Original Article

Hemodynamic stress response during laparoscopic cholecystectomy: Effect of two different doses of intravenous clonidine premedication

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Abstract

Background: Clonidine has emerged as an attractive premedication desirable in laparoscopic surgery wherein significant hemodynamic stress response is seen. The minimum safe and effective dose of intravenous clonidine to attenuate the hemodynamic stress response during laparoscopic surgery has however not yet been determined.

Materials and Methods: This prospective, randomized, double-blind controlled study was conducted on 90 adults of ASA physical status I and II, scheduled for laparoscopic cholecystectomy under general anesthesia. Patients were randomized to one of the three groups (n= 30). Group I received 100 ml of normal saline, while groups II and III received 1 μg/ kg and 2 μg/ kg of clonidine respectively, intravenous, in 100 ml of normal saline along. All patients received glycopyrrolate 0.004 mg/kg and tramadol 1.5 mg/kg intravenously, 30 min before induction. Hemodynamic variables (heart rate, systolic, diastolic, mean arterial pressure), SpO2, and sedation score were recorded at specific timings. MAP above 20% from baseline was considered significant and treated with nitroglycerine.

Results: In group I, there was a significant increase in hemodynamic variables during intubation pneumoperitoneum and extubation ($P<0.001$). Clonidine given 1 μg/kg intravenous attenuated hemodynamic stress response to pneumoperitoneum ($P<0.05$), but not that associated with intubation and extubation. Clonidine 2 μg/kg intravenous prevented hemodynamic stress response to pneumoperitoneum and that associated with intubation and extubation ($P<0.05$). As against 14 and 2 patients in groups I and II respectively, no patient required nitroglycerine infusion in group III.

Conclusions: Clonidine, 2 μg/ kg intravenously, 30 min before induction is safe and effective in preventing the hemodynamic stress response during laparoscopic cholecystectomy.

Key words: Clonidine, laparoscopic cholecystectomy, pneumoperitoneum, stress response

Introduction

Laparoscopic cholecystectomy has become gold standard surgery for cholelithiasis.[1] Advantages of laparoscopic cholecystectomy are shorter hospital stay, early ambulation, smaller scar, and less compromised postoperative respiratory and gastro-intestinal functions. However, the procedure is not risk free as it is associated with significant hemodynamic changes due to creation of pneumoperitoneum, potential for systemic absorption of carbon dioxide, and reverse Trendelenberg position.[2] Postoperative nausea and vomiting is a major drawback of laparoscopic surgery.[3]

Various pharmacological agents like nitroglycerine, ß blocker, and opioids are used to provide hemodynamic stability during pneumoperitoneum,[4] but they have their own disadvantages. Clonidine, a α-2 adrenergic receptor agonist, has shown promising results for attenuation of hemodynamic response associated with laparoscopic surgery.[5-9] However, there is a wide difference in the dose of clonidine used by various authors and there is need for further studies to determine the minimum effective and safe dose of clonidine in laparoscopic surgery. The present study was undertaken with the objective of evaluating the type and extent of hemodynamic changes during laparoscopic cholecystectomy and their modification by two different doses of intravenous clonidine administered as premedication.

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Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/0970-9185.86586

Materials and Methods

After institutional review board approval and informed written consent from the patients, this prospective, randomized, double-blind controlled clinical study was carried out in 90 patients of either sex, aged 20–60 years, of ASA physical status I and II, scheduled for laparoscopic cholecystectomy under general anesthesia from October 2009 to September 2010. Exclusion criteria were patients with anticipated difficult airway; body mass index (BMI) >25, history of cardiopulmonary diseases; psychiatric illness; and therapy with α-2 adrenergic agonists, β blocker, methyldopa, MAO inhibitors, tricyclic antidepressant, and benzodiazepines.

In the pre-anesthetic preparation room, monitoring for heart rate (HR), non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), and end-tidal CO_2 ($EtCO_2$) was instituted. Sedation was rated as per score shown in Table 1.

Patients were randomly divided, by picking up sealed envelopes, into one of the three groups of 30 each. Group I received 100 ml of normal saline, group II, 1 μg/kg of clonidine in 100 ml of normal saline and group III, 2 μg/kg of clonidine in 100 ml of normal saline. The drug was given over 15 min intravenously along with glycopyrrolate 0.004 mg/kg and tramadol 1.5 mg/kg, 30 min before induction of anesthesia.

In the operation theatre, after pre-oxygenation, anesthesia was induced with sleep dose of 2.5% thiopentone sodium followed by succinyl choline, 2 mg/kg to facilitate tracheal intubation. When there was no response to Train-of-Four on peripheral nerve stimulation, trachea was intubated with an appropriate sized cuffed, disposable endotracheal tube. Lungs were mechanically ventilated with O_2 - N_2O (50-50), sevoflurane (1-2%), and vecuronium bromide 0.1 mg/kg bolus followed by 1 mg intermittently for neuromuscular blockade. Tidal volume and ventilator frequency were adjusted to maintain normocapnia ($EtCO_2$ 40 ± 4 mmHg). Pneumoperitoneum (PP) was created by insufflations of CO_2 and operation table was tilted to about 15° reversed trendelenberg. Intra-abdominal pressure was not allowed to exceed 15 mmHg.

Table 1: Sedation score

Score	Level of sedation
0	Awake and agitated
I	Awake and comfortable
II	Asleep but arousable
III	Asleep with sluggish response to verbal command or touch
IV	No response to verbal command or touch

Throughout the study period, all the parameters selected (HR, SBP, DBP, MAP, and SpO_2) were recorded at specified timings. Any change in hemodynamic variables more than 20% on either side of baseline was considered significant. Any increase in MAP up to 20% from baseline was treated by increasing the concentration of sevoflurane to a maximum 2%. Any increase in MAP more than 20% from baseline was treated with nitroglycerine infusion. Nitroglycerine infusion was adjusted to maintain the MAP within 20% of baseline. Time duration from creation of pneumoperitoneum to the release of pneumoperitoneum was taken as duration of pneumoperitoneum. At the end of surgery, neuromuscular blockade was reversed with neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg intravenously. After satisfying the extubation criteria, trachea was extubated and patients were transferred to post-anesthesia care unit (PACU). In PACU, HR, SBP, DBP, MAP, SpO_2, sedation score, and any incidence of complications/adverse event were monitored for next 1 h. Maintenance of MAP and SpO_2 within 20% of baseline and sedation score ≤ 2 was considered criteria for recovery.

Sample size of minimum 29 per group was derived using Cohen's formula based on assumption of α error 0.05 and power of study 80% after permitting β error of 0.2 to detect a difference of at least 4 in the quantitative variables between the groups. Mean and standard deviation were calculated for all the quantitative variables using graph-pad prism statistical software. An intra-group comparison was made using paired Student's t-test and comparison between two groups at a time (inter-group comparison) was done using the unpaired t-test. $P < 0.05$ was considered statistically significant.

Results

All patients (n=90) completed the study. Demographic parameters were comparable among the three groups ($P > 0.05$) [Table 2]. Duration of pneumoperitoneum in all the patients was 80 min or less except one patient in group I in whom the pneumoperitoneum lasted for 90 min. As the monitored hemodynamic variables at 90-min time point were not available in other groups, this time point was excluded. Hemodynamic variables recorded in three groups at specified timings are shown in Figures 1–3. There was an increase in HR, SBP, DBP, and MAP at tracheal intubation in group I ($P < 0.001$) which continued throughout the study period. All the patients in group I required maximum allowable concentration of 2% sevoflurane to maintain MAP within 20% of baseline. Fourteen patients out of 30 (46.67%) in group I required nitroglycerine infusion for more than 20% rise in MAP above baseline.

Table 2: Patient characteristics given as mean± SD

	Group I	Group II	Group III	*P* value
Age (years)	39.25 ± 9.35	38.20 ± 10.28	40.80 ± 14.43	0.77
Weight (kg)	56.60 ± 7.71	60.10 ± 8.37	56.25 ± 7.85	0.26
Height (cm)	164.50 ± 4.98	167.90 ± 5.37	165.95 ± 4.68	0.14
ASA physical status (I:II)	4:26	6:24	6:24	
Sex (M:F)	12:18	10:20	11:19	0.47
Duration of pneumoperitoneum (min)	75.0 ± 12.77	67.50 ± 11.05	66.0 ± 11.42	0.088

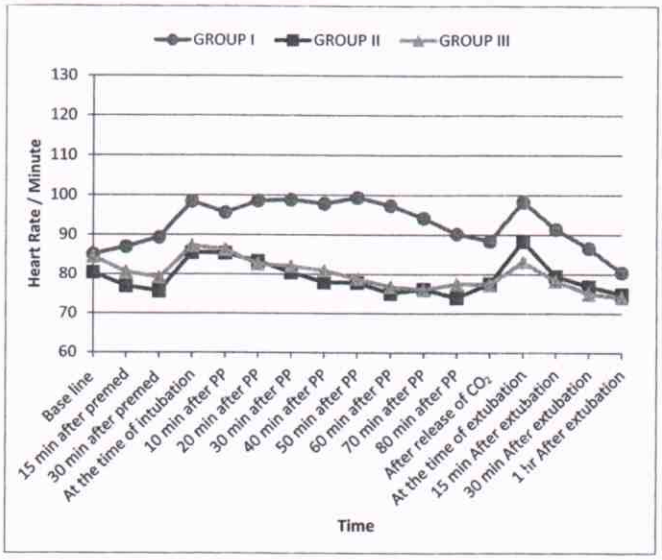

Figure 1: Changes in heart rate at various specified timings in three groups

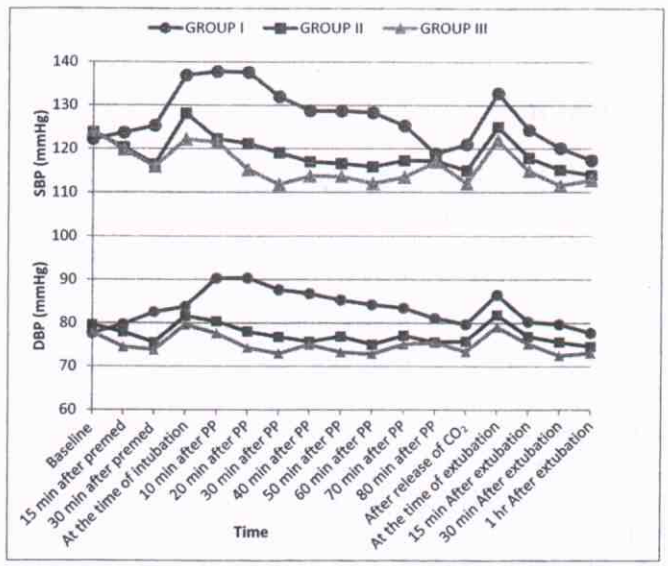

Figure 2: Changes in SBP and DBP at various specified timings in three groups

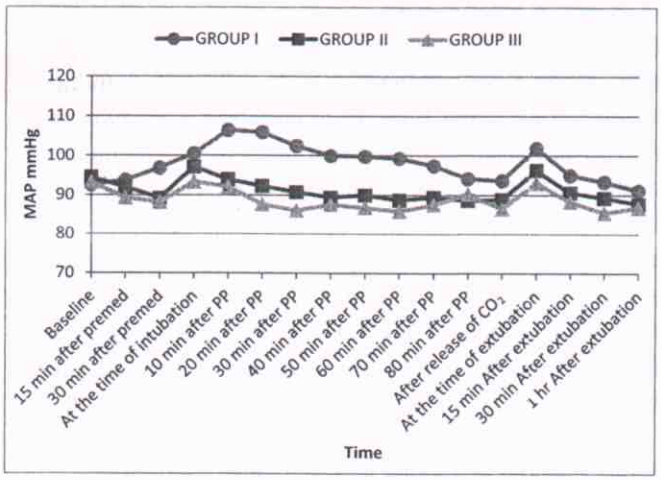

Figure 3: Changes in MAP at various specified timings in three groups

In group II, HR, SBP, DBP, and MAP decreased from baseline within 30 min of clonidine premedication (P <0.05), but the decrease was never more than 20%. HR and SBP increased at the time of intubation (P <0.05), but the increase was less than that observed in group I at the same time (P <0.05). An increase in DBP and MAP at tracheal intubation was not significant as compared to baseline (P >0.05). An increase in hemodynamic variables at the time of intubation approached baseline within 20 min of pneumoperitoneum with a statistically significant decrease observed within 40 min which continued throughout the duration of pneumoperitoneum. At tracheal extubation, HR increased (P <0.05) but a rise in SBP, DBP, and MAP was not statistically significant. The MAP of 20 patients could be maintained with 1% sevoflurane, while 10 patients required an increase up to 2% to maintain MAP within 20% of baseline. Two patients in group II (6.66 %) required nitroglycerine infusion.

In group III, a decrease in HR, SBP, DBP, and MAP from baseline was observed within 15 min of clonidine premedication (P <0.05), but at no time, this decrease was more than 20% from baseline. At tracheal intubation, HR and DBP increased (P >0.05), while SBP decreased (P >0.05) and MAP remained comparable to baseline. Within 40 min of pneumoperitoneum HR and within 20 min SBP, DBP, and MAP decreased (P <0.05) and remained so throughout the study period Hemodynamic variables at the time of extubation remained comparable to baseline. All the patients maintained MAP comparable to baseline with 1% sevoflurane. No patient in group III required nitroglycerine infusion. SpO_2 remained stable and comparable to baseline in all the three groups.