Research Article

Effect of oral clonidine as premedication on hemodynamic changes during laparoscopic cholecystectomy

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ABSTRACT

Background: Pneumoperitoneum created during laparoscopy affects several homeostatic systems leading to alteration in cardiovascular, pulmonary physiology, and stress response. Clonidine, α2 adrenergic receptor agonists, has the property of good anxiolysis, sedation, and analgesic action. Clonidine prevents the hemodynamic response to intubation. **Objectives**: To study the response of oral clonidine premedication on hemodynamic changes during laparoscopy at various stages. **Materials and Methods**: A prospective randomized controlled study of 60 patients undergoing laparoscopic cholecystectomy was carried out at Medical College and S. S. G. Hospital, Baroda during years 2006 to 2008. They were divided into two groups of which Group CL premedicated with tablet Clonidine 3 μg/kg, 90 min before induction while Group C were not given any oral premedication. All hemodynamic parameters were observed intraoperatively and for 2 h postoperatively. **Results:** Demographic data in terms of age, sex, weight, height, and American Society of Anesthesiologists grade were comparable in both groups**.** Preoperative baseline parameter, i.e., pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate and SpO_2 were comparable in both groups. Pulse rate varied from 76.2 ± 7.015 bpm to 88.3 ± 5.4 bpm in Group CL and it varied from 86.7 ± 4.78 bpm to 112.93 ± 5.13 bpm in Group C. SBP varied from 110.8± 9.1 mmHg to 128.13 ± 5.7 mmHg in group CL while it varied from 128.33 ± 6.59 mmHg to 159.6 ± 12.33 mmHg in Group C. DBP varied from 78.53 ± 3.44 to 83.93 ± 4.85 in group CL while it varied from 82.13 ± 3.23 to 99.47 ± 9.01 in Group C. Requirement of isoflurane to maintain MAP intraoperatively was 40% less in Group CL than Group C. There was no significant change seen in SpO_2 in both groups and no fall in SpO_2 seen intraoperatively in both groups. After 90 min of giving clonidine premedication in Group CL, all patients had sedation score of 2 while no sedation was found in patients of Group C. Only 2 patients (6.6%) in Group C had nausea, and one patient (3.3%) of Group CL had subcutaneous emphysema postoperatively. No other complications observed intra- or post-operatively which did not require any treatment. All patients of Group CL had dryness of mouth. **Conclusion**: With clonidine 3 μg/kg there is no rise in pulse rate and BP throughout laparoscopic cholecystectomy at various stages. Patients remain haemodynamically stable throughout laparoscopic surgery with clonidine. Clonidine also decreased the requirement of inhalation agent. No significant perioperative complications were found with the use of clonidine.

KEY WORDS: Oral Clonidine; Pre-anesthetic Medication; Hemodynamic Changes; Laparoscopic Cholecystectomy

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INTRODUCTION

Laparoscopic techniques have become common in clinical practice nowadays. Laparoscopic cholecystectomy has revolutionized gall bladder surgeries and now become gold standard for cholelithiasis. Advantages of laparoscopic cholecystectomy over conventional cholecystectomy

such as shorter hospital stay, early ambulation, smaller scar, less compromised postoperative respiratory, and gastrointestinal tract functions has made it more popular. It still causes stress hormone responses to some extent when CO_2 pneumoperitoneum is used which causes significant hemodynamic changes intraoperatively and make it challengeable to anesthetist. Pneumoperitoneum created during laparoscopy affects several homeostatic systems leading to alteration in cardiovascular, pulmonary physiology, and stress response. Cardiovascular changes include rise in systemic and pulmonary vascular resistance leading to increase in mean arterial pressure (MAP) and decrease in cardiac output. Furthermore, compression of inferior vena cava occurs, which all together compromises tissue perfusion. In addition, ventilatory impairment occurs after laparoscopic cholecystectomy due to diaphragmatic displacement, reduced lung volumes, and compliance, increased V/Q mismatch, hypoxia/hypercarbia. Elevation of stress hormones, cardiovascular instability, and ventilatory impairment has made laparoscopy more challengeable. Various pharmacological agents were chosen to prevent hemodynamic changes associated with pneumoperitoneum intraoperatively. Nitroglycerine, β blockers, inhalation anesthetics, opioids can be used to maintain hemodynamic stability. Nitroglycerine may cause tachycardia. With excessive use of inhalation agent, there may be chances of intraoperative arrhythmia and use of opioids is associated with postoperative nausea and vomiting. α2 adrenergic receptor agonists are also used for prevention of hemodynamic response. Dexmedetomidine is found to effectively reduce maximum heart rate response after intubations and pneumoperitoneum.[1] Clonidine, α2 adrenergic receptor agonists, has the property of good anxiolysis, sedation, and analgesic action. Clonidine prevents the hemodynamic response to intubation.[2,3] It also decreases the doses and minimum alveolar concentration value of inhalational anesthetic agent and prevents postoperative nausea and vomiting. Along with its rapid and smooth postoperative recovery profile, low cost makes it a good premedication of choice. Oral route has the advantage of ease of administration, and it has got excellent oral bioavailability of 95%. Catecholamine and vasopressin are responsible for the increase in systemic vascular resistance caused by pneumoperitoneum. Clonidine inhibits release of catecholamine and modulates hemodynamic changes induced by pneumoperitonium.[4] Considering all these observations and availability of clonidine in India, the present study was designed to evaluate the type and extent of hemodynamic changes during laparoscopic cholecystectomy and also to find the efficacy of clonidine in the prevention of such changes. The objectives of the study were to study the response of oral clonidine premedication on hemodynamic changes during laparoscopy at various stages such as before induction, before and after intubation, during pneumoperitoneum, 10 min after release of CO_2 pneumoperitoneum and after extubation. Furthermore, to observe changes in oxygen saturation and to study level of sedation before induction and postoperatively for 1 h.

MATERIALS AND METHODS

A prospective randomized controlled study of 60 patients undergoing laparoscopic cholecystectomy was carried out at Medical College and S. S. G. Hospital, Baroda during years 2006 to 2008. A detailed preoperative assessment for selection of patient was done. They were divided into two groups of which Group CL premedicated with tablet clonidine 3 μg/kg, 90 min before induction while Group C was not given any oral premedication. All hemodynamic parameters were observed intraoperatively and for 2 h postoperatively.

Inclusion Criteria

1. Patients of either sex of age group 20-60 years
2. American Society of Anesthesiologists (ASA) Grade I and II.

Exclusion Criteria

1. H/o hypertension, ischemic heart disease, valvular heart disease, atrioventricular conduction block
2. H/o asthma, allergy to clonidine or any other drug allergy
3. Patient concomitantly taking clonidine, β blocker, methyldopa, monoamine oxidase inhibitors
4. Patient of psychiatric illness or taking tricyclic antidepressant.

Statistical Analysis

All parameters and variables were subjected to statistical analysis using unpaired *t*-test. Results were expressed as mean±standard deviation.

RESULTS

In total, 60 patients were recruited for the study. 30 patients in each group. There was no premature study withdrawal due to the failure of surgery to proceed as planned or the development of complications hindering the assessment of study variables. All demographic parameters age, weight, and height were compared in both groups as shown in Table 1.

As shown in Table 1, demographic data in terms of age, sex, weight, height, and ASA grade were comparable in both groups. Table also shows the duration of surgery which was also comparable. Preoperative baseline parameter, i.e., pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, respiratory rate and SpO_2 were comparable in both groups. As shown in Table 2, pulse rate varied from 76.2 ± 7.015 bpm to 88.3 ± 5.4 bpm in Group CL and it varied from 86.7 ± 4.78 bpm to 112.93 ± 5.13 bpm in Group C. On

statistical comparison of two groups, significant variation was observed throughout intraoperatively. Baseline pulse rate was 88.3 ± 5.4 bpm in Group CL and 86.7 ± 5.13 bpm in Group C which was comparable in both groups. Intergroup comparison of pulse rate shows comparable baseline pulse rate. A significant difference in pulse rate was started before induction and difference were statistically highly significant after intubation which remained throughout intraoperatively.

Hence, pulse rate remained low and steady throughout the laparoscopic surgery in CL group compared to C group whereas rise was seen in Group C.

SBP varied from 110.8 ± 9.1 mmHg to 128.13 ± 5.7 mmHg in Group CL while it varied from 128.33 ± 6.59 mmHg to 159.6 ± 12.33 mmHg in Group C. On comparison, baseline values were comparable in both groups. Mean baseline systolic BP was 128.13 ± 5.7 mmHg in Group CL while it was 128.3 ± 6.59 mmHg in Group C. SBP was 114.73 ± 10.99 mmHg in Group CL and 133.26 ± 7.19 mmHg in group C before intubation, 114.86 ± 12.88 mmHg in Group CL and 159.6 ± 12.33 mmHg in Group C after intubation, 112.13 ± 10.62 mmHg in Group CL and 139.66 ± 9.23 mmHg in Group C 15 min after pneumoperitoneum. As shown in table SBP after 10 min of CO_2 release was 111.73 ± 8.57 mmHg in Group CL while 129.53 ± 3.002 in Group C, 116.067 ± 7.88 mmHg in Group CL and 145.6 ± 7.055 mmHg in Group C after extubation. This all findings show that SBP raised significantly before induction in Group C compared to Group CL. Highly significant rise in SBP in Group C compared to Group CL was seen after intubation, during pneumoperitoneum and after 10 min of CO_2 release and also after extubation. DBP varied from 78.53 ± 3.44 to 83.93 ± 4.85 in Group CL while it varied from 82.13 ± 3.23 to 99.47 ± 9.01 in Group C. Baseline DBP in Group CL was 83.9 ± 4.8 mmHg and was 82.13 ± 3.23 mmHg in Group C which showed no significant difference. DBP before intubation was 81.96 ± 3.99 mmHg Group CL compared to 87 ± 4.32 mmHg in Group C, was 81.13 ± 4.68 mmHg in Group CL and 99.47 ± 9.01 mmHg in Group C after intubation, 78.53 ± 3.44 mmHg in Group CL and 92.06 ± 6.15 mmHg in Group C after 15 min of pneumoperitoneum, 78.93 ± 2.95 mmHg in Group CL and 88.2 ± 2.69 mmHg in Group C after 10 min of release of CO_2 and was 80.2 ± 3.61 mmHg after extubation in Group CL compared to 95.73 ± 4.77 mmHg in Group C. All above findings shows highly significant rise in DBP in control group compared to clonidine group which was seen before intubation and throughout intraoperatively, even after extubation. The average concentration of isoflurane used in Group CL was from 0.44% to o.61% which was started after intubation and stopped as soon as CO_2 was released. In Group C, concentration of isoflurane used was from 0.71% to 1.19% which was continued even after release of CO_2. The requirement of isoflurane to maintain MAP intraoperatively was 40% less in Group CL than Group C.

Table 3 shows the use of agents other than isoflurane to maintain hemodynamic stability intraoperatively in both groups. None of the patients of Group CL required any supplementation to maintain hemodynamic stability. In Group C, 47% of patients required nitroglycerine infusion 5 µg/kg/min, 43% of patients required injection midazolam 1 mg intravenous (IV) while 10% of patients

Table 1: Demographic data

Parameters	Mean±SD			
	Group CL	Group C	*P* value	Significance
Age (years)	45.1±7.1	45.4±8.2	0.48	NS
Weight (kg)	54.96±6.22	53.93±6.37	0.53	NS
Height (cm)	154.23±4.81	154.96±4.19	0.53	NS
ASA grade (I: II)	21:09	23:07		
Sex (male: female)	14:16	17:13		
Duration of surgery (min)	153.14	153.26		NS

ASA: American Society of Anesthesiologists, SD: Standard deviation, NS: Not significant

Table 2: Changes in pulse rate (beats/min)

Pulse rate	Mean±SD				Intergroup *P* value	
	Group CL		Group C			
	Intragroup *P* value		Intragroup *P* value			
Before premedication	88.3±5.4		86.7±5.13		>0.05	NS
Before induction	87±10.57	>0.05	89.4±4.78	>0.05	>0.05	NS
Before intubation	80.07±10.33	<0.05	89.4±5.69	>0.05	<0.05	S
After intubation	80.87±12.13	<0.05	112.93±5.13	<0.001	<0.001	HS
Before pneumoperitonium	77.8±8.46	<0.05	108.2±4.94	<0.001	<0.001	HS
After pneumoperitonium (15 min)	78.33±8.73	<0.05	110.33±3.89	<0.001	<0.001	HS
After pneumoperitonium (30 min)	78.2±8.44	<0.05	104.86±5.91	<0.001	<0.001	HS
After CO_2 release (10 min)	76.2±7.015	<0.05	106.86±6.22	<0.001	<0.001	HS
After extubation	80.2±7.70	<0.05	110.4±6.85	<0.001	<0.001	HS

SD: Standard deviation, NS: Not significant, HS: Highly significant

needed both midazolam and nitroglycerine to maintain hemodynamic stability. There was no other complication such as bradycardia, arrhythmia, hypotension, ischemia in either group intraoperatively. There was no significant change seen in SpO_2 in both groups and no fall in SpO_2 seen intraoperatively in both groups. Table 4 shows mean values of postoperative hemodynamic and respiratory parameters which were observed every 10 min for 1st h and every 15 min for next hour postoperatively. Significant variation was seen in pulse, SBP, DBP, MAP in both the groups. Pulse, SBP, DBP, MAP were stable in Group CL compared to Group C. No significant changes were observed in respiratory rate and saturation.

Sedation score after 90 min of giving clonidine and postoperatively every 10 min for 1 h and every 15 min for next hour. After 90 min of giving clonidine premedication in Group CL, all patients had sedation score of 2 while no sedation was found in patients of Group C. Postoperatively for initial 20 min, sedation score was high in Group C (3.6-3.98) as compared to Group CL (2.86-3.06) and after that sedation score was less in Group C than in Group CL. Postoperatively at the end of 1 h sedation score in Group CL was 2.45 ± 0.18 in Group CL and 1.36 ± 0.06 in Group C and after 2 h it was 2.03 ± 0.18 in Group CL and 1.06 ± 0.13 in Group C. In Group CL sedation score varied from 3.06 ± 0.18 to 2.03 ± 0.18, showed less fluctuation, patients were awake and comfortable postoperatively. In Group C, it varied from 3.98 ± 0.1 to 1.06 ± 0.13 showed more sedation in initial 30 min of postoperative period. Only 2 patients (6.6%) in Group C had nausea and one patient (3.3%) of Group CL had subcutaneous emphysema postoperatively. No other complications observed intra- or post-operatively which did not require any treatment. All patients of Group CL had dryness of mouth.

Table 3: Use of other agents to maintain intraoperative hemodynamic stability

Agent	Number of patients	
	Group CL	Group C (%)
Injection midazolam 1 mg IV	0	13 (43)
Injection nitroglycerine (5 μg/kg/min)	0	14 (47)
Both	0	3 (10)

IV: Intravenous

Table 4: Postoperative hemodynamic and respiratory parameters

Parameters	Group CL	Group C	*P* value	Significance
Pulse (beats/min)	84.7±9.4	90.3±5.4	<0.05	S
SBP (mmHg)	120±5.6	133±4.5	<0.05	S
DBP (mmHg)	81.6±3.1	89±3.6	<0.05	S
MAP (mmHg)	95±3.75	104±3.4	<0.05	S
SpO_2 (%)	99±1.01	98±0.37	>0.05	NS
Respiratory rate/min	17.26±2.67	17±1.29	>0.05	NS

S: Significant, NS: Not significant, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

DISCUSSION

In our study, patients were randomly divided into two groups. Patients of Group CL were premedicated with tablet clonidine 3 μg/kg per oral 90 min before estimated induction time while no oral premedication was given in Group C. Aho et al., used 3 μg/kg and 4.5 μg/kg clonidine for suppression of hemodynamic response to pneumoperitoneum. Rise in BP and heart rate was less in both the groups but 4.5 μg/kg clonidine produced greater fall in MAP before induction. Malek et al., used 150 μg of clonidine as IV infusion and intramuscularly while Sung et al. and Yu et al., used 150 μg of clonidine as premedication for maintenance of hemodynamic stability during pneumoperitoneum. Das et al.,[5] also used 150 μg of clonidine, 90 min before induction to maintain perioperative hemodynamic stability. We had used 3 μg/kg of clonidine and our study is in consonance with their study in regard to dose of clonidine. Pulse rate varied from 84.2 ± 7.015 bpm to 88.3 ± 5.4 bpm in Group CL and Group C it varied from 85.4 ± 4.78 to 98.4 ± 6.8 bpm. Significant variation was observed throughout intraoperatively between two groups. Before intubation significant rise in pulse rate in Group C compared to Group CL was seen which became highly significant after intubation, during pneumoperitoneum and also observed even after extubation. Pulse rate in Group CL was low compared to baseline throughout intraoperatively. No decrease in pulse rate to that of baseline was seen in Group C, instead a rise of pulse rate was seen after intubation and after extubation. Decrease in sympathetic tone by central action of clonidine may be responsible for decrease in pulse rate. Presynaptically mediated inhibition of norepinephrine and a vagomimetic action at nucleus tractus solitarius are responsible for bradycardia, but no bradycardia was seen in both groups in our study. In a study of Goel and Sinha, three patients had bradycardia that required treatment. Our findings are comparable to Sung et al. and Yu et al., Das et al., and Goel and Sinha who had found lower perioperative heart rate in clonidine group than in placebo group. SBP varied from 110.8 ± 9.1 mmHg to 128.13 ± 5.7 in Group CL while it varied from 128.33 ± 6.59 to 159.6 ± 12.33 mmHg in Group C. On comparison, significant rise in SBP in Group C compare to Group CL was seen before induction; highly significant rise was started before intubation, remained high intraoperatively and even after extubation. As shown in graph SBP was decreased compared to baseline in Group CL, no rise was seen after intubation, extubation or during pneumoperitoneum. While in Group C, SBP was high compared to baseline intraoperatively and significant rise was seen after intubation and after extubation. Goel and Sinha[9] had found significant fall in SBP with clonidine in their study. Our findings are in consonance with their findings of SBP.

DBP was high in Group C compared to Group CL. It increased highly significantly in Group C before intubation (87 ± 4.32 in Group C and 81.13 ± 4.68 in Group CL) and remained high intraoperatively till deflation of pneumoperitoneum. Decrease in DBP in Group CL to that of baseline was seen after intubation which was not seen in Group C. Instead of that there was rise in DBP compared to baseline which was seen maximum after intubation and extubation. Das et al., had found significant rise in SBP, DBP and MAP in placebo group which was >20% from baseline. They observed rise in SBP, DBP and MAP following intubation and pneumoperitoneum but it never crossed baseline value in clonidine group. Thus, our study is comparable to these studies in regard to hemodynamic stability. Average concentration of isoflurane used in Group CL was from 0.44% to o.61% which was given after intubation and stopped as soon as pneumoperitoneum was released. In Group C, concentration of isoflurane used was from 0.71% to 1.19% which was continued even after release of pneumoperitoneum. Requirement of isoflurane to maintain MAP intraoperatively was 40% less in group CL than Group C. Clonidine provides stable hemodynamic condition and also has anxiolytic property it also reduces the awakening concentration of isoflurane.[10] This is the reason of less requirement of Isoflurane in clonidine group. The isoflurane concentration required to maintain hemodynamic stability in study of Sung et al. and Yu et al., was reduced by 30% in patients of clonidine group. Our findings are in consonance with findings of Das et al.[8] They also observed decreased requirement of isoflurane in clonidine group. None of the patients of Group CL required any pharmacological intervention. In Group C, 47% of patients required nitroglycerine infusion (0.5 μg/kg/min), 43% of patients required injection midazolam 1 mg IV while 10% of patients needed both midazolam and nitroglycerine. Sung et al. and Yu et al.[7] in their study required IV esmolol 10 mg in 19 patients of placebo group and 2 patients of clonidine group. 15 patients of placebo group and 4 patients of clonidine group required 5 mg of sublingual nifedipine and 17 patients of placebo group required IV labetolol 2.5 mg. In study of Das et al., 33.3% patients in placebo group required nitroglycerine infusion (0.5 μg/kg/min) for treatment of intraoperative hypertension. Hence, our study is comparable with study of Das et al. and Goel and Sinha. There was no significant change seen in SpO_2 in both the groups and no fall in SpO_2 seen intraoperativelly in both groups. Our study is comparable to Sung et al. and Yu et al., Das et al. They also found no change in oxygen saturation intraoperatively. After 90 min of giving clonidine premedication in Group CL, all patients were sedated having sedation score of 2 while no sedation found in patients of Group C. Postoperatively after extubation for initial 30 min sedation score was high in Group C (between 3 and 4) as compared to Group CL (between 2 and 3) and after that sedation score was less in Group C compared to Group CL. Clonidine has sedative property. The sedation in clonidine is mainly due to stimulation of α2 receptor in the brainstem. The locus corpulus in the brain stem is an important area from which main ascending and descending noradrenergic pathways originate. Activation of α2 receptor suppresses the spontaneous firing rate of locus corpulus. This results in an increasing activity of inhibitory interneuron such as gamma-aminobutyric acid-aergic pathways to produce central nervous system (CNS) depression.[11] Our findings are comparable to Sung et al. and Yu et al., and Das et al. In Group C had nausea and one patient (3.3%) of Group CL had subcutaneous emphysema postoperatively, but there was no respiratory depression. That patient did not require any treatment; emphysema was relieved completely after 5 η. No other complications were observed postoperatively. Sung et al. and Yu et al., found nausea in 15.4% of patients of placebo group and 7% of patients of clonidine group. One patient in placebo group suffered from respiratory depression with co2 retention. In study of Das et al. incidence of nausea-vomiting, hypertension, shivering and shoulder pain were 35.7%, 35.7%, 10.7%, and 14.3% in Group P while incidence of nausea-vomiting was only 6.89% in Group C. Clonidine increases gastrointestinal motility by decreasing sympathetic outflow, increasing parasympathetic outflow from CNS and causes decrease of gastric emptying time. Thus, reduces incidence of nausea and vomiting.

CONCLUSION

With clonidine 3 μg/kg there is no rise in pulse rate and BP throughout laparoscopic cholecystectomy at various stages. Patients remain hemodynamically stable throughout laparoscopic surgery with clonidine. The decrease in pulse rate and BP is not to the extent of bradycardia and hypotension. Clonidine has no effect on respiration. Patients premedicated with clonidine did not require any other pharmacological agent to maintain hemodynamic stability during laparoscopic cholecystectomy. Clonidine also decreased the requirement of inhalation agent. Clonidine has sedative property with the dose of 3 μg/kg. All patients were sedated but comfortable. No significant perioperative complications were found with the use of clonidine (3 μg/kg). Hence, 3 μg/kg oral clonidine has been found to provide stable hemodynamics and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

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