Section: Anaesthesiology

Original Research Article

EFFECT OF ORAL CLONIDINE PREMEDICATION ON PERIOPERATIVE HEMODYNAMIC RESPONSE AND POSTOPERATIVE ANALGESIC REQUIREMENT FOR PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY

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Received *: 04/10/2026*
Received in revised form *: 04/11/2026*
Accepted *: 16/11/2026*

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DOI: 10.70034/ijmedph.2026.4.388

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (4); 2585-2590

ABSTRACT

Background: Laparoscopic surgery has got tremendous popularity due to fast recovery and shortened hospital stay. The hall mark of laparoscopy, pneumoperitoneum is an additive to intubation in stimulating the neuro-humoral responses that create a pathway to hemodynamic instability which is the major hurdle faced by anaesthesiologist during laparoscopic procedure. Among the many drugs that are used to control the effects caused by pneumoperitoneum, Clonidine is a selective partial agonist for alpha 2 adrenoreceptors, with a ratio of approximately 200:1 (alpha 2 to alpha 1). Its antihypertensive effects are caused by central and peripheral attenuation of sympathetic outflow and central activation of noradrenergic imidazoline-preferring receptors. The decrease in central sympathetic outflow reduces activity in peripheral sympathetic neurons without affecting baroreceptor reflexes.

Materials and Methods: After obtaining ethical committee approval a Prospective, Randomized, Single Blinded Study was conducted on 120 patients at a tertiary care hospital in Jaipur to evaluate the effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. An informed written consent was obtained, and the patients were divided into two groups. Group P (Placebo) were given Vitamin C (500mg) 90 mins before surgery. Group C (Clonidine) were given 150mcg of tab clonidine 90 mins before surgery. Sample size of 60 patients in each group had arrived using power analysis.

Results: Demographic data such as age, weight, sex, type of surgery was comparable between the groups. And it shows that effect of clonidine does not depends on age, sex, weight or height of the patient. The heart rate was persistently lower during perioperative period in group C when compared to group P and showed a high statistical significance. Also, it has been noticed that intubation stress response was also blunted in patients who were premedicated with clonidine. Mean arterial blood pressure was also found to be controlled between the range of ±20 mmHg of baseline in patients who have been administered tab clonidine as premedication. Reduced use of isoflurane inspiratory and expiratory concentration in Group clonidine is an added advantage suggested by this study. Ramsay sedation score scale of 3 was also added advantages that were noticed in group C.

Conclusion: The study has shown that clonidine was safe, simple and effective in attenuating the stress response to pneumoperitoneum and provides good

perioperative hemodynamic stability by means of reduced Heart Rate, controlled mean arterial blood pressure, minimal side effect, less postoperative cumulative analgesia requirement.
Keywords: Clonidine, Premedication, Laparoscopic Cholecystectomy

INTRODUCTION

In the last two decades, laparoscopic surgery has got tremendous popularity. The magnitude of laparoscopic technique involves not only in abdominal surgeries but also extended to thoracic, thyroid, urological and gynaecological procedures because of its simplicity and attraction. Although laparoscopic surgeries have numerous benefits, it has its own short comings because of increased intraabdominal pressure created by carbon dioxide insufflation. The haemodynamic changes associated with laparoscopic procedure and general anaesthesia are quite detrimental and bit challenging for anaesthesiologist.

The hallmark of laparoscopy is Pneumoperitoneum (the peritoneal cavity is insufflated with CO2 gas). This creates a working space between the anterior abdominal wall and the viscera allowing endoscopic access to the peritoneal cavity for the safe manipulation of instruments and organs.1 CO2 is the insufflation gas of choice, but carbon dioxide (CO2) insufflation induces a cardiovascular response characterized by abrupt tachycardia, hypertension and increased myocardial oxygen requirements.

Studies have been focused to evaluate and reduce the various effects of pneumoperitoneum especially on hemodynamic changes. Research fellows have tried beta blockers, alpha 2 agonists, magnesium sulphate, opioids, vasodilators, and gasless approach to negate the hemodynamic variations. There are no known directly mediated alpha-2 adrenoceptor effects on the myocardium. Alpha-2 adrenoceptor reduction in sympathetic tone and increase in parasympathetic tone results in a reduced heart rate, systemic metabolism, myocardial contractility and systemic vascular resistance thereby decreasing the myocardial oxygen requirements. Clonidine lowers the 'set point' around which arterial blood pressure is regulated. It also increases the gain of the baroreceptor system, resulting in lower heart rates for a given increase in blood pressure, and widens the range of heart rate responses to changes in blood pressure. These characteristics of alpha 2 agonist are more important and favourable to manage the hemodynamic changes.

In this background, with view of overcoming the consequences happening during pneumoperitoneum, the study was conducted with oral clonidine to attenuate the stress response during laparoscopic procedure with the aim to see the effects of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement of patients undergoing cholecystectomy.

MATERIALS AND METHODS

This prospective, randomized, single blind, comparative study was conducted among patients in a tertiary care hospital in Jaipur for a period of 1 year after receiving approval from institutional ethical committee. The study was performed in adult patients undergoing laparoscopic cholecystectomy surgery. This number of patients was divided into two groups: Group C (n=60) has been given oral clonidine 150 mcg 90 mins before induction and Group P (n=60) has been given oral Vitamin C tablets 500mg 90 mins before induction.

Inclusion Criteria

The study included the patients of either sex, aged 20-60 years, who had an American Society of Anaesthesiologists (ASA) grading of I or II and who were scheduled for elective surgery of Laparoscopic Cholecystectomy Surgery.

Exclusion Criteria

Patients were excluded if there was refusal of participation in the study or concomitant use of monoamine oxidase inhibitors, tricyclic antidepressants or opioids, if patient had history of hypersensitivity to study drug, had history of bronchial asthma, had hypertension or diabetes, had severe coronary insufficiency or recent myocardial infarction.

Sample Size Calculation: G*Power version 3.1.9.7 (Germany) used for calculation of sample size.2

At 95% confidence interval Zα/2=1.96

With 80% power Zβ= 0.84

S1= 4.94

S2=4.78

d=mean difference to be detected= 2.5

So, minimum sample size in each group,

$n= (Z\alpha/2+Z\beta)2 \times (S12+S22) /d2$

$= (1.96+0.84)\ 2 \times (4.942+4.782) / 2.52$

$= 59.27$ i.e. 60

And total sample size was considering both groups (60×2) = 120.

Zα/2 is the critical value of the Normal distribution at α/2 (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96).

Zβ is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84).

Study Procedure: Patients who satisfied the criteria for inclusion were told about the anaesthetic technique and the study design, and informed written consent was obtained. Computer generated random number from www.random.org has been used for random allocation of patients into 2 groups where GROUP C was given clonidine 150 mcg 90 mins before induction and participants from GROUP P received Vitamin C 500 mg 90 mins before induction.

During pre-anaesthetic checkup, a detailed history and examination of each patient was done to optimize them before surgery. On arrival in the operating room, pulse oximetry, ECG and non-invasive blood pressure were recorded, and a wide bore intravenous line was established. Intraoperatively end tidal Carbon dioxide (EtCO2), inspired and expired concentration of isoflurane were also measured.

The patients after preoxygenation (3 mins) were premedicated with intravenous glycopyrrolate 10mcg/kg, Midazolam 0.1 mg/kg, Fentanyl 2mcg/kg. General anesthesia was induced by Propofol 2mg/kg and Atracurium 0.5mg/kg. Before giving Propofol IV Lignocaine (1.5mg/kg) was given to reduce the pain and induction was maintained with Isoflurane 50%N2O /50% 02. Controlled Mechanical Ventilation was applied to maintain end tidal Co2 between 30-40 mmHg. The Mean Arterial Blood Pressure (MABP) was maintained at 20% above or below the pre-operatively value by adjusting the concentration of isoflurane.

In case of severe hemodynamic fluctuations, medical intervention other than adjustment of isoflurane was done. For Bradycardia (Heart Rate <60/min), atropine 0.6mg IV was decided to be administered. For Hypotension (MABP <60 mmHg) IV fluid was decided to be transfused and/or IV Mephentermine 3mg bolus would be given. For Hypertension (MABP>110) treatment was decided with Infusion Nitroglycerine 0.5-5 mcg/kg/min IV.

Hemodynamics and isoflurane concentration was measured at different time points like, prior to induction (T0), 1 min (T1) and 5 min (T2) after endotracheal intubation, at skin incision (T3), at the start of pneumoperitoneum (T4), 15 mins (T5) and 30 mins (T6) after institution of Co2 pneumoperitoneum and 15 mins (T7) after release of pneumoperitoneum. Sedation was assessed using Ramsay sedation score from 1 to 6. Occurrence of any adverse events like nausea, vomiting, hypotension, hypertension, bradypnea and CO2 retention was recorded. Sedation score and adverse events were recorded at 30 min, 60 min, 90 min and 120 min postoperatively. Analgesia was given in the form of a combination of Inj. Diclofenac sodium 75 mg intravenous over 30 min 12 hourly and Inj. Tramadol 50 mg every 4-6 hr. The total dose of post operative analgesia in 24 hours was kept in recordings.

Outcome Measures: This study will primarily compare the two groups in terms of intraoperative hemodynamic changes and postoperative analgesia requirements.

Statistical Analysis: The statistical significance for comparison of proportions of categorical variables was determined by chi-square test. Fisher exact test was used in case one or more expected cell count is less than 5. For comparison of average of continuous variables two sample t-test was applied. Nonparametric “Mann Whitney” test was used for data that did not follow a normal distribution. Results will be expressed as Mean ± SD (standard deviation). A P value < 0.05 was considered significant.

RESULTS

Significant differences across the two study groups did not exist with respect to patient’s baseline characteristics like age, sex, height, weight indicating successful randomization and the homogeneity of groups.

[Table 1] presents comparison of Heart Rate between study groups at different points where although baseline heart rate was not significantly different in Group C (83.3 ± 7.79) and Group D (84.88 ± 5.81), but better control of heart rate is achieved in Group C as compared to Group P in T1, T2, T3, T4, T5, T7 time points which were statistically significant (P value < 0.05).

Table 1: Comparison of Heart Rate (/min) between study groups

Time	Group C	Group P	P value
Baseline (T0)	83.3 ± 7.79	84.88 ± 5.81	0.210
1 min after intubation (T1)	85.23 ± 8.17	94.18 ± 7.92	<0.001 (S)
5 min after intubation (T2)	84.37 ± 8.83	92.38 ± 5.92	<0.001(S)
Skin incision (T3)	87.07 ± 7.96	91.62 ± 5.81	0.001(S)
Start of pneumoperitoneum (T4)	86.07 ± 11.19	91.57 ± 7.11	0.002(S)
15 min after creation of pneumoperitoneum (T5)	85.15 ± 11.39	90.03 ± 8.53	0.009(S)
30 min after creation of pneumoperitoneum (T6)	86.9 ± 10.68	83.95 ± 6.37	0.069
15 min after release of pneumoperitoneum (T7)	84.03 ± 10.54	88.47 ± 8.63	0.013(S)

Similarly, [Table 2] presents comparison of Mean Arterial Pressure between study groups at different points showing better control of MAP is achieved in Group C as compared to Group P.

Table 2: Comparison of Mean Arterial Pressure (MAP, mmHg) among study groups

Time	Group C	Group P	P value
Baseline (T0)	92.63 ± 6.63	93.8 ± 5.70	0.290
1 min after intubation (T1)	92.23 ± 8.18	106.67 ± 7.45	<0.001 (S)
5 min after intubation (T2)	87.98 ± 10.9	104.83 ± 5.26	<0.001 (S)
Skin incision (T3)	90.5 ± 7.76	102.07 ± 4.19	<0.001 (S)
Start of pneumoperitoneum (T4)	94.43 ± 9.6	110.47 ± 5.39	<0.001 (S)
15 min after creation of pneumoperitoneum (T5)	94.8 ± 9.71	109.03 ± 3.71	<0.001 (S)
30 min after creation of pneumoperitoneum (T6)	92.72 ± 9.5	108.53 ± 2.59	<0.001 (S)
15 min after release of pneumoperitoneum (T7)	89.97 ± 6.54	103.08 ± 2.39	<0.001 (S)

[Figure 1 and 2] are suggestive of reduced use of isoflurane inspiratory and expiratory concentration in Group clonidine.

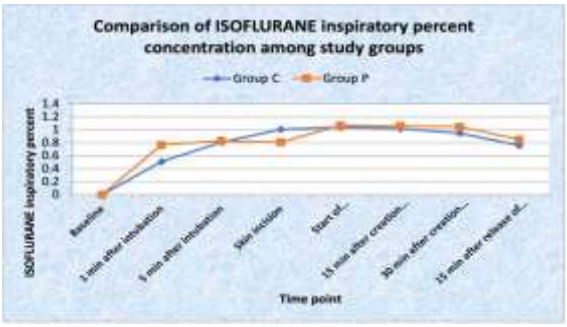

Figure 1: Comparison of ISOFLURANE inspiratory (percent) concentration between study groups at different time points

Incidence of nausea was more in Group P (71.7%) as compared to Group C (1.7%), and this difference was found to be statistically significant (p<0.001). Incidence of vomiting was seen in only 1 patient in Group C. Hypotension was seen in only 3 (5%) patients in Group C. Bradycardia and Bradypnea were not seen in any patients in both the groups [Table 3].

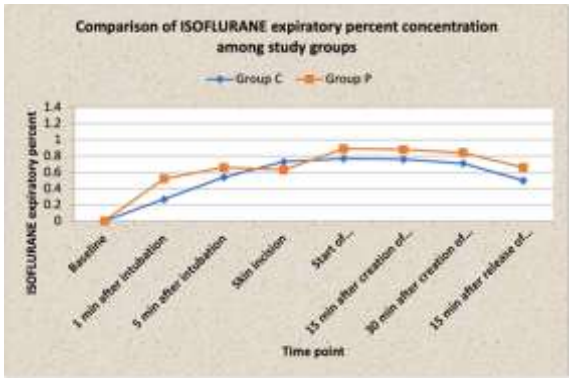

Figure 2: Comparison of ISOFLURANE expiratory (percent) concentration between study groups at different time points

Table 3: Distribution of study subjects according to frequency of complaints

	Group C		Group P		P value
	N	%	N	%	
Nausea	1	1.7	43	71.7	<0.001 (S)
Vomiting	1	1.7	0	0	1.000
Bradycardia	0	0	0	0	-
Hypotension	3	5	0	0	0.242
Bradypnea	0	0	0	0	-

Most of the patients in Group C required 50 mg tramadol (68.3%), while only 2 (3.3%) patients required 100 mg tramadol. 17 patients (28.3%) did not require tramadol. Contrary to this most patients in group P required 100 mg tramadol (93.3%), while 6.7% required 50mg tramadol. This difference in tramadol requirement was found to be statistically significant (p<0.001). [Figure 3]

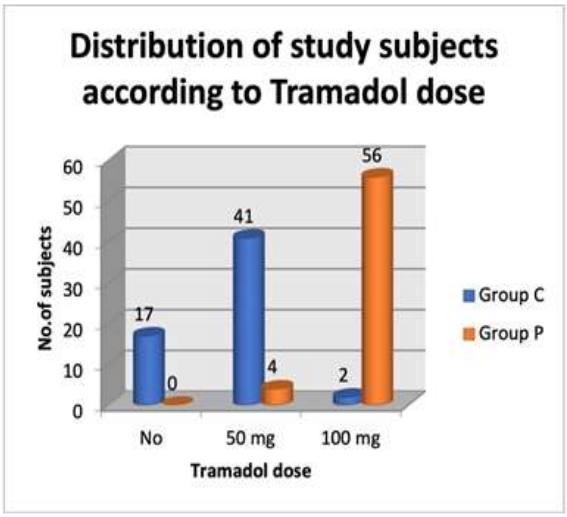

Figure 3: Distribution of study subjects according to Tramadol dose

Most of the patients in Group C required 75 mg Diclofenac (85%), while only 9 (15%) patients required 150 mg Diclofenac. While in group P 37 (61.7%) patients required 150 mg Diclofenac while 38.3% required 75 mg Diclofenac. This difference in Diclofenac requirement was found to be statistically significant (p=0.007). [Figure 4]

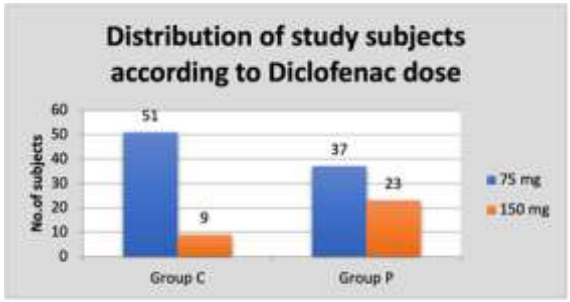

Figure 4: Distribution of study subjects according to Diclofenac dose

More patients in Group C had sedation score 3 at 30 min (58.3%), followed by score 2 at 90 (40%) and only 1 (1.7%) had score 1. In group P, most patients had score 1 (88.3%) and 7 (11.7%) had score 2. This difference in sedation score among the two groups was found to be statistically significant (p<0.001). [Figure 5]

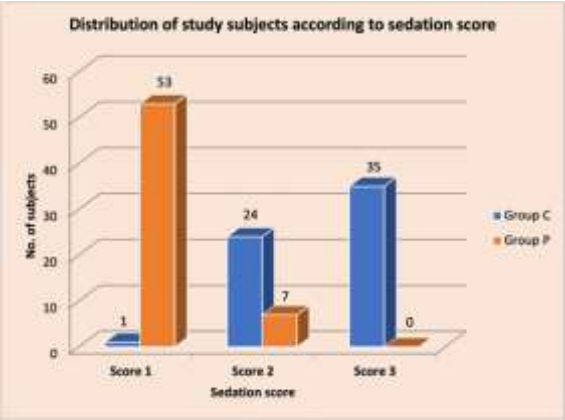

Figure 5: Distribution of study subjects according to sedation score

DISCUSSION

This prospective, randomized, single blinded study was conducted on 120 patients at a tertiary care hospital in Jaipur to evaluate the effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy.

All the patients had undergone Laparoscopic Cholecystectomy surgery. Average duration of pneumoperitoneum was about 60 minutes in all surgeries. Pneumoperitoneum during carbon dioxide insufflation is known to cause significant hemodynamic changes. This is a result of rapid and immediate increase of plasma catecholamines suggesting the involvement of sympathetic nervous system due to rise in intra-abdominal pressure. Many studies have proved the catecholamine response as the cause for these hemodynamic changes. Various pharmacological agents and various techniques have been used to counteract these detrimental effects.

Following pneumoperitoneum with carbon dioxide, patients were hyperventilated to maintain normocapnia. Every effort was made to maintain intraabdominal pressure (IAP) below 15 mm Hg. Ishizaki et al tried to evaluate the safe intra-abdominal pressure during laparoscopic surgery.[3] They observed significant fall in cardiac output at 16 mm Hg of intra-abdominal pressure. Haemodynamic alterations were not observed at 12 mm Hg of intra-abdominal pressure. Based on all these observations it was decided to monitor intraabdominal pressure and to keep it within the range of 12-15mmHg as possible. Despite maintaining intra-abdominal pressure below 15 mmHg significant rise in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was noticed in Group P but not in group C.

Clonidine, an imidazoline derivative is a selective alpha 2 adrenergic agonist. It is a potent antihypertensive drug. It produces a fall in the heart rate and blood pressure associated with decreased Systemic vascular resistance and cardiac output. Some studies used fixed dosage techniques while other studies used dosage/kg body weight. Dose of clonidine varied from 2 to 8 mcg/kg in different studies. Aho et al, Patel M et al used 3mcg/kg and 4.5 mcg/kg clonidine for suppression of haemodynamic response to pneumoperitoneum respectively.[4,5] Rise in blood pressure and heart rate was less in both the groups but 4.5 mcg/kg clonidine produced greater fall in mean arterial pressure before induction. Patta S et al used 300µg orally as premedication in a similar design of study conducted by him.[6] Joris et al used very high dose of clonidine (8 mcg/kg) for reducing the level of catecholamine following pneumoperitoneum.[7] Malek et al compared 150 mcg of clonidine as intravenous infusion and intramuscularly.[8] While Singh S et al, Chandrashekaraiah MM et al, Bhandari D et al , Das M et al , Sung et al and Yu et al used 150 mcg of oral clonidine as premedication for maintenance of haemodynamic stability during pneumoperitoneum.[9-13] Based on the above references it was decided to use 150mcg in the present study. It was the same used by Uchida et al and Karmegam G et al.[14,15]

The mean heart rate ranged from 83.3 ± 7.79 to 84.03 ± 10.54 in group C, whereas in group P, it ranged from 84.88 ± 5.81to 88.47 ± 8.63 intraoperatively. When compared to group P, the heart rate was persistently lower in group C in all the intervals. Especially, it was highly significant between 1 minute after intubation till 15 minutes after the release of pneumoperitoneum. This changes in the mean heart rate between the two groups was statistically significant with a p value of <0.05. Decrease in the sympathetic tone by central action of the clonidine may be responsible for the decrease in the heart rate. Presynaptically mediated inhibition of norepinephrine and a vagomimetic action at nucleus tractus solitarius are responsible for bradycardia (Patel et al).[5] Although bradycardia has not been seen in any patient in this study. Findings of this study is also comparable to Sung et al, Yu et al, Das et al, who had found lower perioperative heart rate in clonidine group than in placebo group.[13,16,17]

The mean arterial blood pressure ranged from 92.63 ± 6.63to 89.97 ± 6.54 in group C, whereas in group P, it ranged from 93.8 ± 5.701to 103.08 ± 2.3. The Trend shows statistically significant difference between Group P and Group C starting from 1 minute after intubation up till 30 minutes after the release of pneumoperitoneum. This shows that mean arterial Blood Pressure is better achieved in Group C than Group P. In both groups, an increasing trend of pressures from baseline was noticed at pneumoperitoneum period. These results were similar to the study by Rao AS et al where they observed rise in MAP compared to baseline in group P which was seen maximum after intubation and 15mins after pneumoperitoneum, while in group C, a decline in MAP was seen after intubation and 15mins after pneumoperitoneum. 18 These changes in MAP when compared between the two groups of patients were found to be statistically highly significant.

Though not a part of study objective but this aspect of usage of isoflurane to maintain a mean arterial blood pressure within ±20 mmHg range has shown a significant difference between the two groups. The usage of isoflurane is far less in group C than group P in maintaining mean arterial blood pressure. As there is a significant difference ($p < 0.05$) in isoflurane inspiratory concentration specially at 1 min after intubation, Skin incision, 30 min after creation of pneumoperitoneum and 15 min after release pneumoperitoneum. And also there is a significant difference in expiratory concentration of isoflurane from 1minute after intubation till 3o minutes after the release of pneumoperitoneum between the two groups. So, there is significant decline of usage of isoflurane in patients premedicated with clonidine.

Nausea is found to be more common in group P patients. Vomiting is seen in 1 patient in group C. 3 Patient in group C experienced Hypotension. Cause of nausea might be because of pain and less sedation as seen by Ramsay Hunt Score of 1 in Group C patients.

120 patients have been assessed every 2 hourly for 24hour. Analgesia was given when VAS score >4. The use of Tab diclofenac and Tab Tramadol for postoperative pain has been seen to be statistically difference.

Most of the patients (96%) in group P had sedation score of 1 (Ramsay 1- Anxious, agitated, restless) in all the four-time intervals. In group C, Ramsay score 3 (Responsive to commands only) was achieved by 60% at 90 minutes and Ramsay score 2 by 120 mins. This was not seen in group P at all.

Limitations: The studies have limitations like the single-centre design, and the absence of ASA class III and IV patients, which makes it difficult to apply the investigations to higher-risk populations. These findings need to be validated with additional studies, preferably at the scale of the centres, corroborated by surgery type and comorbidities, and larger studies.

CONCLUSION

On comparing the efficacy of oral clonidine 150mcg, 90 minutes prior to induction with placebo in patients undergoing laparoscopic cholecystectomy surgeries, the study has shown that clonidine was safe, simple and effective in attenuating the stress response to pneumoperitoneum and provides good perioperative hemodynamic stability by means of reduced Heart Rate, controlled Mean Arterial Blood Pressure, minimal side effect, less postoperative cumulative analgesia requirement.

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