 1.89	17.62 ± 2.07	0.14
Duration of surgery (min)	81.16 ± 8.94	83.42 ± 9.26	0.30

**Table 2:** Mean heart rate during surgery (Mean ± SD)

Variables	Group C	Group F	P value
Before Premedication	78.74 ± 4.73	79.94 ± 6.16	0.36
After Premedication	74.32 ± 5.71	75.53 ± 5.87	0.39
After Induction	71.13 ± 5.32	72.28 ± 4.06	0.31
After Intubation	80.14 ± 6.53	86.63 ± 5.37	0.001*
After pneumoperitoneum	82.24 ± 4.84	89.03 ± 4.38	0.001*
Intraoperative period	75.41 ± 5.74	77.83 ± 5.29	0.07
After extubation	85.53 ± 5.06	93.31 ± 5.27	0.001*

**Table 3:** Mean arterial blood pressures during surgery (Mean ± SD)

Variables	Group C	Group F	P value
Before Premedication	104.34 ± 11.23	100.57 ± 9.92	0.14
After Premedication	93.31 ± 8.03	84.41 ± 7.62	0.001*
After Induction	89.67 ± 10.48	80.71 ± 9.76	0.001*
After Intubation	98.73 ± 11.37	95.51 ± 8.89	0.19
After pneumoperitoneum	93.38 ± 9.91	90.35 ± 10.06	0.21
Intraoperative period	83.31 ± 8.59	80.44 ± 10.19	0.20
After extubation	96.48 ± 8.73	99.32 ± 9.15	0.39

**Table 4:** Adverse Events

Variables	Group C	Group F
Nausea/Retching/Vomiting	0/0/1	0/0/0
Desaturation (SpO <sub>2</sub> < 94%)	0	0
Bradycardia	4	6
Shivering	6	8

## DISCUSSION

We evaluated the role of preoperative fentanyl and Clonidine medication in patients posted for laparoscopic cholecystectomy under general anaesthesia. However, we observed attenuation of haemodynamic responses with both the drugs but a near stable haemodynamics with Clonidine makes it a more favourable drug.

We observed a comparable difference in between both the groups on monitoring the mean heart rate and mean arterial pressure before premedication. After premedicating the patients with either Clonidine or fentanyl as per the study protocol, a significant difference in mean arterial pressure was observed in fentanyl group but the mean heart rate had a comparable fall. The more near stable

haemodynamic characteristics were observed with Clonidine group.

The haemodynamic pressor response to laryngoscopy and intubation due to sympathetic stimulation was first described by Reid and Brace.<sup>[11]</sup> Excessive sympathetic stimulation particularly in patients with haemodynamic compromise or elderly can lead to catastrophic events like cerebral haemorrhage, myocardial ischemia and thereby increases the morbidity/mortality of the patients.<sup>[12-14]</sup> Various pharmacological agents (lignocaine, esmolol, nitroprusside) have been proposed by different researchers to eliminate the pressor response of this laryngoscopy and intubation. We evaluated the role of fentanyl and Clonidine for eliminating such response in our study. After intubation, both the agents were observed to be beneficial in providing

the stability of haemodynamic characters in our study but the role of Clonidine is more appreciable. Clonidine has anaesthetic sparing effect and thereby it decreases the dose of anaesthetic agents during the surgical procedure.<sup>[15]</sup> Laisalmi et al<sup>[16]</sup> observed that Clonidine reduces the perioperative doses of narcotic agents when it is used as premedication by blunting the stress response to anaesthesia/surgical stimuli. Sung et al<sup>[17]</sup> and Hayashi & Maze<sup>[18]</sup> observed that Clonidine imparts better haemodynamic stability by potentiating parasympathetic system during intraoperative period in patients undergoing laparoscopic cholecystectomy. We observed a significant change in the mean heart rate in the fentanyl group after creation of pneumoperitoneum. However, the mean arterial pressure was observed to be more near normal in intraoperative period in both the groups.

The use of propofol and Clonidine in our study advocates the need of anticholinergic agent during the episode of bradycardia. Four patients in Clonidine group and six patients in fentanyl group experienced bradycardia in our study which was treated with Inj. Atropine (0.5 mg IV) successfully. Only one patient in Clonidine group experienced vomiting in our study. During laparoscopic cholecystectomy nausea/vomiting has an incidence of 42% due to peritoneal distension and manipulation. We administered Inj. Metaclopramide (10 mg IV) as a rescue antiemetic and the thus the emesis was successfully managed. Shivering is a less understanding symptom after general anaesthesia encountered in six patients in Clonidine group and eight patients in fentanyl group in our study. Since shivering increases the oxygen consumption, it was managed with Inj. Tramadol (50 mg IV) successfully. One of the limitation in our study is that we had not given preoperative analgesia in Clonidine group as giving such analgesic could bias the study results.

## CONCLUSION

From our study, we concluded that premedication with intravenous Clonidine or fentanyl successfully attenuated haemodynamic stress responses in the patients undergoing laparoscopic cholecystectomy. Although, better haemodynamic stability and near normal cardiac parameters were observed in Clonidine group, so we propose premedication with Clonidine drug in cardiac compromised patients.

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