The comparative evaluation of intravenous with intramuscular clonidine for suppression of hemodynamic changes in laparoscopic cholecystectomy

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ABSTRACT

Background: Clonidine diminishes stress response by reducing circulating catecholamines and hence increases perioperative circulatory stability in patients undergoing laparoscopic surgeries. The aim of this study was to compare intravenous (IV) clonidine (2 μg/kg) with intramuscular (IM) clonidine (2 μg/kg) for attenuation of stress response in laproscopic surgeries. **Methods:** Eighty adult patients classified as ASA physical status I or II, aged between 20 and 60 years undergoing elective cholecystectomy under general anesthesia were enrolled for a prospective, randomized, and double-blind controlled trial. They received either IV clonidine (2 μg/kg) 15 min prior to the scheduled surgery (Group I) or IM clonidine (2 μg/kg) 60-90 min prior to the scheduled surgery (Group II). Hemodynamic variables (Heart rate, systolic (SBP), diastolic (DBP), mean arterial pressure (MAP)), SpO_2 and $EtCO_2$ were recorded at specific times - baseline, prior to induction, 1 min after intubation, before CO_2, insufflation, after CO_2 insufflation at 1,5,10,20,30,45,60 min, after release of CO_2, at 1 and 10 minutes after extubation. Secondary outcomes included evaluation of adverse effect profile of the two groups. **Results:** No significant difference was observed in the HR throughout the intraoperative period in between the two groups ($P > 0.05$). There was statistically significant difference in SBP between the two groups starting from 1 minute after induction till 1 min after extubation ($P < 0.05$) but not in DBP except at 1 minute after intubation ($P = 0.042$). Significant difference in MAP was noted at 1 minute after intubation ($P = 0.004$) and then from 5 minutes after CO_2 insufflation to 1 minute after extubation ($P < 0.05$). Incidence of adverse effects were higher in group II ($P = 0.02$) especially incidence of hypertension requiring treatment (0.006). **Conclusion:** We conclude that under the conditions of this study, hemodynamic parameters (SBP, DBP and MAP) were better maintained in the IV as compared to the IM route that had significantly higher incidence of hypertension requiring treatment.

Key words: *Clonidine, hemodynamic response, laproscopic cholecystectomy, pneumoperitoneum, stress response*

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INTRODUCTION

The laparoscopic approach for both diagnostic and operative surgeries is considered to be safe and reliable

technique with several advantages over the standard open procedures.[1,2] However, it is not completely safe in the elderly and is hemodynamically compromised. During laparoscopy, the main trespasses to physiological hemostasis in an anesthetized patient include the patient's positioning, creation of pneumoperitoneum by the insufflating gas and extubation. These result in complex hemodynamic, pulmonary and metabolic effects on the blood flow, tissue perfusion, and pulmonary mechanics.

Various pharmacological and nonpharmacological methods have been used by the anesthesiologists and surgeons over the years to prevent or attenuate these adverse hemodynamic

changes associated with pneumoperitoneum. Many pharmacological agents like adrenoreceptor blockers,[3] beta blockers,[4] Ca channel blockers, lidocane,[5] opioids,[6] pregabalin,[7] magnesium sulfate[8] and vasodilators[9] have been used to attenuate these responses and improve quality of recovery. However, quest for ideal drug for this purpose and its route of administration continues.[10]

Clonidine, a centrally acting α_2-adrenergic receptors agonist has sedative, anxiolytic, analgesic properties and stabilizes circulatory system.[11] It diminishes stress response by reducing circulating catecholamines[3] and hence increases perioperative circulatory stability[12] in patients undergoing laparoscopic surgeries. In addition, it increases cardiac baroreflex sensitivity in hypertensive individual, and thus, stabilizes blood pressure by enhancing the role of changes in heart rate.[13]

Oral clonidine has been commonly employed for hemodynamic control during various laparoscopic studies.[7,14-16] There are few studies demonstrating the effectiveness of intravenous (IV)[17,18] or intramuscular (IM)[19,20] clonidine individually in attenuation of hemodynamic response during laparoscopy. However, there is limited literature, comparing the intravenous and intramuscular routes of clonidine premedicant in laparoscopic surgery. Hence the present study was undertaken to evaluate the effects of clonidine premedication on the adverse hemodynamic changes that occur during laparoscopic cholecystectomy and also compare the efficacy of IV and IM clonidine premedication.

METHODS

This study was a randomized, double-blind, comparative and prospective study. After approval from the institutional ethical committee and written informed consent, 80 adult patients in the age group of 20-60 yrs., of either sex and of American Society of Anesthesiologists (ASA) grade I or II, posted for elective cholecystectomy under general anesthesia were randomly allocated into two groups using computer-generated randomization list.

Group I - Patients received injection Clonidine 2 µg/kg in 100 ml normal saline as intravenous infusion, 15 minutes prior to anesthesia

Group II - Patients received injection Clonidine 2 µg/kg, intramuscularly, 60-90 minutes prior to anesthesia.

Exclusion criteria included patients with uncontrolled hypertension, ischemic heart disease, chronic reactive airway disease, aortic stenosis, left ventricular failure, AV conduction block, any rhythm other than sinus rhythm,

patient's receiving Clonidine/Methyl Dopa/B-blocker/ Benzodiazepines/MAO inhibitor, any drug dependence and allergy to Clonidine.

After 6 hours fasting and premedicating with Tab. Diazepam 5 mg on the night prior to surgery, patients were preloaded with 500 ml of lactated ringer's solution in the operation theater prior to induction of anesthesia. Patients assigned to group I received 2 µg/kg of inj. Clonidine in 100 ml of normal saline as intravenous infusion, 15 min prior to the scheduled surgery and those assigned to group II were given 2 µg/kg of inj. Clonidine, intramuscularly, 60-90 min before the scheduled time of surgery. The observer was blinded to the drug being received by the patient.

A standard anesthetic technique was followed for all the patients. Patients were induced with thiopentone sodium 5 mg/kg IV and succinylcholine 1-1.5 mg/kg IV to facilitate tracheal intubation. Anesthesia was maintained with 50% oxygen in nitrous oxide, 0.5-1% isoflurane and injection vecuronium bromide 0.1 mg/kg bolus. This was followed by 0.02 mg/kg for maintenance of muscle relaxation.

Controlled mechanical ventilation with a tidal volume of 8 ml/kg and ventilatory frequency of 14 breaths/min was done to maintain end-tidal carbon dioxide ($EtCO_2$) at 35-45 mmHg and any increase was adjusted with increase in respiratory rate and/or ventilation accordingly.

Pneumoperitoneum was created by insufflation of CO_2 and operation table was tilted to about 15 degrees reverse trendelenburg position. Intra-abdominal pressure (IAP) was maintained between 12-15 mmHg throughout surgical procedure. At the end of the surgery, residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg IV after return of protective reflexes.

Intraoperative monitoring included heart rate (HR), continuous electrocardiography, noninvasive systolic (SBP), diastolic (DBP), mean blood pressure (MBP), pulse oximetry (SpO_2), and $EtCO_2$. The hemodynamic parameters were recorded at the baseline (before premedication), prior to induction, 1 min after intubation, before insufflation of CO_2 after insufflation of CO_2 at 1,5,10,20,30,45,60 min, after release of CO_2, at 1 and 10 minutes after extubation. Patients were also observed for drowsiness, dry mouth, skin rashes, nausea and vomiting.

All the episodes of circulatory derangements were recorded. Hypertension (defined as SBP >170 mmHg) was treated with isoflurane (0.20% increments) at 2-minute intervals up to 2% if required. Tachycardia (defined as heart rate >90 beats/min) was treated with bolus dose of fentanyl 25 mcg.

Hypotension (defined as SBP <90 mmHg) was treated by reducing the concentration of isoflurane and 250 ml bolus dose of lactated Ringer's solution over 5 minutes followed by ephedrine 6 mg, if the patient was unresponsive. Bradycardia (defined as heart rate <50 beats/min associated with hypotension) was treated with atropine 0.6 mg and repeated once if necessary.

Statistical analysis

The data collected was tested for normalcy. Normally distributed parametric data was analyzed using unpaired Students 't' test while Chi-square test was performed for categorical data. The data for which the distribution was not normal 'Mann-Whitney' test was used. For comparison within the group, ANOVA test was used. $P<0.05$ was considered statistically significant.

RESULTS

The baseline demographic variables and baseline hemodynamic parameters (HR, SBP, DBP, MAP, SpO2) were statistically comparable in between the two groups [Table 1].

Heart rate

In group I, the mean HR varied form 78.88±13.64 beats per min (bpm) to 85.25±11.88 bpm and in group II, the mean HR varied from 80.20±11.77 bpm to 86.53±14.50 bmp [Figure 1]. On comparison within the group, the variation in HR from baseline was not found to be statistically significant ($P>0.05$) in both the groups. No significant difference was observed in the HR throughout the intra-operative period in between the two groups. On comparison, no significant difference was observed in the highest and the lowest heart rate between the two groups statistically. For bradycardia, five patients in group I and

Table 1: Distribution of subjects according to baseline demographic profile and baseline hemodynamic parameters

	Group I	Group II	P value	Significance
Age (yrs.)	44±10.55	43.95±10.62	0.983	NS
Sex (M/F)	7/33	8/32	0.775	NS
Weight (Kg)	60.8±13.46	61.3±9.98	0.851	NS
ASA grade (I/II)	28/12	30/10	0.617	NS
Duration of surgery	1.81±0.39	1.84±0.50	0.796	NS
Heart rate (HR)	80.68±10.44	80.20±11.77	0.849	NS
Systolic blood pressure	122.75±13.58	128.25±15.71	0.98	NS
Diastolic blood pressure	80.45±6.57	81.95±9.66	0.419	NS
Mean arterial pressure	94.54±8.17	97.38±10.67	0.185	NS
SpO2	98.98±1.02	99.05±0.90	0.730	NS

Parametric data expressed as mean±SD and categorical data expressed as frequency. *P*<0.05 is statistically significant

three patients in group II required treatment which was, however, statistically not significant ($P=0.46$).

Systolic blood pressure

In group I, the mean SBP varied from 112.00±17.99 mm Hg to 125.05±16.17 mm Hg and in group II, the mean SBP varied from 124.33±20.93 mm Hg to 141.75 ± 20.69 mm Hg [Figure 2]. The SBP was maintained near the baseline throughout the intraoperative period in both the groups.

On comparing the change in SBP within the group from baseline, no significant statistical difference was found ($P>0.05$) except for at 5 minutes after CO_2 insufflation ($P=0.021$), where it was significant.

A statistically significant difference was noted between the two groups starting from 1 minute after induction till 1 min after extubation ($P<0.05$). This difference was found to be highly significant at 5 minutes ($P<0.0001$), 30 minutes ($P<0.0001$), and 45 minutes after CO_2 insufflation ($P<0.0001$) and at 1 minute after extubation ($P<0.0001$) but was found to be statistically comparable at 1 minute after CO_2 insufflation and at 10 minutes after extubation.

Diastolic blood pressure

The mean DBP in group I varied from 80.45±6.57 mmHg (baseline) to 85.50±11.46 (1 min after CO_2 insufflation) and in group II, the mean DBP varied form 80.60±12.53 mmHg (before CO_2 insufflation) to 87.05±10.26 mmHg (at 1 minute after CO_2 insufflation). In both the groups, on intragroup comparative analysis from the baseline DBP, the variation was not found to be significant ($P>0.05$) [Figure 3].

When the two groups were compared for trends in DBP, the DBP at 1 minute after intubation was found to be significant ($P=0.042$). There was no other statistically significant difference in DBP throughout the intraoperative period between the two groups.

Mean arterial blood pressure

In group I, the MAP was in the range of 91.03±11.48 mmHg (before CO_2 insufflation) to 98.78±10.75 mmHg (at 10 minutes after CO_2 insufflation) and in group II, the range was from 95.17±14.00 mmHg (before CO_2 insufflation) to 105.27±11.82 mmHg (at 5 minutes post-CO_2 insufflation). On comparison within the group II, the MAP at 5 minutes post-CO_2 insufflation was found to be significant ($P=0.020$). Apart from this, no statistically significant difference was noted in MAP at any other point within group II intraoperatively [Figure 4].

On statistical comparison in between the two groups, significant difference in MAP was noted at 1 minute after

intubation ($P=0.004$) and then from 5 minutes after CO_2 insufflation to 1 minute after extubation the difference was significant statistically in between the two groups ($P<0.05$).

The saturation in both the groups was maintained in the range of 96-100% and there was no statistical difference found between the two groups. Normocapnia was maintained throughout the surgery and there was no statistically significant difference between the two groups in $EtCO_2$. Overall, adverse effects noted with IV clonidine were statistically less than with IM clonidine ($P=0.02$). No statistically significant difference was found in between the two groups with regards to individual adverse effect profile [Table 2] except for hypertension. Nine patients (22.5%) in group I and 21 patients (52.5%) in group II had high SBP and DBP that required treatment that was statistically significant ($P=0.006$).

DISCUSSION

Alteration in hemodynamic and pulmonary physiology during laparoscopy can be potentially hazardous especially in elderly and patients with comorbidities. The transient acute hemodynamic response which usually occurs at laryngoscopy and tracheal intubation is also seen during insertion of the Veress needle, trocar and during the period of the pneumoperitoneum in patients undergoing laparoscopic surgical procedures. The sympathetic effects associated with insufflation of CO_2, as well as the shifts in intravascular volume resulting from the Trendelenburg position, can lead to hemodynamic perturbations during surgery. Various studies done over the years have proved these detrimental effects occurring during pneumoperitoneum in the intraoperative period. Various pharmacological and nonpharmacological interventions have been used to re-establish the baseline hemodynamic parameters to allow for safe performance of laparoscopy and clonidine is one of them.

The number of females who underwent laparoscopic cholecystectomy was more when compared to the males in both the groups, this was in consensus with the well established fact that cholecystitis is more common in females and similar to study results of Das M *et al*.[21]
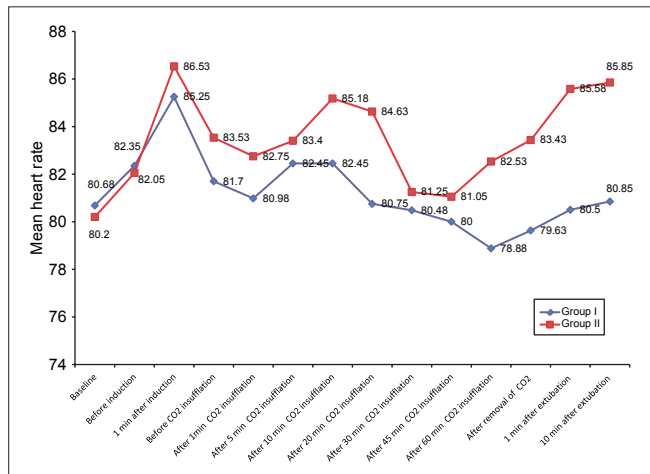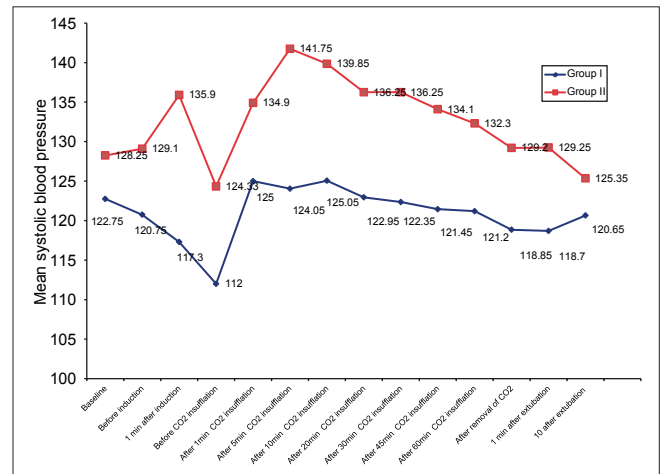

Figure 1: Trends in heart rate

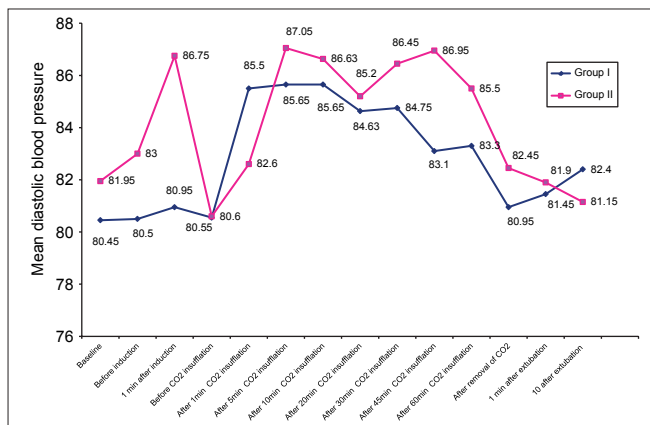**Figure 2:** Trends in systolic blood pressure

Figure 3: Trends in diastolic blood pressure
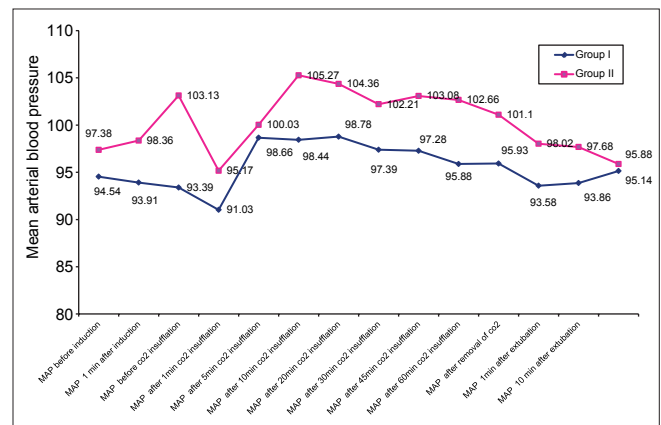

Figure 4: Trends in mean arterial pressure

Table 2: Comparison of adverse effect profile in both the groups

Adverse effect	Group I	Group II	P value
Drowsiness	14 (35)	13 (32.5)	0.83
Dry mouth	24 (60)	27 (67.5)	0.633
Skin rash	0 (0)	0 (0)	
Nausea	5 (12.5)	7 (17.5)	0.69
Vomiting	0 (0)	0 (0)	
Tachycardia	12 (30)	16 (40)	0.35
Bradycardia	5 (12.5)	3 (7.5)	0.46
Hypertension	9 (22.5)	21 (52.5)	0.006*
Hypotension	0	0	
Total adverse effects	69	88	0.02*

Data expressed as frequency (%) using Chi-square analysis. *$P<0.05$ is statistically significant

Dose selection is in consensus with previous studies by Tripathi *et al.*[17] We chose to administer IM clonidine 60-90 min prior to induction and IV clonidine 15 min prior to induction. In view of the fact that, clonidine has a half-life of 8-12 hrs with peak effect achieved in 1-1.5 hrs after IM administration and 20 minutes after IV administration.[22-24] IAP was maintained between 12 and 15 mmHg based upon left ventricle ejection fraction observations by Cunningham *et al.*[25] and Dorsay *et al.*[26]

Our results show, that the hemodynamic parameters (HR, SBP, DBP, and MAP) were comparable to the baseline in both the groups, thereby, providing stable hemodynamics and protection against stress response triggered by pneumoperitoneum as well as by laryngoscopy and intubation in patients undergoing laparoscopic cholecystectomy. The hemodynamic parameters (SBP, DBP and MAP) were better maintained in the IV as compared to the IM route while the HR was comparable in both the groups. The incidence of hypertension, which required treatment, was significantly higher in the IM group but there were no episodes of hypotension in either group.

Laisalmi *et al.* found that clonidine (4.5 mcg/kg IM) blunted the deleterious hemodynamic stress response during laparoscopic surgery, had opioid sparing effect and maintained renal integrity.[19] Joris *et al.* found that clonidine premedication (8 mcg/kg) IV improved intraoperative and postoperative hemodynamic stability and smoothed the changes in HR, arterial pressure, systemic vascular resistance and cardiac output.[23] A significant reduction was noted in the HR and MAP when compared to placebo. Reduction in the level of catecholamine and vasopressin following pneumoperitoneum by clonidine is considered responsible for such a change.

Overall, the SBP was maintained near the baseline SBP throughout the surgery with no wide fluctuations during laryngoscopy, surgical incision or pneumoperitoneum in both the groups. The highest SBP was noted after 5-10 min of CO_2 insufflation and the lowest SBP was noted before CO_2 insufflation in both the groups. This inference was corroborated to the study done by Aho *et al.*[27] who had studied the effect of IM clonidine on hemodynamic and plasma beta-endorphin responses in 90 patients undergoing gynecologic laparoscopy. The women in the study group received IM clonidine 3 (group I) or 4.5 (group II) mcg/kg, 45-60 minutes before induction of anesthesia while the control group (group III) recieved 2 ml IM saline. In all the groups, the MAP increased after the beginning of laparoscopy but the control group showed a greater increase in MAP than the study group. Thereafter, MAP decreased and was lower than the baseline value indicating that clonidine effectively prevents the maximal hemodynamic responses to tracheal intubation and to gynecologic laparoscopy.

Ray *et al.*[28] and Altan *et al.*[29] used IV 3 μg/kg clonidine 15 min prior to induction, followed by continuous infusion and found significant incidence of bradycardia and hypotension. We used 2 μg/kg clonidine 15 min prior to induction and gave no intraoperative infusion; hence incidence of hypotension and bradycardia were insignificant. Overall, adverse effects noted with IV clonidine were less than with IM clonidine (*P*=0.02). Patients receiving IV clonidine had better control of hemodynamics than those receiving IM clonidine as IM group had significantly higher SBP, MAP and more patients with incidence of hypertension requiring treatment. Limitation of the study was that the sample size in our study was small but had significantly important results, and we suggest future studies to be undertaken with a larger population size.

CONCLUSIONS

The results of the study recommends routine use of clonidine premedication in ASA I or II patients undergoing laparoscopic surgery by either route but IV route should be preferred due to better control of hemodynamic changes which occur during laryngoscopy and pneumoperitoneum.

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