Research Article

Effect of intravenous clonidine premedication on perioperative hemodynamic response in patients undergoing laparoscopic cholecystectomy: a case–control study

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Abstract

Background: Laparoscopic cholecystectomy involves the creation of pneumoperitoneum that causes changes in cardiovascular and pulmonary physiology and stress response.

Objective: To evaluate the effects of clonidine as premedication on hemodynamic response during laparoscopic cholecystectomy.

Materials and Methods: Sixty adult patients belonging to ASA physical status I or II, scheduled for laparoscopic cholecystectomy, were divided into two groups randomly, to receive (group S) intravenous clonidine (1.5 μg/kg) before intubation or (group C) normal saline as a placebo.

Result: Significant rise in blood pressures [systolic, diastolic, and mean arterial blood pressures (MAP)] and heart rate was observed in group C during laryngoscopy and intubation when compared with group S (MAP, 121.5 ± 8.45 to 120.5 ± 6.58 mm Hg in group S vs. 118.96 ± 13.07 to 143.6 ± 21.5 mm Hg in group C; heart rate, 85.77 ± 6.56 to 86.46 ± 7.80 bpm in group S vs. 81.13 ± 5.88 to 95.87 ± 3.74 bpm in group C). Similar results were obtained during creation of pneumoperitoneum.

Conclusion: Premedication with 1.5 μg/kg body weight of intravenous clonidine offers steady hemodynamics and prevention against stress response activated by pneumoperitoneum in laparoscopic cholecystectomy patients and, thus, can be advocated as a habitual premedication.

KEY WORDS: Clonidine, laparoscopic cholecystectomy, hemodynamic stability

Introduction

Minimally invasive surgeries are rapidly replacing traditional open surgeries. Laparoscopy has developed remarkably in both extent and volume since the preamble of first laparoscopic cholecystectomy procedure.[1] The advantages of laparoscopic surgeries include minimal postoperative stay, less invasive procedure, and early return to normal life, which provides economic advantages to the patient.[2,3] It also involves potential disadvantages such as inadvertent visceral injuries, pneumoperitoneum-induced hemodynamic changes, and nonphysiological position of the patient during surgery leading to hemodynamic compromise. Hemodynamic changes such as reduced cardiac output, increased systemic vascular resistance, and increased pulmonary vascular resistance are owing to combined effects of mechanical and neurohumoral factors.[4,5]

Clonidine is a highly selective partial $\alpha 2$ agonist, which reduces central sympathetic discharge.[6] Thereby, it helps in blunting laryngoscopic response and decreases systemic and pulmonary vascular resistances.[7–9] Owing to its sedative

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property, it also reduces minimal alveolar concentration of inhalational agents.[10,11] Very few studies are available, which have used intravenous clonidine as premedication for preventing adverse hemodynamic changes during laparoscopic cholecystectomy.[12,13] Taking these considerations into account, this study was designed to evaluate the efficacy of intravenous clonidine as premedication in prevention of such hemodynamic changes during laparoscopic cholecystectomy.

Materials and Methods

A prospective double-blind randomized-controlled trial was carried out at Adichunchanagiri Institute of Medical Sciences, BG Nagara, Bellur, Mandya, Karnataka, India, during the study period from July 2014 to April 2015. Sixty patients who underwent elective laparoscopic surgeries under general anesthesia were included in the study. Approval from Institutional ethics committee was obtained to carry out this study. After obtaining written informed consent from the patients, this study was carried out in 60 patients who satisfied the following inclusion and exclusion criteria.

Inclusion criteria:

- patients with body weight of 30–80 kg;
- patients aged between 18 and 68 years;
- patients with ASA grades I and II status.

Exclusion criteria:

- obese patients with body mass index > 30 kg/m^2;
- patients with severe cardiovascular abnormalities (ischemic heart disease, valvular heart diseases, and AV conduction blocks);
- pregnant women;
- patients with ASA grades III and IV.

The patients were randomly divided into two groups, with a sample size of 30 each: the study group (group S) who would receive intravenous clonidine (1.5 μg/kg) diluted in 10 mL saline15 min before intubation and a control group (group C) who would receive 10 mL normal saline as a placebo.

All the patients were evaluated with a common protocol for preanesthetic evaluation on the day before surgery, and the routine blood investigations were carried out. The patients were then graded according to American Society of Anesthesiologist classification and prescribed 0.5 mg of alprazolam and 150 mg of ranitidine orally, to be taken on the night before surgery. Patients were also advised to be nil orally from 10 pm onward on the night before surgery.

On the day of surgery, after confirming the fasting status of minimum 8 h, an intravenous line was established with an 18-G cannula, and the patients were shifted into the operation theater where the monitors were attached, and baseline values of heart rate (HR), blood pressure—systolic (SBP), diastolic (DBP), and mean arterial blood pressures (MAP), and peripheral oxygen saturation were noted.

The patients belonging to group S received intravenous clonidine (1.5 μg/kg) diluted in 10 Ll saline 15 min before induction and those in group C were given 10 mL normal saline as a placebo. The patients were then administered general anesthesia according to a standardized regimen for both the groups, which included intravenous injections of ondansetron (0.1 mg/kg body weight), midazolam (0.05 mg/kg body weight), glycopyrrolate (0.01 mg/kg body weight), and fentanyl (2 μg/kg body weight) for analgesia. Induction was done with intravenous injection of propofol (2 mg/kg body weight), and endotracheal intubation was facilitated by injection succinylcholine (1.5 mg/kg body weight). Anesthesia was maintained with 33% oxygen in nitrous oxide and 0.5% halothane with muscle relaxation being provided by injection vecuronium (0.1 mg/kg body weight) bolus followed by 1 mg intermittently for continued neuromuscular blockade. End-tidal carbon dioxide was maintained between 35 and 45 mm Hg by adjusting the mechanical ventilator settings. Intraabdominal pressure was maintained less than 15 mm Hg throughout the procedure.

The parameters selected [HR, SBP, DBP, MAP, oxygen saturation(SpO_2) and end-tidal carbon dioxide] were observed in both the groups and recorded at baseline and at specific timings following intubation (1, 3, and 5 min) and creation of pneumoperitoneum (1 min before and 1, 3, 5, 15, 30, 45, and 60 min after creation of pneumoperitoneum).

At the end of surgery, residual neuromuscular block was reversed with injection neostigmine (0.05 mg/kg body weight) and glycopyrrolate (0.01 mg/kg body weight) intravenously. Patients were extubated when all the extubation criteria were fulfilled and transferred to recovery room. In the postanesthesia care unit, they were monitored for any evidence of complications or adverse events.

The results obtained in the study were presented in a tabulated manner, and statistical analysis was done by Students *t* test. ANOVA and c^2 test were performed for nonparametric values, and corresponding *P* value was computed. *P* value <0.05 was considered statistically significant.

Results

As per the study, the two groups were similar in age, sex, weight, and ASA physical status. Patients belonging to both the groups showed similar preoperative HR (mean of 85.77 bpm in the clonidine group and 81.13 bpm in the control group) and blood pressure (mean SBP of 122.87 mm Hg in the clonidine group and 120.13 mm Hg in the control group; mean DBP of 80.07 mm Hg in the clonidine group and 74.60 mm Hg in the control group; and a mean MAP of 75.77 ± 9.86 mm Hg in the clonidine group and 84.33 mm Hg in the control group).

The HR and blood pressures were significantly lower in the clonidine group (group S) when compared with the control group (group C) during each event in surgery such as intubation and creation of pneumoperitoneum. There was a 9% difference in the HR between the two groups 1 min, 12% at 3 min, and 14% at 5 min after intubation. During the creation of pneumoperitoneum, the difference in the HR was 16% at

1 min before the creation of pneumoperitoneum and 16%, 18%, 24%, 23%, 26%, 28%, and 30% at 1, 3, 5, 15, 30, 45, and 60 min, respectively, after the creation of pneumoperitoneum [Table 1].

Similar results were obtained for the SBP (with the difference being 13%, 16%, and 17% at 1, 3, and 5 min, respectively, after intubation; 20% at 1 min before the creation of pneumoperitoneum; 20%, 21%, 23%, 25%, 26%, 26%, and 26% at 1, 3, 5, 15, 30, 45, and 60 min, respectively, after the creation of pneumoperitoneum), DBP (with the difference being 9%, 13%, and 14% at 1, 3, and 5 min, respectively, after intubation; 16% at 1 min before the creation of pneumoperitoneum; and 19%, 19%, 20%, 20%, 23%, 24%, and 24% at 1, 3, 5, 15, 30, 45, and 60 min, respectively, after the creation of pneumoperitoneum), and MAP (with the difference being 14%, 17%, and 20% at 1, 3, and 5 min, respectively, after intubation; 21% at 1 min before the creation of pneumoperitoneum; and 21%, 22%, 23%, 24%, 24%, 25%, and 27% at 1, 3, 5, 15, 30, 45, and 60 min, respectively, after the creation of pneumoperitoneum.

There was no difference in the oxygen saturation of the two groups but the end-tidal carbon dioxide concentration showed a difference of 3%, with the lower values being in the clonidine group [Tables 2–5].

The above data clearly indicate that clonidine as a premedication offers much greater hemodynamic stability during laparoscopic surgeries.

Discussion

Clonidine, a centrally acting $\alpha 2$ adrenergic agonist, was originally developed as a nasal decongestant and vasoconstrictor and, subsequently, as an antihypertensive agent.[14] The drug is being now used as anesthetic premedication,[15] providing sedative, anxiolytic, and analgesic effects.[15] Clonidine attenuates hypertension,[16] tachycardia, and norepinephrine release in response to stress induced by anesthetic and surgical procedures. Hence, clonidine may prevent perioperative myocardial ischemia by improving myocardial oxygen balance.

This study was designed to study the effectiveness of intravenous clonidine in attenuating the hemodynamic response to pneumoperitoneum during laparoscopic surgeries.

Table 1: The difference in the heart rates between the two groups

Heart rate	Group	*N*	Mean	SD	*P*
Baseline	Clonidine	30	85.77	6.569	0.006
	Control	30	81.13	5.888	
After intubation					
1 min	Clonidine	30	84.97	6.014	0.000
	Control	30	94.07	4.152	
3 min	Clonidine	30	82.13	7.899	0.000
	Control	30	94.33	3.717	
5 min	Clonidine	30	81.43	7.802	0.000
	Control	30	95.87	3.471	
1 min before pneumoperitoneum	Clonidine	30	81.20	7.858	0.000
	Control	30	96.73	4.741	
After pneumoperitoneum					
1 min	Clonidine	30	82.67	8.066	0.000
	Control	30	98.67	4.498	
3 min	Clonidine	30	81.07	7.404	0.000
	Control	30	99.20	5.573	
5 min	Clonidine	30	78.83	6.534	0.000
	Control	30	100.23	5.764	
15 min	Clonidine	30	78.33	6.804	0.000
	Control	30	101.53	6.902	
30 min	Clonidine	30	76.47	5.776	0.000
	Control	30	102.63	6.478	
45 min	Clonidine	30	75.67	6.002	0.000
	Control	30	103.33	7.053	
60 min	Clonidine	30	74.63	6.014	0.000
	Control	30	104.27	7.856	

Table 2: Changes in systolic blood pressure

Systolic blood pressure	Group	*N*	Mean	SD	*P*
Baseline	Clonidine	30	122.87	7.408	0.159
	Control	30	120.13	7.445	
After intubation					
1 min	Clonidine	30	122.27	4.891	0.000
	Control	30	135.47	4.424	
3 min	Clonidine	30	119.53	5.877	0.000
	Control	30	135.47	4.783	
5 min	Clonidine	30	119.00	5.552	0.000
	Control	30	136.40	4.248	
1 min before pneumoperitoneum	Clonidine	30	117.13	5.399	0.000
	Control	30	137.20	4.536	
After pneumoperitoneum					
1 min	Clonidine	30	118.93	5.219	0.000
	Control	30	138.67	5.665	
3 min	Clonidine	30	117.70	5.553	0.000
	Control	30	139.00	6.275	
5 min	Clonidine	30	116.63	5.129	0.000
	Control	30	139.93	6.898	
15 min	Clonidine	30	115.67	5.435	0.000
	Control	30	140.60	6.946	
30 min	Clonidine	30	114.07	5.669	0.000
	Control	30	140.53	6.847	
45 min	Clonidine	30	113.70	5.772	0.000
	Control	30	140.13	7.143	
60 min	Clonidine	30	113.83	5.596	0.000
	Control	30	139.73	7.329	

We studied 60 ASA physical status I and II patients in the age group of 18–68 years scheduled for elective laparoscopic surgeries. The patients were randomly allocated to two groups of 30 each. Study group S received clonidine (1.5 μg/kg) and study group C received normal saline.

Joris et al.[17] used 8 μg/kg of intravenous clonidine in laparoscopic cholecystectomy and compared the hemodynamic and endocrine changes with the placebo group. They observed that clonidine significantly reduced MAP and HR, and increased SVR. They have opined that clonidine before pneumoperitoneum reduces catecholamine release and attenuate hemodynamic changes during laparoscopic cholecystectomy.

Laisami et al.[18] used 4.5 μg/kg of intravenous clonidine or saline and studied the effects on hemodynamics, neuroendocrine response, and renal parameters in patients undergoing laparoscopic cholecystectomy. They observed that clonidine decreased sympathetic tone, blood pressure, and HR and diminished the need for intraoperative analgesia. They concluded that clonidine enabled stable hemodynamics and prevented activation of RAAS.

Málek et al.[19] used 0.15 mg clonidine as infusion 15 min before laparoscopic cholecystectomy and 0.15 mg clonidine by intramuscular route 60–90 min before surgery and studied the hemodynamic changes and their suppression with clonidine premedication. They observed a significant drop in the incidence of both SBP and DBP during procedure after clonidine administration in both routes and recommended intravenous clonidine use as a routine procedure before laparoscopic cholecystectomy.

In another study done by Joris et al.[17] used clonidine 4 μg/kg intravenously over 10 min and the same dose infused for 1 h before pneumoperitoneum. This was compared with placebo group for hemodynamic changes induced by pneumoperitoneum during laparoscopic cholecystectomy. They observed that MAP and HR were significantly lower in the clonidine group and opined that clonidine gives better hemodynamic stability during the procedure.

Aho et al.[20] used clonidine 3 or 4.5 μg/kg or saline intramuscularly 30 to 45 min before induction of anesthesia in gynecological laparoscopy. They studied hemodynamic and plasma endorphin responses. They concluded that intramuscularly administered clonidine prevents the maximal hemodynamic responses to tracheal intubation and to gynecological laparoscopy.

Table 3: Changes in the diastolic blood pressure

Diastolic blood pressure	Group	*N*	Mean	SD	*P*
Baseline	Clonidine	30	80.07	7.022	0.005
	Control	30	74.60	7.614	
After intubation					
1 min	Clonidine	30	78.43	7.798	0.000
	Control	30	87.87	6.056	
3 min	Clonidine	30	76.73	6.757	0.000
	Control	30	90.00	5.705	
5 min	Clonidine	30	76.60	6.284	0.000
	Control	30	90.60	4.207	
1 min before pneumoperitoneum	Clonidine	30	75.30	4.921	0.000
	Control	30	91.67	4.521	
After pneumoperitoneum					
1 min	Clonidine	30	74.77	4.883	0.000
	Control	30	93.60	4.910	
3 min	Clonidine	30	74.77	5.367	0.000
	Control	30	94.00	3.601	
5 min	Clonidine	30	75.00	6.231	0.000
	Control	30	94.80	3.727	
15 min	Clonidine	30	74.83	7.037	0.000
	Control	30	95.20	4.189	
30 min	Clonidine	30	72.73	5.471	0.000
	Control	30	95.33	4.498	
45 min	Clonidine	30	72.10	6.110	0.000
	Control	30	95.73	4.479	
60 min	Clonidine	30	71.60	5.618	0.000
	Control	30	95.47	5.507	

Kulka et al.[21] studied the dose response effects of intravenous clonidine on stress response in CABG patients. They used 0, 2, 4, or 6 μg/kg clonidine as an intravenous infusion 30 min before induction of anesthesia. They observed that 4 and 6 μg/kg of clonidine significantly attenuated hemodynamic and adrenergic response to stress. They opined that 4 μg/kg of clonidine intravenous was the appropriate dose to attenuate the stress response to laryngoscopy in CABG patients.

Das et al.[22], Sung et al.,[23] Yu et al.,[24] and Passi et al.[25] used 150 μg/kg clonidine per orally 60–90 min before induction of anesthesia in laparoscopic cholecystectomy and studied the effect on hemodynamic changes induced by pneumoperitoneum. They concluded that oral clonidine premedication helps to provide perioperative hemodynamic stability, reduced the requirements of postoperative analgesia, and reduced the incidence of nausea, vomiting, and shivering in laparoscopic cholecystectomy.

Ghignone et al.[26,27] used 5 μg/kg of clonidine per orally and studied the effects on perioperative hemodymics and isoflurane requirements in elective surgeries. They observed that clonidine pretreatment resulted in a reduction of preoperative SBP and DBP and blunted the cardiovascular response to intubation. They opined that preoperative administration of clonidine results in improved perioperative hemodynamic stability in patients with mild to moderate arterial hypertension and in a reduction of anesthetic requirement.

Raval and Mehta[28] used tablet clonidine (4 μg/kg) and studied the attenuation of hemodynamic response to laryngoscopy and intubation. They conclude that premedication with oral clonidine produces less sedation and same level of anxiolysis when compared with diazepam with regard to its antisialagogue effect and blunting hemodynamic responses during laryngoscopy and endotracheal intubation.

In our study, we observed similar hemodynamic responses during pneumoperitoneum in laparoscopic cholecystectomy with 1.5 μg/kg of intravenous clonidine.

Conclusion

Laparoscopy as a revolution or evolution has found its place in the history of medicine. It challenges the anesthesiologists as much as it challenges the operating laparoscopist, and it is important that new anesthetic approaches are developed to ensure that these techniques are truly

Table 4: Changes in the mean arterial pressure

Mean arterial pressure	Group	*N*	Mean	SD	*P*
Baseline	Clonidine	30	75.77	9.863	0.001
	Control	30	84.33	9.308	
After intubation					
1 min	Clonidine	30	75.23	10.595	0.000
	Control	30	89.53	6.548	
3 min	Clonidine	30	73.50	9.522	0.000
	Control	30	90.77	6.301	
5 min	Clonidine	30	71.63	9.877	0.000
	Control	30	91.80	6.713	
1 min before pneumoperitoneum	Clonidine	30	72.40	8.811	0.000
	Control	30	93.13	7.286	
After pneumoperitoneum					
1 min	Clonidine	30	73.20	9.672	0.000
	Control	30	94.27	7.348	
3 min	Clonidine	30	72.43	9.669	0.000
	Control	30	94.07	7.620	
5 min	Clonidine	30	71.63	9.877	0.000
	Control	30	94.67	8.006	
15 min	Clonidine	30	70.97	9.470	0.000
	Control	30	95.07	8.626	
30 min	Clonidine	30	70.10	9.061	0.000
	Control	30	94.37	8.447	
45 min	Clonidine	30	69.57	8.633	0.000
	Control	30	94.97	7.942	
60 min	Clonidine	30	68.80	8.568	0.000
	Control	30	95.60	7.775	

Table 5: Changes in SpO_2 and $ETCO_2$

Parameters	Group	*N*	Mean	SD	*P*
SPO_2	Clonidine	30	99.93	0.254	0.155
	Control	30	100.00	0.000	
$ETCO_2$	Clonidine	30	34.17	1.533	0.000
	Control	30	37.20	1.937	

safe and associated with minimal complications and rapid recovery. The essential prerequisites for a safe outcome in laparoscopic procedures are a proper technique providing stable hemodynamics, better surgical condition, and pain-free postoperative period with minimal postoperative sequelae, thus increasing the patient's compliance. In conclusion, premedication with 1.5 µg/kg body weight of intravenous clonidine has been found to be safe and effective method that provides stable hemodynamics and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

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