

A comparative study for efficacy and safety of low doses of clonidine for hemodynamic stability in patients undergoing laparoscopic cholecystectomy

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ABSTRACT

Background: This randomized prospective double-blind study was designed to evaluate the efficacy and side effects of low doses clonidine for perioperative haemodynamic stability and postoperative recovery.

Methods: Patient's with ASA grade I–II undergoing laparoscopic cholecystectomy were randomized into three groups of 30 patients each. All patients received either normal saline 10 ml (Group I) or 0.8 µg/kg (Group II) or 1 µg/kg (Group III) over duration of 180 seconds, 10 min prior to laryngoscopy and intubation. Anaesthesia was induced with 1% propofol (2 mg/kg) and maintained with nitrous oxide 60% in oxygen and isoflurane. The parameters assessed at various time intervals were heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and sedation score.

Results: Both doses of clonidine proved to be effective in perioperative haemodynamic stability. Clonidine 0.8 mcg/kg was as effective and safer to Clonidine 1 mcg/kg for attenuation of the hemodynamic responses to laparoscopy. There were no significant differences in the parameters of recovery between groups.

Conclusions: Significant hemodynamic derangements can occur during laparoscopic cholecystectomy at intubation, pneumoperitoneum and extubation. These were effectively attenuated by premedication with 0.8 mcg/kg and 1 mcg/kg of intravenous clonidine. Dose of 1 mcg/kg though found to be effective but produced adverse effects in form of hypotension and bradycardia.

Keywords: Clonidine, Hemodynamic response, Laparoscopic cholecystectomy, Laryngoscopy, Pneumoperitoneum

INTRODUCTION

Laparoscopic cholecystectomy was introduced by Phillipe Mouret in 1987 since then, it quickly was apparent that laparoscopy results in multiple benefits.¹ There are various advantages of laparoscopic cholecystectomy like shorter duration of stay in hospital, smaller scar, easy and early ambulation and less compromised postoperative respiratory and gastrointestinal functions. However the procedure may be associated with significant hemodynamic changes due to

creation of pneumoperitoneum, reverse Trendelenberg position and due to the intubation and is not free of risks. Various pharmacological agents were used to provide haemodynamic stability in laparoscopic cholecystectomy like nitroglycerine, β-blocker, lignocaine and opioids.²⁻¹⁰ Clonidine is a α-2 adrenoreceptor agonist which has demonstrated promising results for attenuation of haemodynamic responses associates with laparoscopic procedures.^{11,12} Premedication with clonidine blunts the hemodynamic changes in laparoscopic cholecystectomy and the doses of narcotic and anesthetic drugs are also

reduced. But there is wide difference in doses of clonidine used in various studies. So there as need for further evaluation for determining minimum and safe dose of intravenous clonidine. Accordingly, this study was designed to evaluate the effects of different doses of intravenous clonidine premedication on haemodynamic response.

METHODS

After taking approval from institutional ethics committee of Subharti Medical College and Hospital, Meerut, and written informed consent, this prospective, randomized, double-blind controlled clinical study was carried out on Ninety patients between 16- 65 years of age, ASA grade I and II scheduled for laparoscopic cholecystectomy. Patients were randomly divided, by picking up sealed envelope, in to three groups of 30 patients each:

Group I: Received IV normal saline 10 ml,

Group II: Received IV clonidine 0.8 mcg/kg in 10 ml normal saline,

Group III: Received IV clonidine 1 mcg/kg in 10 ml normal saline.

The drug was given intravenously over 180 seconds, 10 min before intubation. Exclusion criteria were patients with morbid obese patients, hypertensives, renal, cardiac, cerebrovascular, hepatic diseases and endocrine dysfunction, alcohol or drug abuse, patients taking antidepressants or antihypertensives or antiepileptic drugs, pregnancy and known drug hypersensitivity.

In the pre-anesthetic preparation room monitoring of heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) peripheral was instituted. After recording of base line parameters all patients were pre-medicated with metoclopramide (10 mg IV), Fentanyl (1 mcg/kg IV), Midazolam (1 mg IV). After premedication patients received normal saline 10 ml (group 1) or 0.8 µg/kg (group 2) or 1 µg/kg (group 3) over a duration of 180 seconds, 10 min prior to laryngoscopy and intubation. The test drug was prepared by a senior anesthesiologist who was not involved in the

study. Observer and patients were blinded for the study. Anesthesia was induced with propofol (1%) 2 mg/kg, followed by vecuronium bromide 0.1 mg kg⁻¹ to facilitate direct laryngoscopy and intubation in all patients. Just after intubation nitrous oxide 60% in oxygen and isoflurane was started at dial setting 1 and anaesthesia was maintained throughout the surgery on nitrous oxide, oxygen and isoflurane. Supplemental vecuronium was given to maintain neuromuscular blockade. At the end of surgery, the residual neuromuscular block was antagonized with appropriate doses of neostigmine (0.05 mg kg⁻¹) and glycopyrrolate (0.02 mg kg⁻¹) and extubation was performed when respiration was adequate and patient was able to obey verbal commands. Sedation at end of the surgery was evaluated with Ramsay Sedation Score.¹³

Throughout study period, parameters assessed were HR, SBP, DBP, MAP and SpO₂ and were recorded at specified time-intervals. Any change in hemodynamic variables >20% on either side of the baseline was considered clinically significant and treated by increasing the concentration of isoflurane or fentanyl or beta blockers or fast IV fluids or atropine.

Statistical analysis

Sample size of minimum 29 in each group was derived using Cohen's formula with an assumption of α error of 0.05 and power of study of 80% after permitting β error of 0.02 for detecting difference of at least 4 in the quantitative variables between groups. Mean and standard deviation was calculated for all quantitative variables using SPSS software. An intergroup comparison was made using paired student's t- test and comparison between two groups (intergroup comparison) was done using the unpaired t-test. A p value of <0.01 was considered statistical significant.

RESULTS

All patients (90) completed the study and the groups were comparable with respect of age, sex, body weight and duration of surgery (p>0.05). There was no statistical significant difference in baseline SBP, DBP, HR and MAP (Table 1).

Table 1: Demographic and baseline characteristics.

Variables	Group1 (n=30)	Group2 (n=30)	Group 3 (n=30)	P value
Age (years)	39.30±11.71	38.70±11.82	41.23±10.86	NS
Weight (Kgs)	57.93±7.29	57.77±6.85	58.10±7.29	NS
Sex (male/female)	5/25	4/26	6/24	NS
Duration of surgery (min)	98.17±11.17	90.83±9.04	100.83±8.31	NS
Basal HR (per min)	82.47±7.38	83.87±7.24	81.57±6.88	NS
Basal SBP (mmHg)	127.8±5.97	130.77±13.3	125.90±4.45	NS
Basal DBP (mmHg)	82.17±4.45	79.40±5.7	80.67±4.8	NS
Basal MAP (mmHg)	97.39±4.37	95.59±8.30	96.52±4.8	NS
Basal O ₂ saturation (%)	98.97	98.97	99.00	NS

NS (Not significant) - p>0.01

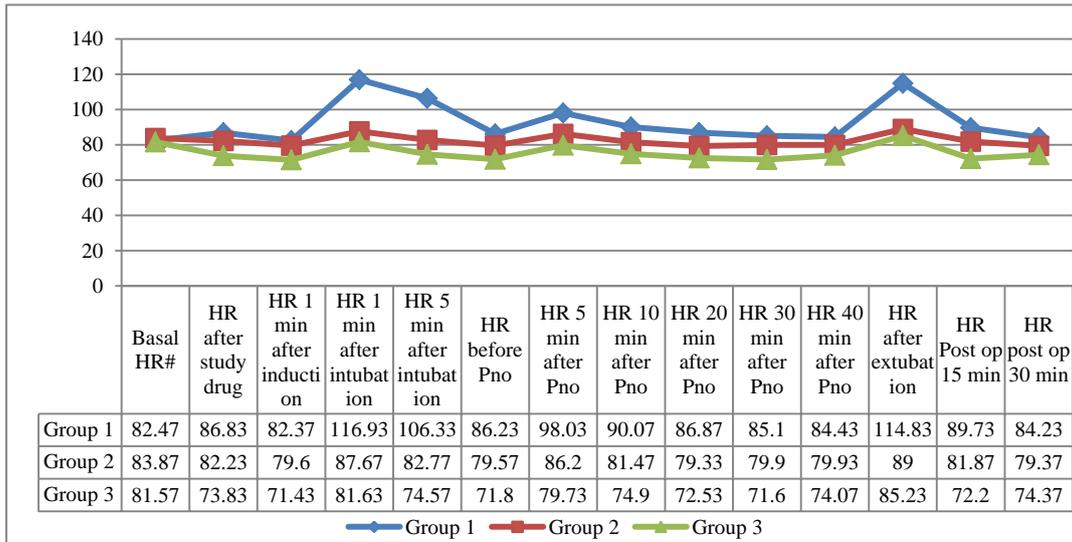


Figure 1: Mean heart rate at specified time points in three groups.

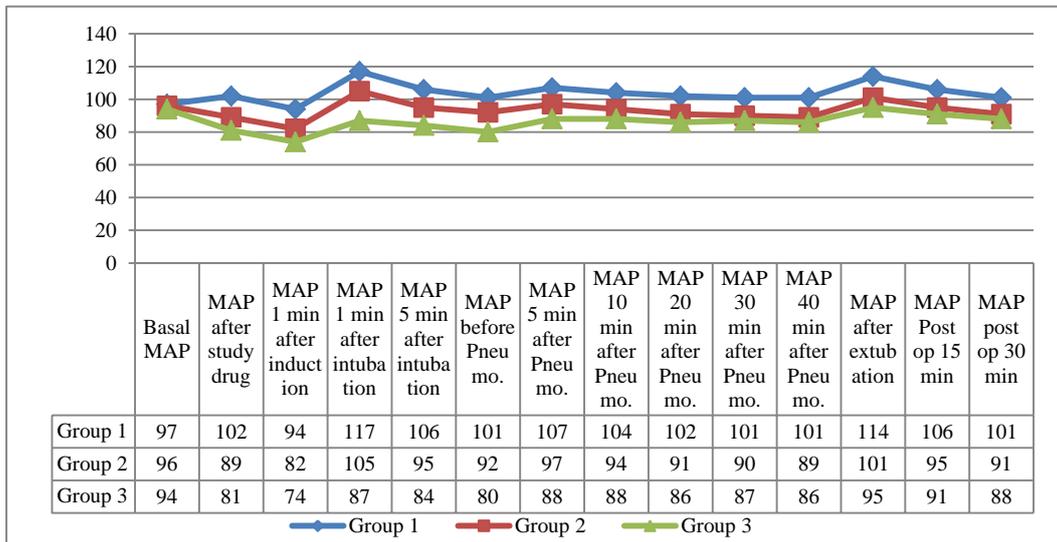


Figure 2: Mean artery pressure at specified timings in three groups.

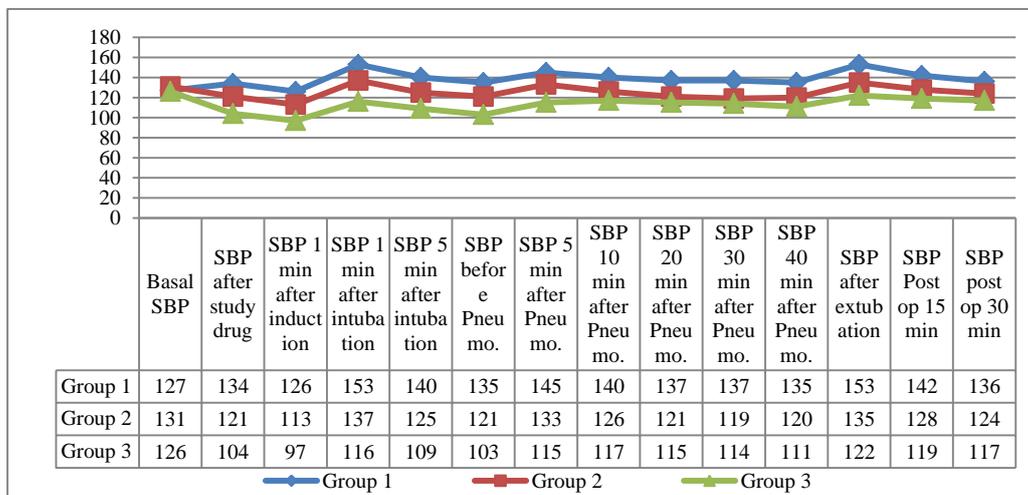


Figure 3: Mean systolic blood pressure at specified timings in three groups.

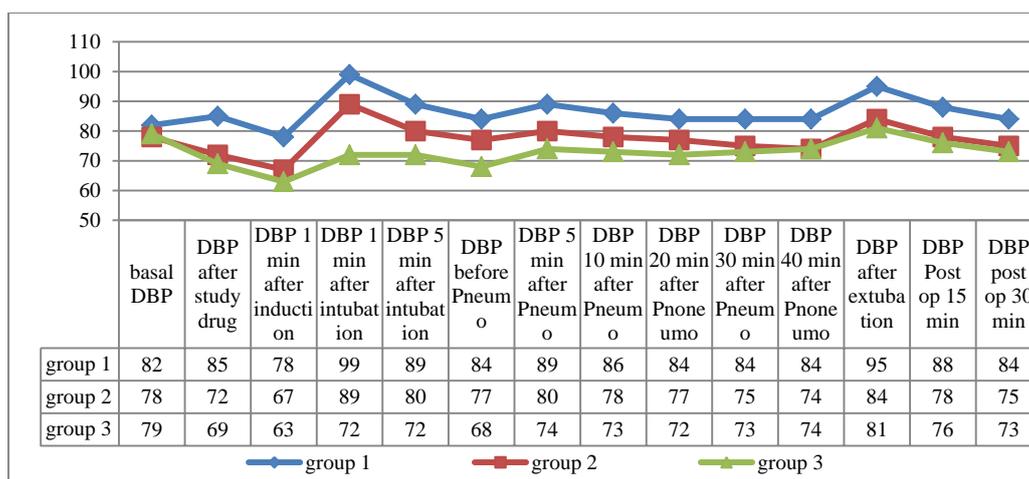


Figure 4: Mean diastolic blood pressure at specified timings in three groups.

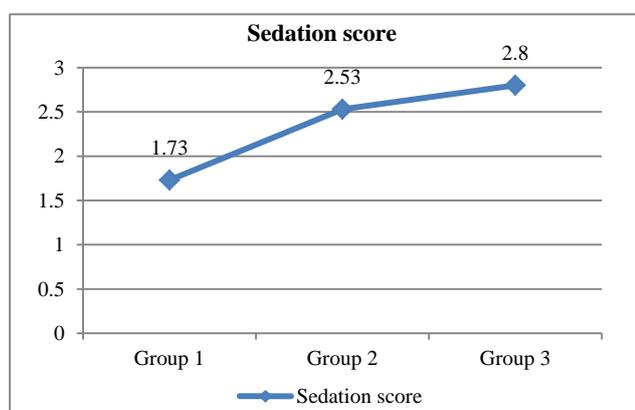


Figure 5: Mean sedation score in all three groups.

The difference in mean HR observed in Group 2 and 3 was statistically significant when compared to mean HR in the group 1 at all-time points except basal HR ($p < 0.05$) as shown in Figure 1. There was marked increase in mean arterial pressure observed in Group 1 ($p < 0.01$) as compared to increase in MAP Group 2 and 3 (Figure 2). Also increase in mean systolic blood pressure and diastolic blood pressure observed in Group 2 and 3 was statistically significant when compared to increase in mean SBP in the group 1 ($p < 0.001$) at all-time point except basal SBP as shown in Figure 3.

Hence it is reflected that in group 2 and 3 the hemodynamic response after intubation, pneumoperitoneum and extubation was effectively attenuated. Patients in clonidine groups (2 and 3) are more sedated than the patients in group 1 (control). Maximum sedation was found in group 3, which was in the dose dependent manner as shown in Figure 5.

In group 1 and 3, in total 11 (36.66%) and 4 patients rescue medication was given to maintain the hemodynamic stability, while in group 2 no rescue medication was given to any patient.

DISCUSSION

During laproscopic cholecystectomy major hemodynamic changes (HR, SBP, DBP and MAP) are observed after intubation, pneumoperitoneum and extubation.¹⁴⁻¹⁶ Sometimes these transient changes in haemodynamics can result in potentially harmful effects like left ventricular failure, pulmonary edema, myocardial ischemia, and cerebral haemorrhage.⁸⁻¹⁰ If no specific measures are taken to attenuate these hemodynamic responses, heart rate can increase from 26-66% depending on method of induction and arterial systolic BP can increase from 36-45%.^{6,15} These adverse hemodynamic responses can affect the outcome of the patient.⁶

Many methods like use of inhalational anesthetic agents, lidocaine, opioids, direct acting vasodilators, and calcium channel blockers have been tried by various author's for blunting hemodynamic responses to laryngoscopy and intubation.^{2,3,7-10,17} Though, all such maneuvers have their own limitations. Hence a drug which can blunt both HR and BP response of laryngoscopy and intubation, pneumoperitoneum and extubation without having any side effects like respiratory depression and postoperative nausea and vomiting, is need of the day.

Clonidine, an $\alpha-2$ agonist, has been found by various authors to blunt the hemodynamic response occurring during surgery.^{18,19} Though various studies found that intravenous Clonidine is effective in attenuating the hemodynamic changes during laproscopic surgery, there is a wide difference in doses. In our study we observed effects of two different doses of clonidine as adjuvant to general anesthesia. Altman and Turgot used clonidine 3 mcg/kg intravenously over a period of 15 minutes before induction and 2 mcg/kg/hour by continuous infusion intraoperatively.¹⁹ They observed significant incidences of bradycardia and hypotension in their study. Based on these observations, Ray, Bhattacharjee administered clonidine 3 mcg/kg I.V.²⁰ 15 minutes before induction and reduced the infusion to 1 mcg/kg/hour intraoperatively. In

spite of this reduced infusion rate of clonidine, they observed significant incidences of bradycardia and hypotension. They suggested that further studies using lesser dose of clonidine should be done.

In this study intravenous clonidine in dose of 0.8 and 1 mcg/kg was used to achieve hemodynamic stability. The effect of clonidine was dose dependent. The attenuation of hemodynamic response was more in the clonidine 1 mcg/kg. But four patients had a fall of MAP more than 20% and were maintained with fast IV fluids. It could be explained by dose dependent fall in blood pressure and heart rate. However significant rise in HR, SBP, DBP and MAP was observed in Group 1. In group 1, 36.6% patients had a rise in mean arterial pressure >20% from base line and required intravenous fentanyl or increased concentration of isoflurane.

The possible mechanism to explain the effect of clonidine is that it being α_2 agonist causes stimulation of centrally located presynaptic α_2A receptor in the lower brain region, thereby decreasing norepinephrine release. It also acts via imidazoline receptors (I1, I2 and I3) causing a fall in BP and HR. It decreases the discharge in sympathetic preganglionic fibers in the splanchnic nerve and in post ganglionic fibers of cardiac nerves. Clonidine by stimulating parasympathetic outflow leads to increased vagal tone which along with diminished sympathetic drive contributes to the slowing of the heart i.e. decrease in heart rate.²¹

CONCLUSION

Significant hemodynamic derangements occurring during laproscopic cholecystectomy at intubation, pneumoperitoneum and extubation was effectively attenuated by premedication with 0.8 mcg/kg and 1 mcg/kg of intravenous Clonidine. We recommend use of 0.8 mcg/kg intravenous Clonidine, 10 minutes before intubation to attenuate the hemodynamic stress response of pneumoperitoneum and tracheal intubation or extubation in otherwise healthy patients as it is effective and safe.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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