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# Low dose oral clonidine as premedication in laparoscopic surgery

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## Abstract

**Introduction:** Clonidine modulates the cardiovascular changes caused by pneumoperitoneum in laparoscopic procedures. This study aims at comparing the haemodynamic variation, requirement of intraoperative opiods (fentanyl) and inhalational agents(isoflurane), incidence of postoperative complications and postoperative analgesic and oxygen requirement between low dose oral clonidine(100mcg) and placebo group in laparoscopic surgeries.

**Materials and Method:** Study group was randomly administered either tablet Clonidine 100mcg (test group) or a multivitamin tablet (control group) 90 minutes before the induction of anaesthesia. Intraoperative heart rate and arterial blood pressure (systolic, diastolic and mean) were recorded at various intervals. Intraoperative requirement of opioids (fentanyl) and inhalational agents (isoflurane) were recorded. Presence of sedation, nausea, vomiting and shivering in postoperative period were noted. Requirement of oxygen and analgesics in the postoperative period were also recorded.

**Results:** Clonidine group had a significantly low heart rate and arterial pressure (systolic, diastolic and mean) compared to placebo group at various interval. Intraoperative requirement of opioids(fentanyl) and inhalational agents(isoflurane) were lower in test group. Postoperative sedation and oxygen requirement was similar in both groups. Postoperative complications (vomiting, nausea, pain and shivering) were also less in test group.

**Discussion:** Low dose oral clonidine(100mcg) is an efficient cardiovascular modulator when given as premedication in patients undergoing laparoscopic surgeries. It not only provides good perioperative haemodynamic control but also lowers the requirement of anaesthetic agents. It has an added advantage of lesser postoperative complications like shivering, pain, nausea and vomiting. Postoperative analgesic and oxygen requirement is also less in patients taking low dose oral clonidine as premedication.

**Conclusion:** Low dose oral clonidine is a very efficient, easy to administer and cost effective premedication drug during laparoscopic procedures.

**Keywords:** Low dose clonidine, Pneumoperitoneum, Laparoscopic surgery, Heart rate, Blood pressure

## Introduction

Laparoscopic procedures have revolutionised abdominal surgeries with smaller incision. However pneumoperitoneum in laparoscopic procedures causes significant changes like tachycardia, raise in arterial pressure and arrhythmias in elderly and hemodynamically compromised patients.(1) Peritoneal cavity is insufflate with gas (Carbon-dioxide) to create space between the viscera and the anterior abdominal wall to allows endoscopic access in laparoscopic surgery. Pneumoperitoneum with carbon-dioxide(CO2) affects several systems like respiratory system, cardiovascular system, acid-base balance and stress level in the patient.(1) To control the haemodynamic changes associated with pneumoperitoneum different drugs were tried. Clonidine is a selective alpha2 adrenergic receptor agonist. It prevents the release of vasopressin and catecholamines which controls the cardiovascular changes caused by pneumoperitoneum. This study was designed to evaluate the role of low dose oral clonidine (100mcg) in prevention of haemodynamic changes associated with laparoscopic surgery. Laparoscopic cholecystectomies and laparoscopic hernia repairs were usually completed in 90 to180 minutes in our hospital, hence these surgeries were included in this study. We decided to use low dose oral clonidine(100 mcg) in our study as previous study with 150 mcg resulted in postoperative sedation, bradycardia and hypotension.(2,3) The effectiveness of clonidine in preventing postoperative adverse effects of pneumoperitoneum (pain, nausea and vomiting) and general anaesthesia (shivering and postoperative oxygen requirement) were also taken into consideration. This study aims at (1). To observe the variation in heart rate and blood pressure (systolic, diastolic and mean) between low dose oral clonidine (100mcg) and placebo group associated with pneumoperitoneum in laparoscopic surgeries. (2). To observe the requirement of intraoperative opioids (fentanyl), inhalational agents (isoflurane) and postoperative analgesics between two groups. (3). Incidence of postoperative adverse effects like nausea, vomiting, pain, shivering, sedation and oxygen requirement between the two groups.

## Materials and Method

After obtaining ethical committee approval from our institute, 60 consecutive patients undergoing laparoscopic procedures of 90 to 180 minutes were enrolled into the study. Inclusion criteria was ASA (American Society of Anaesthesia) I and II in the age group of 18 and 70 years. Exclusion criteria were patients of ASA III and IV, patients on antihypertensive medications and patients with known cardiac disease. A

written informed consent was obtained from all patients. A detailed preanaesthetic assessment was done.

The study population were randomly allocated into two groups (test and control). Randomization was done by closed envelope method. An anaesthesia registrar not involved in management of the case opened a sealed envelope in a serial order and administered either tablet Clonidine 100mcg (test group) or a multivitamin tablet (control group) 90 minutes before the induction of anaesthesia. The principle investigator blinded to the premedication drug conducted the intraoperative anaesthetic management and monitoring. The pulse rate, electrocardiogram, oxygen saturation and arterial pressure (systolic, diastolic and mean) were recorded.

After securing an intravenous access and pre-oxygenation with 100% oxygen for 3minutes, all patients received inj glycopyrrolate (anti-sialagogue) 0.2mg and inj midazolam (anxiolytic) 2mg intravenously. Analgesic used in all patients was inj fentanyl 1mcg/kg of body weight intravenously. Inj Lignocaine in a dose of 1.5mg/kg was administered intravenously to all patients 90 seconds before intubation to attenuate intubation response.

Induction and intubation were achieved in all patients with inj propofol 2mg/kg and 1.5mg/kg of inj succinylcholine intravenously. Intubation was done rapidly after 60 seconds of succinylcholine administration to avoid distention of the stomach. Inj ondansetron 4mg iv was given to all patients to reduce postoperative nausea and vomiting. Anaesthesia was maintained with 33% of oxygen & 66% nitrous oxide, 1% isoflurane and vecuronium. Pneumoperitoneum was created with insufflation of carbon-dioxide. Patient was adequately ventilated to maintain the end tidal carbon-dioxide between 30 and 35. Intra abdominal pressure was maintained within 15 mmhg throughout the surgical procedure. Intraoperative heart rate and blood pressure (systolic, diastolic and mean) were recorded prior to intubation, prior to pneumoperitoneum, 15, 30, 60, 90 and 120 minutes of pneumoperitoneum, after carbon-dioxide release and after extubation.

An increase in heart rate by 15 beats or mean arterial pressure by 15% from baseline was managed with additional bolus of 20 mcg of inj fentanyl iv and increase of isoflurane by 1% to 1.5% alternatively. Fall in heart rate below 50 bpm with the drop in BP was given inj atropine 0.6mg iv. Intraoperative requirement of opioids(fentanyl) and inhalational agents(isoflurane) were recorded. Patient was reversed with inj neostigmine 2.5mg and inj glycopyrrolate 0.2 mg intravenously and extubated. Postoperative sedation was score by 5 point sedation score, pain by 10 point visual analog scale and presence of nausea, vomiting and shivering were recorded. Post operative requirement of oxygen was also recorded.

The data was entered and analyzed using "SPSS for windows (Version 17)" statistical software. All the continuous variables were described using descriptive statistics and dichotomous variables using proportions. Student's t test and Pearson's Chi square test was the statistical test of significance. P value lesser than 0.05 was considered as significant.

## Results

The mean age was 41.23 and 46.47 in the clonidine and placebo groups respectively. Sex ratio and BMI were comparable between both groups. Of the 60 cases, 54 were laparoscopic cholecystectomies and 6 were laparoscopic hernia repair, which was comparable between the two groups. Total number of ASA I patients were 39 of which 22 were in clonidine group and 17 were in the placebo group. Total number of ASA II patients were 21, of which 8 were in the clonidine group and 13 in the placebo group. These parameters were comparable between both the two groups and were not statistically significant. Total duration of surgery were within our inclusion criteria. The duration of surgery in test group was 137±31.8 mts and with control group 138±42 mts. The total duration of surgery were comparable between both clonidine and placebo group and was not statistically significant.

Table 1 shows there is statistically significant difference and reduction in heart rate in clonidine group compared to placebo group at various interval.

**Table 1: Heart rate (in Bpm)**

| Heart rate | Test | | Control | |
|---|---|---|---|---|
| | Mean | std | Mean | std |
| Prior to intubation | 80.2 | 9.672 | 80.37 | 11.193 |
| Prior to Pneumoperitoneum | 78.6 | 11.294 | 86.20 | 15.990 |
| 15 mts of pneumoperitoneum | 78.73 | 10.255 | 87.90 | 14.216 |
| 30 mts of pneumoperitoneum | 77.93 | 9.131 | 87.47 | 12.320 |
| 60 mts of pneumoperitoneum | 74.77 | 16.283 | 85.13 | 12.875 |
| After $co_2$ release | 76.23 | 10.237 | 81.70 | 11.639 |
| After extubation | 80.63 | 11.186 | 90.13 | 8.609 |

Heart rate in 25 surgeries which extended beyond 60 minutes and 12 surgeries which extended beyond 90 minutes of pneumoperitoneum were comparable but not statistically significant between the two groups.

Table 2 shows a significantly lower arterial blood pressure (systolic, diastolic and mean) immediately after pneumoperitoneum, various intervals during surgery and after extubation between the clonidine and placebo group.

**Table 2: Blood pressure (in mm of Hg)**

| | Mean Systolic blood pressure | | Mean Diastolic Blood pressure | | Mean arterial pressure | |
|---|---|---|---|---|---|---|
| | Test | Control | Test | Control | Test | Control |
| Prior to intubation | 119.27 | 122.86 | 73.3 | 78.20 | 89.23 | 93.30 |
| Prior to Pneumoperitoneum | 104.47 | 114.27 | 65.97 | 70.17 | 79.93 | 86.03 |
| 5 mts of Pneumoperitoneum | 123.43 | 139.43 | 80.07 | 87.17 | 95.63 | 105.67 |
| 30 mts of pneumoperitoneum | 129.10 | 134.23 | 79.1 | 84.33 | 95.60 | 102.43 |
| 60 mts of Pneumoperitoneum | 123.47 | 129.27 | 78.9 | 80.93 | 95.03 | 98.47 |
| After $co_2$ release | 123.87 | 131.00 | 76.8 | 80.07 | 93.93 | 98.70 |
| After extubation | 131.97 | 144.33 | 79.33 | 84.37 | 97.5 | 105.60 |

At 90 and 120 minutes, systolic and mean arterial blood pressure were similar between the clonidine and placebo group. However, at 90 minutes the diastolic blood pressure was lower in the test group, but at 120 mts there was no statistically significance between the two groups (p=0.951).

The Clonidine group required lower doses of fentanyl and inhalational agent than the control group. The postoperative sedation and oxygen requirement were similar in the two groups. Postoperative requirement of analgesics were more in the placebo group. Nausea and vomiting were present in 11 patients of the control group and none in test group. All the 6 patients who had shivering were in the control group.

## Discussion

Pneumoperitoneum, changes in patient position and surgical stress during laparoscopic procedures produces cardiovascular changes, which can be dangerous in elderly and hemodynamically compromised patients.[4,2]

Increased intra abdominal pressure associated with pneumoperitoneum may compress venous capacitance vessels causing sustained decrease in pre-load.[5] Calculated systemic vascular resistance (SVR) will be high due to compression of the arterial vasculature. Cardiac index may also be significantly reduced. The magnitude of these effects are proportional to intra-abdominal pressure achieved.[6]

In this study, low dose of clonidine (100mcg) was decided to avoid complications as noted in previous studies with higher dose (150mcg).[7,1,2,3] The plasma concentration level peaks at 60 to 90 minutes after oral clonidine administration.[2] Considering the above fact and the ease of administration, 100mcg of tablet clonidine was given 90 minutes before the scheduled laparoscopy surgery.

In our study, heart rate was comparable in both groups at an average of 80/mt prior to intubation. However the mean heart rate was significantly higher in the placebo group during the entire duration of pneumoperitoneum and after extubation ($p<0.05$). Similar findings were also reported by Mrinmoy Das et al,[1] Deepshika et al,[3] Amirul Islam et al[8] and Shivender Singh et al[2] in their study with clonidine in laparoscopic surgeries. A decrease in sympathetic tone by central action and pre-synaptically mediated inhibition of norepinephrine and vagomimetic action at nucleus tractus solitarius are responsible for significantly lower heart rate in the clonidine group.[3] However, heart rate were similar between the groups at 90 and 120 minutes of pneumoperitoneum. Also the heart rate between both the groups were similar after carbon-dioxide release. This fall in heart rate in placebo group was probably due to removal of stimulation by pneumoperitoneum. Shivender Singh et al[2] observed similar finding after carbon-dioxide release in his study.

Patients pre-medicated with low dose clonidine had more stable haemodynamics than those pre-medicated with placebo drug in our study. The arterial pressures (systolic, diastolic and mean) were significantly lower in the clonidine group ($p<0.05$) at 15 and 30 minutes of pneumoperitoneum and after extubation. Similar observations were noted in study done by Mrinmoy Das et al,[1] Shivender Singh et al[2] and Amirul Islam et al.[8] However all these studies were done with 150 mcg of oral clonidine which showed remarcable reduction of pressures with higher incidence of complications (sedation, bradycardia, hypotension). However at 60 minutes of pneumoperitoneum all the pressures were comparable and there was no significant difference between the two groups. For surgeries which continued beyond 60 minutes both groups had similar arterial pressures at 90 and 120 minutes of pneumoperitoneum. This may be due to higher concentration of the inhalation anaesthetic and higher doses of fentanyl supplementation used intra-operatively among the placebo group to suppress cardiovascular response and also the small sample size (only 25 surgeries extended beyond 60mts of pneumoperitoneum).

A reduction in requirement of inhalational agents (isoflurane) and opioids(fentanyl) were noted in patients premedicated with low dose clonidine and this was statistically significant ( $p=0.000$). This was in

concordance with findings of Inomata et al[9,10] and Shivender Singh et al.[2] Postoperative pain and analgesic requirement were also very much lower with clonidine premedicated group, in our study. The intraoperative and postoperative analgesic requirement were reduced by low dose clonidine due to its non-opioids antinociceptive properties and synergistic analgesic effect with opioids.[11,12]

Clonidine by its primary sympatholytic effect decreases peripheral norepinephrine release by stimulating prejunctional inhibitory adreno receptors. Also it inhibits central neural transmission in the dorsal horn by acting at presynaptic and postsynaptic junction. It also improves analgesic effects of anti-inflammatory agents and has significant antinociceptive properties.[12] All these effects enhances the analgesic properties of traditional analgesics and results in opioid sparing effect. Ghaffari et al,[12] S. A. Jeffs et al,[13] Joseph Park et al,[11] and Shivinder et al[12] observed similar analgesic sparing effect with clonidine premedication.

In laparoscopic surgeries a greater sympathetic tone and catecholamine release may trigger nausea and vomiting.[14] Clonidine increases gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic outflow from the central nervous system and reduces the postoperative nausea and vomiting. In our study, clonidine group did not have nausea and vomiting but the placebo group had significant patients with nausea and vomiting. Similar observation was seen in studies done by B Ghrab et al[15] and Javaher Froosch et al.[16]

Susan Soltani et al[17] did a study with oral clonidine premedication and observed the incidence of postoperative shivering in general anaesthesia. Anurag Tewari et al[18] did the same on spinal anaesthesia. Both their studies stated that incidence ($p<0.001$) was very low among the clonidine group. Shivering can adversely increase the metabolic rate and cardiac work and may also disrupt surgical repair and result in wound dehiscence. Clonidine acting at 3 levels (hypothalamus, locus coeruleus and spinal cord) of central nervous system reduces the incidence of shivering. In hypothalamus there is higher density of α2 adrenoreceptors. Clonidine by acting on them reduces the thermoregulatory threshold for vasoconstriction and shivering. Locus coeruleus is a pro shivering centre in pons and clonidine inhibits its spontaneous firing. At the spinal cord level, it acts at α2 adreno receptors and release dynorphine, norepinephrine and acetylcholine. Depressor effect of these neurotransmitters, acting at the dorsal horn modulates the cutaneous thermal inputs.[19] The incidence of post operative shivering was nil in the clonidine group but was recorded in six patients of control group ($p=0.000$).

Sedative effect of clonidine is by action at the locus coeruleus, by inhibiting the regulation of sleep and wakefulness.[20] Minroy Das et al[1] in his study with 150 mcg of oral clonidine premedication observed incidence of sedation was higher in clonidine group (33%). Deepshika et al[3] also noted that premedication with 2mcg/kg intravenous clonidine causes greater postoperative sedation than 1mcg/kg ($p<0.05$). Higher the dosage, greater the degree of sedation. In our study, the clonidine premedication of 100mcg is relatively a lower dose. Degree of sedation was comparable between both the groups and there was no significant difference ($p=1.00$).

Clonidine by reducing sympathetic over activity and plasma catecholamine concentration decreases the overall body metabolism and cardiac oxygen demand.[21,22] Thereby reduces postoperative oxygen requirement. In our study, number of patients requiring postoperative oxygen were 2 in the clonidine group and 6 in the placebo group. Though we were not able to achieve a statistical significance ($p=0.129$), because of lower incidence of postoperative complication number of patients requiring post operative oxygen in clonidine group was low.

## Conclusion

Low dose oral clonidine is a very efficient, easy to administer and cost effective premedication drug during laparoscopic procedures. It provides good perioperative haemodynamic control and lesser requirement of anaesthetic agents. It has an added advantage of lesser postoperative complications like shivering, pain, nausea and vomiting. Postoperative analgesic and oxygen requirement is also less with clonidine.

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