Original Article

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Anaesthesia Section

Effect of Oral Clonidine Premedication on Induction Dose of Propofol and Perioperative Haemodynamic Parameters in Patients undergoing Laparoscopic Cholecystectomy: A Double-blinded Randomised Controlled Study

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ABSTRACT

Introduction: Clonidine increases the effects of anaesthesia and possesses antihypertensive qualities. During laparoscopic cholecystectomy, pneumoperitoneum is created by inflating Carbon Dioxide (CO_2), which stimulates autonomic pathways, resulting in catecholamine release, activation of the renin-angiotensin system and vasopressin release. Clonidine may be an ideal agent for controlling the stress response to pneumoperitoneum during laparoscopic surgery.

Aim: To observe the clinical efficacy of two different dosages of oral clonidine premedication on the induction dose of propofol and changes in perioperative haemodynamic parameters in patients undergoing laparoscopic cholecystectomy.

Materials and Methods: This randomised, double-blinded study was conducted at the Department of Anaesthesiology, Uttar Pradesh University of Medical Sciences (UPUMS), Saifai, Etawah, India, from January 2019 to December 2020. The study examined 60 patients with American Society of Anaesthesiologists (ASA) grades I and II who were scheduled for elective laparoscopic cholecystectomy under general anaesthesia. One hour before induction, the patients were randomly assigned to three groups for premedication: Group A (n=20) received a placebo, group B (n=20) received 150 µg of oral clonidine and group C (n=20) received 300 µg of oral clonidine. The patients were managed with standard general anaesthesia. Haemodynamic parameters and the propofol induction dose of the three groups were compared using an unpaired t-test and one-way Analysis of Variance (ANOVA); a p-value of <0.05 was considered statistically significant.

Results: A total of 60 patients were included in the study, with 20 patients in group A (Placebo), 20 in group B (150 µg oral clonidine) and 20 in group C (300 µg oral clonidine). When comparing the two different dosages of oral clonidine (150 µg vs 300 µg), it was found that the higher dose (300 µg) was more effective in attenuating the pressure responses to laryngoscopy, intubation, pneumoperitoneum and extubation. In comparing the clonidine groups, group C (1.42±0.14 mg/kg) and group B (1.61±0.02 mg/kg) both exhibited a substantial reduction in the induction dose of propofol compared to the placebo group A (1.84±0.13 mg/kg).

Conclusion: Throughout the perioperative periods, the clonidine groups (C>B) maintained haemodynamic variables better than the placebo group (A) and the clonidine groups also experienced a significant reduction in the induction dose of propofol. In comparing the two dosages of oral clonidine, it was found that the higher dose (group C) was superior in attenuating the pressure response to laryngoscopy, intubation, pneumoperitoneum and extubation.

Keywords: Airway extubation, Antihypertensive agent, Extubation, Laryngoscopy, Pneumoperitoneum

INTRODUCTION

These days, the most popular minimally invasive surgical technique for removing a diseased gallbladder is laparoscopic cholecystectomy. During laparoscopy, pneumoperitoneum is created by inflating CO_2 and adjusting the patient's posture from Trendelenburg to reverse Trendelenburg [1]. The stimulation of autonomic pathways during pneumoperitoneum results in the release of catecholamines, activation of the renin-angiotensin system and release of vasopressin [2,3]. This potent endogenous hormone can cause intense vasoconstriction and an increase in Mean Arterial Pressure (MAP). Patient positioning, such as steep Trendelenburg positioning during pneumoperitoneum, may augment venous return and cardiac filling, while a reverse Trendelenburg position can increase Systemic Vascular Resistance (SVR) and cause minor reductions in Cardiac Index (CI) [4].

One of the most frequently prescribed induction medications for patients undergoing general anaesthesia is propofol. Following a bolus, the median Effective Dose (ED50) of propofol for achieving unconsciousness is typically between 1 and 1.5 mg/kg. However, when anaesthesia is induced, the primary side-effect of propofol is a reduction in arterial Blood Pressure (BP). An induction dose of 2 to 2.5 mg/kg can result in a 25-40% reduction in Systolic Blood Pressure (SBP), regardless of existing cardiovascular disease. Both mean blood pressure and Diastolic Blood Pressure (DBP) exhibit similar changes [5].

An uneventful perioperative course is facilitated by adequate preoperative preparation, premedication and haemodynamically stable induction and maintenance of anaesthesia. In addition to achieving anxiolysis, premedication aims to produce several significant effects, including analgesia, fatigue, forgetfulness, attenuation of autonomic reflexes, facilitation of smooth induction of anaesthesia [6,7] and a reduction in the required dose of anaesthetic. To achieve this objective, numerous drugs have been studied,

including pretreatment with nitroglycerin, beta-blockers, calcium channel blockers, gabapentin, opioids like fentanyl and remifentanil, clonidine and various other medications [8-12].

Clonidine, a central sympatholytic and α-2 adrenoreceptor agonist, has a half-life of 9 to 12 hours. Clonidine premedication lowers the doses of anaesthetic and narcotic medications while also diminishing the stress response to surgical stimuli [13-18]. Moreover, clonidine decreases SBP and stabilises BP by enhancing the sensitivity of the heart's baroreceptor reflex [19]. Initially, clonidine may raise BP, SVR and cardiac output momentarily due to the activation of post-junctional alpha-2 receptors in the peripheral vasculature. This is followed by a more sustained drop in Heart Rate (HR) and BP, resulting from an increase in vagal activity and a decrease in sympathetic tone that is mediated centrally [20]. Importantly, clonidine does not affect the heart's ability to contract and maintain its output. Both systemic and coronary vascular resistance are reduced and clonidine provides significant sedation with minimal respiratory depression [21].

As there are currently no studies directly comparing two different dosages of oral clonidine as premedication, we planned this clinical trial to evaluate and compare the effectiveness of two different oral clonidine doses on the induction dose of propofol and perioperative haemodynamic parameters in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

The present randomised, double-blinded (both the patient and researcher blinded) study was conducted at the Department of Anaesthesiology, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, India, from January 2019 to December 2020. Ethical clearance for the study was obtained from the Institute's Ethical Committee prior to its commencement (ethics clearance number: 128/2018) (Ref No. 1371/UPUMS/Dean(M)/ethics/2020-21).

Inclusion criteria: Patients of either sex with American Society of Anaesthesiologists (ASA) I and II physical status, aged 20 to 60 years, who were scheduled to undergo elective laparoscopic cholecystectomy, were enrolled in the study.

Exclusion criteria: Patients with a history of neurological diseases, pregnancy, severe renal or hepatic dysfunction, asthma, substance misuse, use of clonidine, sedatives, or antidepressant medication, or a Body Mass Index (BMI) over 30 kg/m^2 were excluded from the study.

Sample size calculation: For the present study, the authors compared vital parameters across three groups using the following formula to calculate the sample size:

$$n=\{z(1-\alpha/2)\}^2\times SD^2/d^2$$

Where: z(1-α/2)=standard normal deviate for 95% confidence=1.96

SD=Standard deviation of MAP=11 mm Hg [22]

d=precision=5%

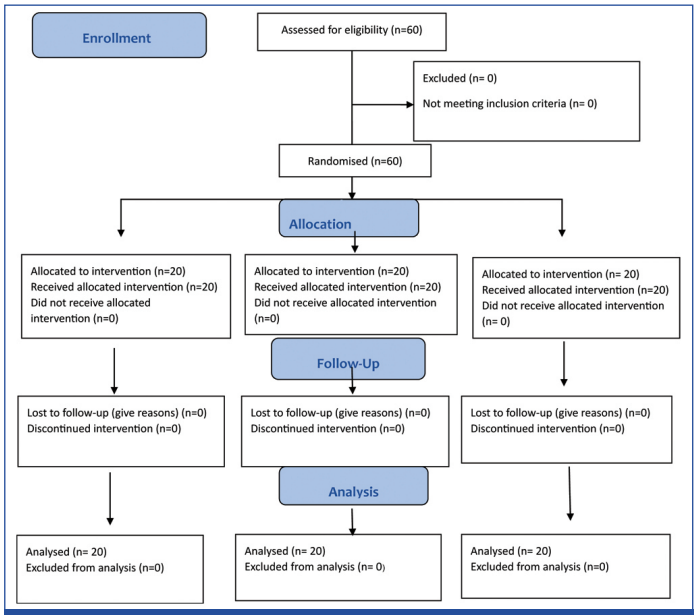
$n=(1.96)^2\times(11)^2/(5)^2$

n=18.59

The calculated sample size is 18.59 and is capped at 20 patients in each group.

Study Procedure

A sample size of 60 was calculated based on a 95% confidence interval and a 5% margin of error, with 20 participants assigned to each of the three groups. To maintain randomisation, 60 opaque envelopes were used, equally divided into three groups labelled A, B and C, with each group containing 20 envelopes. A staff nurse carefully organised and separated the tablets: clonidine 150 mcg, clonidine 300 mcg and a placebo (Tab. Pantoprazole 40 mg) into three equal sets of 20 tablets each. These sets were then placed into the envelopes, ensuring that each envelope contained one tablet from the respective study group, thus maintaining a randomised distribution of the investigational medications across the participants [Table/Fig-1].



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) diagram.

A total of 60 minutes prior to surgery, patients were randomly assigned an envelope containing the formulations by another staff nurse in the preoperative room. An 18 G intravenous cannula was employed to secure intravenous access in the operating room. Each of the three groups received anaesthesia using the same method. Premedication of the patients involved administering fentanyl (2 μg/kg), glycopyrrolate (0.2 mg) and midazolam (1.0 mg). Following a three-minute preoxygenation period, patients received a 50 mg/min infusion of propofol and the induction dosage (measured in mg/kg) was recorded when verbal commands were lost. Vecuronium injection (0.1 mg/kg) was administered to facilitate the endotracheal intubation process. General anaesthesia was maintained with 67% N_2O in 33% O_2 and isoflurane at 0.75 percent using controlled ventilation. Maintenance of neuromuscular blockade was achieved with vecuronium (0.01-0.02 mg/kg). Vital parameters were monitored throughout the procedure. HR, bpm and non invasive BP were measured prior to the administration of clonidine (baseline) and at 30, 40 and 60 minutes following drug administration, immediately following premedication, induction and pneumoperitoneum, as well as at 30, 45, 60, 75 and 90 minutes intraoperatively, immediately following extubation and at 15, 30, 45 and 60 minutes postoperatively. Three BP readings were taken: the MAP, mmHg, the DBP, mmHg and the SBP, mmHg. To reverse any residual neuromuscular blockade after the operation, an intravenous dose of neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg) was administered.

STATISTICAL ANALYSIS

A frequency distribution was used to describe the data and the quantitative variables were presented as mean±SD (standard deviation). To compare quantitative variables between groups, an unpaired t-test was employed. The Chi-square test was utilised to evaluate the correlation between the qualitative variables. A statistically significant p-value was defined as being less than 0.05. An Excel spreadsheet was used to store the data and the open-source 'R' programming language was employed to conduct the statistical analysis.

RESULTS

Three groups were randomly allocated from a total of 60 patients who met the sampling criteria. A tablet containing 40 mg of pantoprazole

was given to group A, 150 µg of clonidine was administered to group B and 300 µg of clonidine was given to group C, 60 minutes prior to surgery.

Regarding ASA physical status, duration of surgery and demographic data, no statistically significant differences (p>0.05) were observed among the three groups [Table/Fig-2].

Variables	Group A	Group B	Group C	One-way ANOVA p-value
Age (years)	37.60±9.67	38.1±6.945	38.75±7.25	0.70
Gender (M/F)	8/12	8/12	8/12	1.0
Height (cm)	163.05±4.68	163.25±5.15	162.50±5.83	0.86
Weight (Kg)	64.35±5.9	64.60±6.35	65.60±6.29	0.58
Duration of surgery (min)	58.50±14.52	59.25±7.66	64.30±15.00	0.082
ASA Grade (I/II)	12/8	13/7	10/10	0.619

[Table/Fig-2]: Comparison of demographic variables and duration of surgery.

The baseline HR was similar across all three groups. At 60 minutes post-drug administration, group A had a significantly higher mean HR than groups B and C; however, the difference between groups B and C was not significant. After intubation, groups B and C demonstrated a significant reduction in mean HR compared to group A, with group C also showing a significantly lower HR than group B. Following pneumoperitoneum, groups B and C again had significantly lower HRs than group A. The HR differences between groups B and C remained significant during laparoscopic cholecystectomy after intubation, pneumoperitoneum and extubation [Table/Fig-3].

The change in SBP was significant (p<0.05) in comparisons between groups A and B and A and C, after 60 minutes of drug administration and continued to be significant until the postoperative period. The SBP in group B compared to group C was also found to be significant (p<0.05) immediately after induction, after intubation, after pneumoperitoneum and at 30 minutes and 60 minutes intraoperatively, as well as immediately after extubation [Table/Fig-4].

In intergroup comparisons (A vs B, A vs C and B vs C), changes in DBP immediately following premedication, induction, intubation, pneumoperitoneum creation and at 30 minutes were significant (p<0.05) in all three groups. Changes in DBP were not significant (p>0.05) in comparisons between group B and group C, but were significant (p<0.05) in comparisons between groups A and B and A and C during the intraoperative period. When comparing the three

Time point Heart rate (beats/minute)	Group A	Group B	Group C	One-way ANOVA	p-value
	Mean±SD	Mean±SD	Mean±SD	p-value	A vs B A vs C B vs C
Preoperative					
Baseline	81.40±5.15	81.25±2.47	82.55±4.98	0.307	-
30 minutes after drug administration	83.30±3.85	82.45±1.7	83.00±2.1	0.344	-
60 min after drug administration	83.70±6.33	73.10±3.81	71.70±2.39	<0.001*	<0.001 <0.001 0.086
Intraoperative					
After premedication	88.75±7.12	70.05±4.39	70.40±6.29	<0.001*	<0.001 <0.001 0.420
Just after induction	80.95±4.59	69.85±5.76	68.60±3.05	<0.001*	<0.001 <0.001 0.198
Just after intubation	105.80±7.72	86.65±4.31	81.75±3.97	<0.001*	<0.001 <0.001 <0.001
Just after pneumoperitonium	117.55±8.17	89.70±7.03	84.70±5.8	<0.001*	<0.001 <0.001 0.009
30 minutes	108.85±8.42	78.75±5.04	75.40±5.77	<0.001*	<0.001 <0.001 0.029
45 minutes	98.40±6.19	70.65±3.86	70.20±6.32	<0.001*	<0.001 <0.001 0.394
60 minutes	91.58±4.72	67.88±3.07	69.46±6.27	<0.001*	<0.001 <0.001 0.190
75 minutes	87.50±5.51	69.50±0.71	68.20±6.87	<0.001*	0.006 0.001 0.405
90 minutes	85.00±4.24	64.50±0.71	65.50±0.71	<0.001*	0.011 0.012 0.146
Postoperative					
Just after extubation	114.30±6.5	85.65±4.33	81.15±4.93	<0.001*	<0.001 <0.001 0.002
15 minutes	101.95±7.09	76.15±4.77	71.85±6.1	<0.001*	<0.001 <0.001 0.009
30 minutes	93.00±5.1	69.40±3.19	68.35±6.23	<0.001*	<0.001 <0.001 0.253
45 minutes	88.75±4.25	67.35±3.63	67.05±6.35	<0.001*	<0.001 <0.001 0.428
60 minutes	87.05±4.78	67.95±3.05	67.00±3.57	<0.001*	<0.001 <0.001 0.186

[Table/Fig-3]: Comparison of Heart Rate (HR) among the groups at various time points.

Time point Systolic blood pressure (mmHg)	Group A	Group B	Group C	One-way ANOVA	p-value
	Mean±SD	Mean±SD	Mean±SD	(p-value)	A vs B A vs C B vs C
Preoperative					
Baseline	122.45±5.06	122.90±1.55	122.40±1.05	0.403	-
30 minutes after drug administration	122.90±3.92	123.20±1.44	123.45±1.79	0.406	-
60 minutes after drug administration	123.20±4.32	116.10±2.94	115.60±2.72	<0.001*	<0.001 <0.001 0.290
Intraoperative					
After premedication	126.20±3.64	114.30±4.17	113.10±2.92	<0.001*	<0.001 <0.001 0.149
Just after induction	110.75±3.37	107.15±6.18	103.00±4.23	<0.001*	0.014 <0.001 0.009
Just after intubation	128.90±2.55	126.70±4.41	118.00±3.74	<0.001*	0.031 <0.001 <0.001
Just after pneumoperitoneum	135.60±3.99	132.55±4.82	122.80±4.75	<0.001*	0.018 <0.001 <0.001
30 minutes	125.25±5.25	119.85±3.51	115.25±3.91	<0.001*	<0.001 <0.001 <0.001
45 minutes	120.90±4.38	113.30±2.92	110.25±4.67	<0.001*	<0.001 <0.001 0.009

60 minutes	122.82±3.06	111.53±2.43	109.15±4.38	<0.001*	<0.001 <0.001 0.034
75 minutes	122.25±2.36	113.50±0.71	113.20±3.9	<0.001*	0.004 0.002 0.461
90 minutes	120.00±2.83	112.50±0.71	110.50±2.12	<0.001*	0.034 0.031 0.167
Postoperative					
Just after extubation	131.20±3.58	125.90±4.52	122.20±3.69	<0.001*	<0.001 <0.001 0.004
15 minutes	121.80±5.4	117.15±3.17	115.35±3.86	<0.001*	<0.001 <0.001 0.057
30 minutes	119.65±4.25	111.75±2.59	111.85±3.05	<0.001*	<0.001 <0.001 0.456
45 minutes	119.80±4.26	111.60±2.39	111.00±4.09	<0.001*	<0.001 <0.001 0.287
60 minutes	120.05±4.7	103.50±3.43	105.63±5.23	<0.001*	<0.001 <0.001 0.069

[Table/Fig-4]: Systolic Blood Pressure (SBP) among the groups at various time points.

groups (A vs B, A vs C and B vs C), changes in DBP immediately following extubation were significant (p<0.05) [Table/Fig-5].

The MAP showed significant differences (p<0.05) among all groups immediately after premedication, induction, intubation, creation of pneumoperitoneum and at 30 minutes. During the intraoperative period (45-90 minutes), MAP differences were significant between groups A and B and A and C, but non significant between groups B and C. After extubation, all intergroup comparisons demonstrated significant changes in MAP. Postoperatively, MAP differences at 15 to 60 minutes were significant between groups A and B and A and C, but remained non significant between groups B and C [Table/Fig-6].

The mean induction doses of propofol in groups A, B and C were 1.84±0.13 mg/kg, 1.61±0.20 mg/kg and 1.42±0.14 mg/kg, respectively. In intergroup comparisons, a statistically significant difference (p<0.001) was found among all three groups: A vs B, A vs C and B vs C [Table/Fig-7].

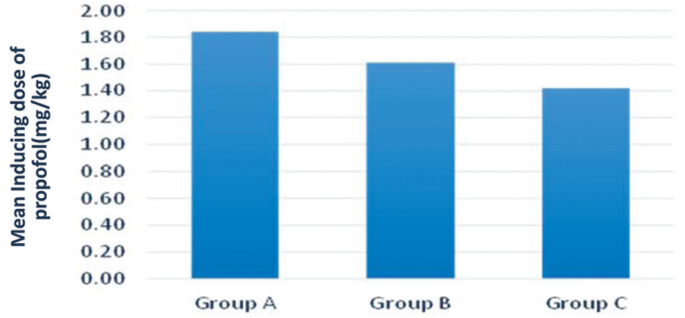
Time point Diastolic blood pressure (mmHg)	Group A	Group B	Group C	One-way ANOVA	p-value
	Mean±SD	Mean±SD	Mean±SD	p-value	A vs B A vs C B vs C
Preoperative					
Baseline	82.15±0.99	82.25±1.25	82.00±2.97	0.689	-
30 minutes after drug administration	81.15±0.88	81.00±1.56	81.80±1.82	0.129	-
60 min after drug administration	81.00±2.18	70. 10±2.59	68.00±1.52	<0.001*	<0.001 <0.001 0.002
Intraoperative					
Just after premedication	83.00±1.69	69.55±2.56	65.35±2.58	<0.001*	<0.001 <0.001 <0.001
Just after induction	72.45±3.05	63.55±5.15	59.35±3.92	<0.001*	<0.001 <0.001 0.003
Just after intubation	87.40±2.46	80.55±3.61	74.75±5.13	<0.001*	<0.001 <0.001 <0.001
Just after pneumoperitoneum	92.00±3.28	83.95±4.07	77.55±4.49	<0.001*	<0.001 <0.001 <0.001
30 minutes	85.10±3.85	75.10±3.92	72.50±5.62	<0.001*	<0.001 <0.001 0.049
45 minutes	81.25±3.06	69.30±1.72	68.80±6.05	<0.001*	<0.001 <0.001 0.362
60 minutes	80.17±2.92	69.71±4.1	70.69±6.68	<0.001*	<0.001 <0.001 0.311
75 minutes	79.50±1.29	70.50±0.71	74.60±4.45	<0.001*	<0.001 0.037 0.137
90 minutes	82.00±0	70.00±1.41	69.50±2.12	<0.001*	0.003 0.007 0.404
Postoperative					
Just after extubation	86.90±3.28	82.65±3.05	80.80±3.38	<0.001*	<0.001 <0.001 0.039
15 minutes	81.60±2.85	75.15±3.05	73.40±4.55	<0.001*	<0.001 <0.001 0.080
30 minutes	79.45±2.8	69.15±2.48	70.75±6.46	<0.001*	<0.001 <0.001 0.154
45 minutes	80.05±2.28	68.10±2.86	69.95±7.04	<0.001*	<0.001 <0.001 0.142
60 minutes	80.85±2.23	64.45±3.59	66.30±5.3	<0.001*	<0.001 <0.001 0.102

[Table/Fig-5]: Diastolic Blood Pressure (DBP) among the groups at various time points.

Time point Mean arterial pressure (mmHg)	Group A	Group B	Group C	One-way ANOVA	p-value
	Mean±SD	Mean±SD	Mean±SD	p-value	A vs B A vs C B vs C
Preoperative					
Baseline	94.90±1.86	95.45±0.89	95.15±2.13	0.238	-
30 minutes after drug administration	94.70±1.26	94.75±1.29	94.20±0.83	0.111	-
60 minutes after drug administration	94.80±2.24	85.10±2.2	83.55±1.23	<0.001*	<0.001 <0.001 0.005
Intraoperative					
After premedication	97.05±2.14	84.45±2.7	80.90±2.38	<0.001*	<0.001 <0.001 <0.001
Just after Induction	84.80±2.88	77.75±5.19	73.35±2.74	<0.001*	<0.001 <0.001 <0.001
Just after Intubation	100.85±2.16	95.40±3.36	88.35±4.39	<0.001*	<0.001 <0.001 <0.001
Just after pneumoperitoneum	106.10±3.04	99.85±3.65	92.70±4.17	<0.001*	<0.001 <0.001 <0.001
30 minutes	98.15±3.8	89.65±3.34	86.55±4.78	<0.001*	<0.001 <0.001 0.011
45 minutes	94.20±3.09	83.50±2.19	82.75±5.64	<0.001*	<0.001 <0.001 0.291
60 minutes	93.92±2.43	83.35±3	82.58±5.2	<0.001*	<0.001 <0.001 0.309

75 minutes	93.25±0.96	84.50±0.71	87.00±3.81	<0.001*	<0.001 0.008 0.211
90 minutes	94.50±0.71	86.50±0.71	82.50±2.12	<0.001*	0.004 0.008 0.064
Postoperative					
Just after extubation	101.55±2.76	96.75±3.04	94.15±3.69	<0.001*	<0.001 <0.001 0.010
15 minutes	94.65±2.01	88.55±2.7	86.95±4.05	<0.001*	<0.001 <0.001 0.075
30 minutes	92.60±2.6	83.00±2.41	84.20±5.13	<0.001*	<0.001 <0.001 0.175
45 minutes	92.90±2.25	82.45±1.99	83.30±5.57	<0.001*	<0.001 <0.001 0.262
60 minutes	93.25±2.53	77.20±2.71	79.15±4.58	<0.001*	<0.001 <0.001 0.055

[Table/Fig-6]: Mean Arterial Pressure (MAP) among the groups at various time points.



[Table/Fig-7]: Inducing dose of propofol among the groups.

The incidence of nausea and vomiting was lower in the clonidine groups compared to the control group. In group A (n=20), nausea was reported in 4 patients (20%) and vomiting in 2 patients (10%). In group B (n=20), 3 patients (16%) experienced nausea and 1 patient (5%) had vomiting. In group C (n=20), nausea occurred in 2 patients (10%) and vomiting in 1 patient (5%). Hypotension was observed only in the clonidine groups, with 1 patient (5%) in group B and 2 patients (10%) in group C experiencing this side-effect. Bradycardia was noted in 1 patient (5%) in group C; however, it was clinically non significant. No other adverse effects were observed in any group.

DISCUSSION

Recent studies have increasingly emphasised the use of non opioid medications within a multimodal approach to mitigate the intubation response, stabilise perioperative haemodynamics, reduce anxiety and decrease the need for anaesthetic drug doses. Among these non opioid options, clonidine has demonstrated promising outcomes [23-26].

The present study demonstrated that oral clonidine premedication provided stable perioperative haemodynamics and reduced the induction dose of propofol in patients undergoing laparoscopic cholecystectomy. The demographic data across all three groups (A, B and C) were comparable. Clonidine-premedicated patients (B and C) exhibited lower propofol induction doses and more stable haemodynamics compared to the placebo group (A). A higher dose of clonidine (300 mcg) proved superior to a lower dose (150 mcg) in terms of haemodynamic stability and propofol dose reduction. These findings align with previous studies, including Masud M et al., who also reported greater haemodynamic stability in clonidine-treated patients during the pneumoperitoneum, intubation and extubation phases, with significant differences in HR and MAP ($p<0.05$) [6]. Similarly, Prasad JN et al., found a significant reduction in propofol induction doses in patients receiving clonidine ($p<0.001$), mirroring the present findings of lower propofol requirements in the clonidine groups [7].

The attenuation of cardiovascular responses to intubation, pneumoperitoneum and extubation with clonidine premedication is well documented. The present findings are consistent with the observations of Sung CS et al., who noted that clonidine premedication reduced haemodynamic fluctuations and the requirement for isoflurane while also decreasing postoperative analgesic needs [8]. The significant reduction in SBP, DBP and HR in the present clonidine groups was similarly reported by Kotwani DM et al., who found consistently lower HR, SBP and DBP values in clonidine-premedicated patients at multiple intraoperative time points [9]. Khatavkar S et al., also reported significant differences ($p<0.05$) in HR and MAP between clonidine and control groups at various intraoperative stages, reinforcing the efficacy of clonidine in maintaining perioperative haemodynamic stability [10].

Clonidine's impact on intraoperative and postoperative cardiovascular parameters was further corroborated by Kumar S et al., who noted a higher incidence of intraoperative tachycardia and hypertension in the control group [11]. In the present study, the placebo group exhibited significantly greater increases in HR, SBP, DBP and MAP compared to the clonidine groups. Parlow JL et al., also highlighted clonidine's ability to enhance postoperative baroreceptor response, lower catecholamine concentrations and decrease mean HR and BP intraoperatively, findings that strongly correlate with the present results [4]. Bhuava A et al., demonstrated a dose-dependent reduction in HR and BP, emphasising the significant differences between clonidine and placebo groups at all intraoperative and postoperative time points. This is in agreement with the present study's findings that 300 mcg clonidine was more effective than 150 mcg in stabilising haemodynamics [13].

The ability of clonidine to mitigate the haemodynamic stress response associated with laparoscopic cholecystectomy has been further supported by various studies. Tripathi DC et al., found that intravenous clonidine at 1 µg/kg attenuated the haemodynamic response to pneumoperitoneum but was less effective against intubation and extubation responses [14]. In contrast, 2 µg/kg intraperitoneal clonidine significantly reduced stress responses at all stages. The present findings corroborate these results, as both 150 µg and 300 µg oral clonidine effectively blunted the haemodynamic stress response to pneumoperitoneum, intubation and extubation, with the 300 µg dose proving more efficacious. Overall, the present study contributes to the growing body of evidence supporting the use of oral clonidine premedication for perioperative haemodynamic control and reduced anaesthetic drug requirements.

Limitation(s)

The present study was conducted at a single centre, lacked long-term follow-up and excluded high-risk patients. Furthermore, the generalisability of the findings is limited, as not all surgical procedures and anaesthetic protocols were represented.

CONCLUSION(S)

Oral clonidine is an effective premedication for attenuating perioperative cardiovascular stress responses. Both 150 µg and 300 µg doses significantly reduced haemodynamic fluctuations during laryngoscopy, intubation, pneumoperitoneum and extubation compared to placebo. The 300 µg dose provided superior control of haemodynamic parameters and greater stability throughout the perioperative period. Additionally, clonidine reduced the induction dose requirement for propofol in a dose-dependent manner. Higher doses of clonidine were associated with better suppression of stress responses without major adverse effects. Overall, oral clonidine proved to be a safe and beneficial adjunct for improving perioperative outcomes.

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