

## Effect of Oral Clonidine Premedication on Perioperative Haemodynamic Response and Postoperative Sedation for Patients undergoing Laparoscopic Cholecystectomy

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### Abstract

**Background:** Laparoscopy is now preferred because of various advantages such as reduced post operative pain, faster recovery and shorter hospital stays. It is associated with pneumoperitoneum, variations in patient positioning, and stress response leading to various haemodynamic changes. Various anaesthetic interventions like epidural, combined epidural and general anaesthesia, and pharmacologic interventions like nitroglycerine, esmolol have been used. **Aims and objectives:** To evaluate and compare the effects of oral clonidine v/s placebo in obtunding haemodynamic response to laryngoscopy, intubation and pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. Postoperative sedation and other side effects were also observed. **Materials and Methods:** Patients were randomized into two groups- Group C: 150 mcg of clonidine. Group P: Vitamin - C tablets 500mg, each receiving drugs orally 90 minutes before induction. Effect of oral clonidine in obtunding hemodynamic response and post operative sedation were monitored. **Result:** No significant difference was observed in mean age, gender and preoperative vital parameters ( $p>0.05$ ). Significant difference in Heart rate, SBP, DBP, MAP after intubation, during incision, starting and release of pneumoperitoneum between the two Groups ( $p<0.05$ ). Post-operatively patients in group C were sedated but aurosa as compared to Group P. **Conclusion:** Premedication with 150 mcg of oral clonidine is safe and improves perioperative haemodynamic stability and reduces postoperative sedation, nausea and vomiting in patients undergoing laparoscopic cholecystectomy.

**Keywords:** Laparoscopy; Haemodynamic Response; Postoperative Sedation.

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### Introduction

Laparoscopic cholecystectomy is the treatment of choice for symptomatic cholelithiasis. Laparoscopic cholecystectomy was introduced by Phillippe Mouret in 1987 [1]. It has various advantages such as better maintenance of

homeostasis [2], reduced post operative pain, faster recovery and shorter hospital stay.

Intra-abdominal CO<sub>2</sub> insufflation combined with the variations in patient positioning from Trendelenburg to reverse Trendelenburg leads to changes in varied haemodynamic responses. Various anaesthetic interventions like use of

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epidural, segmental spinal [3], combined epidural and general anaesthesia[4], use of various pharmacologic interventions like nitroglycerine [5], esmolol [6], magnesium sulphate [7] have been used with varying success and practical limitations.

Clonidine is an imidazoline compound, stimulates  $\alpha_2$  adrenergic receptors in the nucleus tractussolitarii resulting in central sympatholysis causing lowering of both cardiac output and peripheral resistance . It tends to attenuate the haemodynamic response to any nociceptive stimulus and improves overall peri-anaesthetic cardiovascular stability. It is well absorbed on oral administration (2-5mcg/kg) with peak plasma concentration achieved in 75 to 90 minutes with a half life of 9-12 hrs [8].

Premedication with clonidine reduces the stress response to surgical stimuli and the narcotic and anaesthetic doses. Premedication dose of clonidine ranges from 2 to 5 mcg/kg [9]. A total dose of 150 mcg oral clonidine approximates 2.7 mcg/kg [8] was used in this study.

The present study was designed to evaluate the effects of premedication with oral clonidine on haemodynamic responses and post operative sedation in patients undergoing laparoscopic surgery and side effects if any.

## Methodology

After Institute Ethics Committee (ICE) clearance, a prospective, randomized, double-blind, comparative study was conducted on 60 patients belonging to ASA I and II, aged 18 to 60 years; undergoing elective laparoscopic cholecystectomy surgeries. Patients belonging to ASA III or more, with anticipated difficult intubation, on any opioid or sedative medication, with history of alcohol or drug abuse, or known allergy to clonidine were excluded. All the patients were

randomly divided into two groups of 30 each, group C and group P, using computer generated random number table.

On arrival in the pre operative room all patient's heart rate and blood pressure recorded before premedication. 90 minutes prior to surgery Group C patients were pre-medicated with 150 mcg clonidine and group P patients with 500 mg vitamin - C.

Inside the operation theatre baseline readings, pulse oximeter, ECG and non-invasive blood pressure were recorded and a wide bore 20 G intravenous line established. Pre-medication with intravenous glycopyrrolate 0.004 mg/kg, midazolam 0.02 mg/kg, ondansetron 0.1 mg/kg, fentanyl 2 mcg/kg or pentazocine 0.3 mg/kg given. General anaesthesia was induced with propofol 2 mg/kg and vecuronium 0.1 mg/kg and maintenance with isoflurane in 60% N<sub>2</sub>O / 40% O<sub>2</sub> mixture. End tidal CO<sub>2</sub> was maintained between 30-40 mmHg with controlled mechanical ventilation. Heart rate, Systolic, diastolic and mean arterial pressure were recorded prior to induction, 5 min after endotracheal intubation, at skin incision, start of pneumoperitoneum, 15 min, 30 min, 45 min and 60 minutes. Ramsay sedation score and adverse events were observed immediately after surgery, 15 min, 30 min, 45 min and 60 minutes post operatively.

Results were statistically analyzed, using parametric test and the final interpretation was based on Z-test [standard normal variate] with 95% level of significance (p value < 0.05 as significant), using student 't' test for Quantitative data and chi square test for Qualitative data.

## Results

All the enrolled 60 patients (30 patients in each group) completed the study. The demographic profile of two groups was similar in age, gender, weight, height and ASA grading. No statistically significant

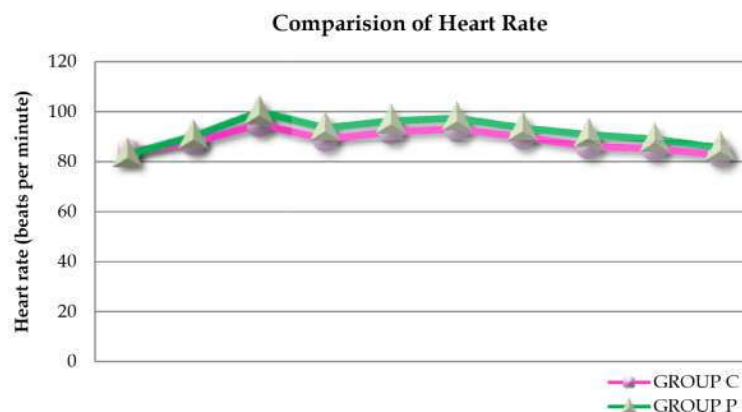


Fig. 1: Line diagram showing comparison of heart rate in study groups

differences between the two groups with respect to preoperative vital parameters (HR, SBP, DBP, MAP).

With regards to HR statistical difference existed between Group C and Group P. Values were relatively lower in Group C at 1 min, 5 min after intubation, during incision, starting of pneumoperitoneum, 15min, 30 min, 60 min of pneumoperitoneum, and 15 min after release of pneumoperitoneum and the difference was found to be statistically significant ( $p < 0.05$ ) (Figure 1).

MAP was significantly lower in Group C than Group P at at 1 min, 5 min after intubation, during incision, starting of pneumoperitoneum, 15min, 30 min, 60 min of pneumoperitoneum, and 15 min

after release of pneumoperitoneum which was statistically significant ( $p < 0.05$ ) (Figure 2).

We found relatively lower heart rate in Group C with respect to post operative heart rate immediate after surgery, 15 min, 30 min, 45 min and 60 min after surgery and the difference was found to be statistically significant ( $p < 0.05$ ) (Figure 3).

Statistical significant difference was observed between Group C and Group P with respect to post operative mean arterial pressure immediately after surgery, 15 min, 30 min, 45 min and 60 min after surgery. Values were relatively lower in Group C and the difference was found to be statistically significant ( $p < 0.05$ ) (Figure 4).

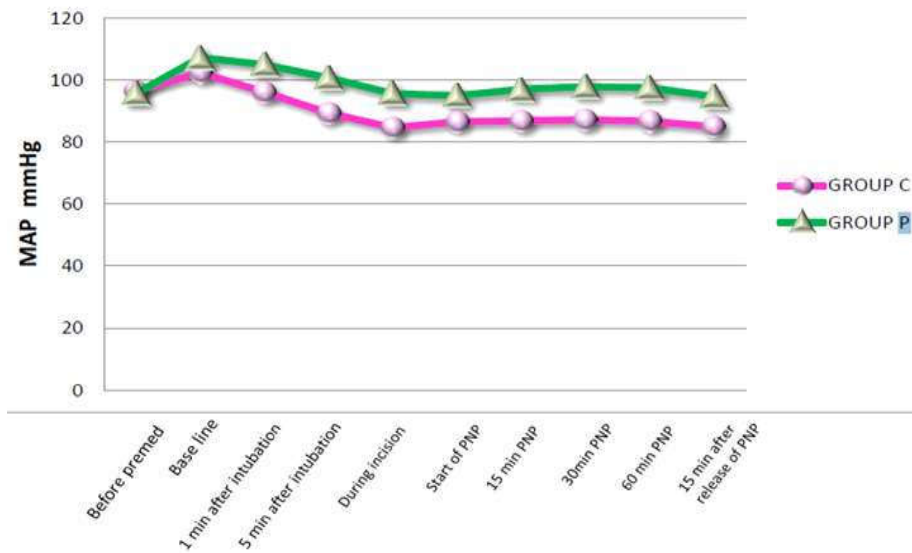


Fig. 2: Line diagram showing comparison of MAP in study groups

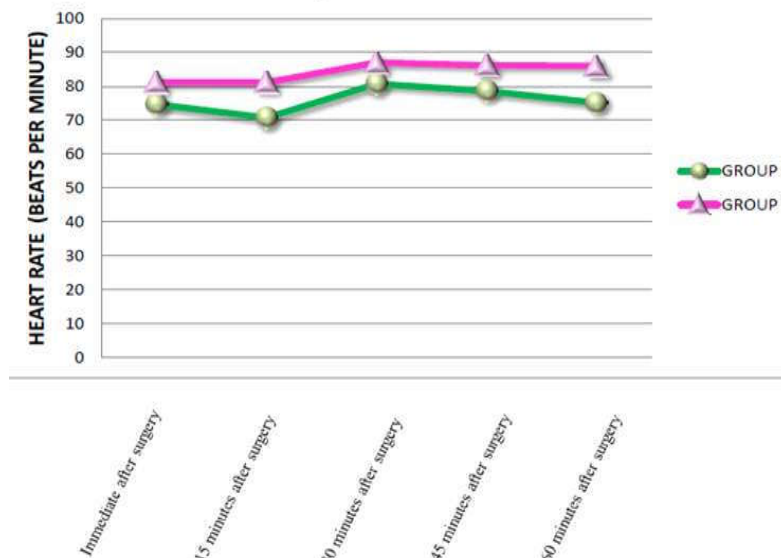


Fig. 3: Line diagram showing comparison of postoperative Heart rate between two groups

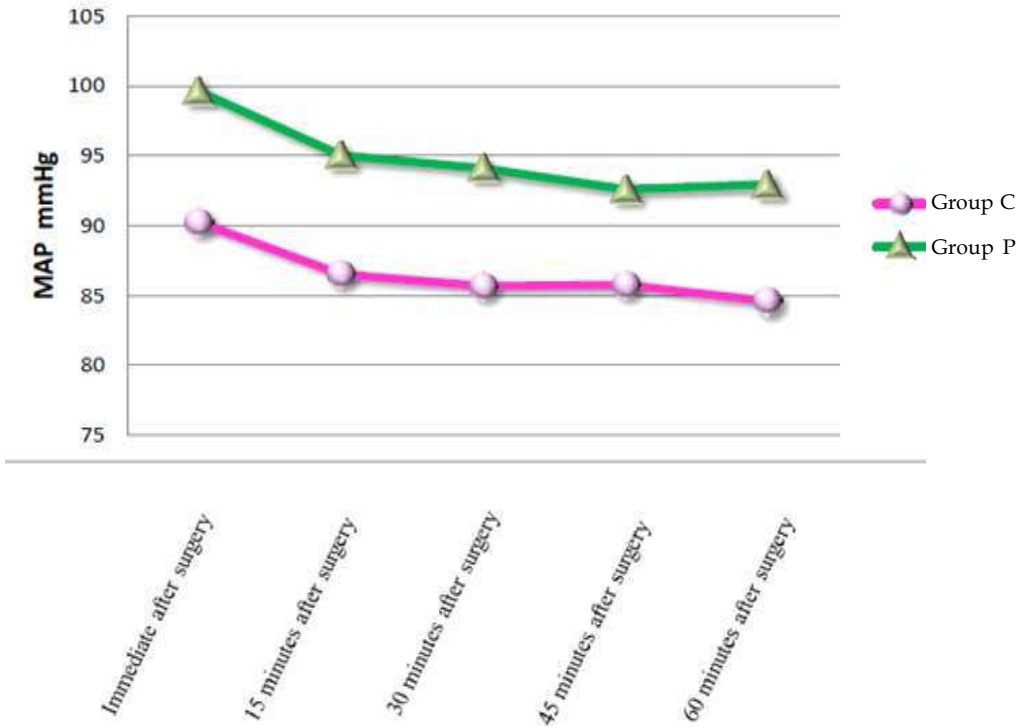


Fig. 4: Line diagram showing comparison of post operative MAP between two groups

Table 1: Comparison of Ramsay sedation scores of patients in both groups

Ramsay sedation score	Group c	Group p	P value	Significance
Immediate after surgery	2.76 ± 0.43	0.83 ± 0.46	0.00	Significant
15 min post operatively	2.63 ± 0.49	0.63 ± 0.49	0.00	Significant
30 min post operatively	2.56 ± 0.50	0.6 ± 0.49	0.00	Significant
45 min post operatively	2.56 ± 0.50	0.63 ± 0.49	0.00	Significant
60 min post operatively	2.6 ± 0.49	0.5 ± 0.50	0.00	Significant

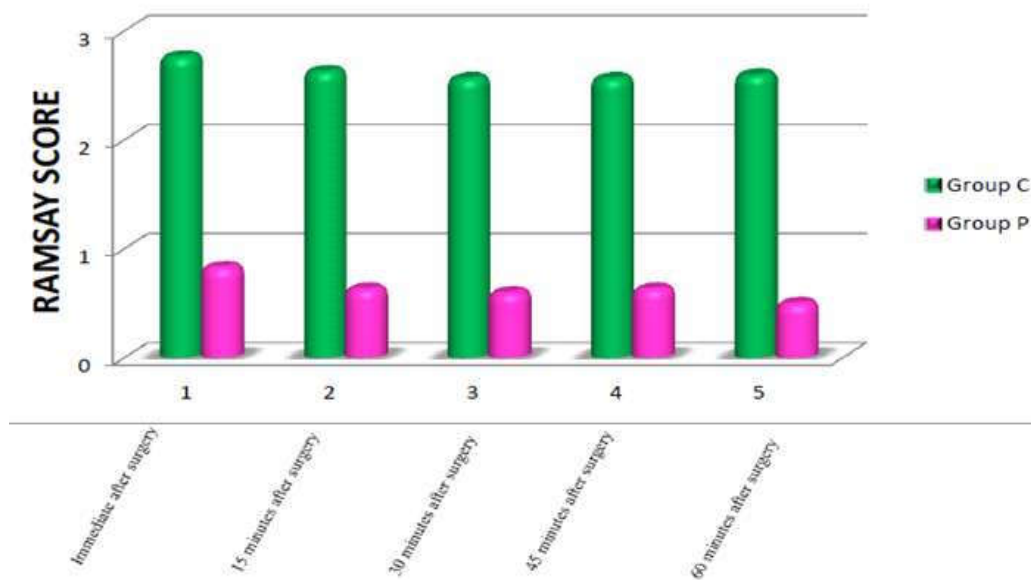
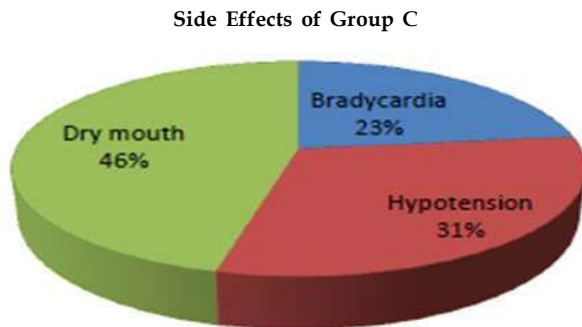


Fig. 5: Bar diagram showing comparison of Ramsay sedation score between two groups

**Table 2:** Comparison of side effects in two groups

Side Effects	Group C	Group P
Bradycardia	3	0
Hypotension	4	0
Dry mouth	7	3



**Fig. 6:** Pie chart showing side effects in group C

Values were higher in Group C with respect to sedation score values at immediately after surgery, 15 minutes post operatively, 30 minutes post operatively, 45 minutes post operatively, 60 minutes post operatively and the difference was found to be statistically significant ( $p < 0.05$ ) (Table 1 and Figure 5).

Incidences of side effects were minimum in both groups and were not found to be statistically significant ( $p$  value  $> 0.05$ ). Bradycardia was treated immediately by inj. Atropine (0.6 mg) IV (Table 2 and Figure 6).

### Discussion

Laparoscopy has several advantages like minimum tissue trauma, reduced postoperative pain, quicker recovery and shorter hospital stay. However, pneumoperitoneum induces an increase in mean arterial pressure, decrease in cardiac output leading to hypertension, tachycardia, compromised tissue perfusion and absorption of CO<sub>2</sub> affecting acid-base balance [10]. Techniques like gasless laparoscopies using abdominal elevators and lower intra-abdominal pressure have been used with limited success [11]. Therefore use of anaesthetic interventions is required for maintaining homeostasis.

Clonidine is a partial agonist with a high affinity and high intrinsic activity at  $\alpha$ -2 receptors, especially  $\alpha$ -2A sub type in brain stem. This central sympatholysis obtunds tachycardia and

hypertension seen after peritoneal insufflations. Oral clonidine was used as it is ease to administer, has good bioavailability and safety profile along with properties like analgesia, sedation [12], anxiolysis, antiemesis and anti-shivering [13].

We used oral clonidine 150 mcg (2.7mcg/kg) 90 minutes before surgery in our study. Sung et al. [14] and Yu et al. [15] used 150 mcg of oral clonidine as premedication for maintenance of haemodynamic stability during pneumoperitoneum.

The main aim of our study was to compare the effect of oral clonidine 150 mcg v/s placebo (vitamin-C 500 mg) in obtunding haemodynamic response to intubation, pneumoperitoneum perioperatively and postoperative sedation and other side effects in patients undergoing laparoscopic cholecystectomy.

Demographic profiles of subjects in both groups were comparable.

Our study showed rise in the heart rate in group P after intubation and pneumoperitoneum. In group C there was a fall in heart rate after pre medication, which was not raised after intubation or pneumoperitoneum. Thus, heart rate remained more stable in clonidine group as compared to placebo. Post-operatively upto one hour the heart rate remained stable in group C as compared to group P. Values were relatively lower in Group C and the difference was found to be statistically significant ( $p < 0.05$ ). Ketaki Marodkar et al. [16] in 2003 studied 60 patients, premedicating with oral Clonidine 150 mcg for weight  $< 55$  kg and 200 mcg for weight  $> 55$  kg 90 minutes before induction compared to the placebo group (oral vitamin C), they concluded that oral clonidine maintained stable intra-operative and post-operative heart rate.

The Mean arterial pressure showed rise in group P after intubation and pneumoperitoneum. Comparatively the MAP remained more stable in clonidine group. Post-operatively upto one hour the mean arterial pressure remained stable in group C as compared to group P. Values were relatively lower in Group C and the difference was found to be statistically significant ( $p < 0.05$ ). Brinda B et al. [17] in 2014 performed study on 100 patients, age group 18-65 years and administered 4 mcg/kg body weight oral clonidine, 90 minutes before induction and concluded it provides stable mean arterial pressure in patients undergoing laparoscopic cholecystectomy.

We relatively lower heart rate, systolic, diastolic and mean arterial pressure in Group C as compared to Group P immediately after surgery, 15 min, 30 min, 45 min and 60 min after surgery. The difference was found to be statistically significant ( $p < 0.05$ ).

Ketaki Marodkar et al. [16] in 2003 studied Clonidine 150 mcg for weight <55 kg and 200 mcg for weight >55 kg per oral compared with placebo group receiving oral vitamin C, 90 minutes before induction. Oral clonidine is able to maintain stable intra-operative haemodynamics and achieves a calm post-operative period during laparoscopic surgeries in ASA I/II patients.

There was significant difference with respect to sedation score, immediately after surgery, 15 minutes, 30 minutes, 45 minutes and 60 minutes post operatively between the two Groups. Values were higher in Group C and the difference was found to be statistically significant ( $p < 0.05$ ). The data was comparable to that of study by Wright et al. [18] to evaluate the effect of clonidine as pre-anaesthetic medication and found that clonidine produced a significant reduction in anxiety ( $p < 0.05$ ) and caused sedation.

In group C bradycardia was seen in 3 patients who responded to atropine, 4 patients had hypotension which was treated by reducing inhalational agents and giving bolus fluids and 6 patients complained of dryness of mouth in Group C in our study. Side effects were found to be statistically significant ( $p > 0.05$ ). As was comparable to that of study by Brinda B et al. [17] in 2014, observed most common adverse effects as dry mouth, drowsiness, hypotension and bradycardia and insignificant.

#### *Limitations*

Small sample as limited numbers of people were willing to participate in the study. We did not record total postoperative analgesic requirement. Our study was conducted on ASA I and II grade patients. Further studies on elderly and compromised cardiac function patients are required to recommend its use in such high risk patient.

#### **Conclusion**

We conclude that Premedication with 150 mcg of oral clonidine in laparoscopic cholecystectomy is a safe and inexpensive strategy to maintain peri-operative haemodynamic stability and sedation; with added advantage of reduced postoperative nausea, vomiting and shivering.

*Support:* Nil

*Conflicts of interest:* Nil

There was no conflict of interest during the undertaking of the study. The study was started only after clearance from the Ethical Comity was confirmed and the anaesthetic drugs used during the study were provided by the institute (Dr. DY Patil Medical College and Hospital).

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