Original Research Article

Efficacy of different doses of oral clonidine as premedicationin attenuating haemodynamic response to pneumoperitoneum in patients during laparoscopic cholecystectomy

Abstract :

Laparoscopy procedures have gained an increasing demand over the years and rightly so due to its numerous advantages proving it superior to open surgeries. This is therefore important to all the anaesthesiologists to learn the physiological changes during laparoscopic surgery as well how to manipulate and blunt the hemodynamics as well. We have taken one such drug, an alpha agonist, oral clonidine and compared its different doses to conclude the most efficacious and safe dosage amongst it. From the results we conclude

that, 1) Premedication with oral clonidine is a safe and effective method that provides haemodynamic stability against the neuroendocrine responses due to carboperitoneum in patients undergoing laparoscopic cholecystectomy

2) Escalation of doses from 100 microgram to 150 microgram increases adverse effects and does not enhance efficacy

Keywords : laparoscopy, pneumoperitoneum, clonidine

Introduction

Laparoscopic procedures have been undoubtedly the essence of this modern era in surgical interventions of which laparoscopic cholecystectomy has been the frontrunner. In India alone, it is estimated that 10% of the total population of women and 3% of the men have gallstones. So it one of the most common procedure experienced by an anaesthetist. Over the years, there has been much documentation of the physiological changes that lead to pneumoperitoneum. Many anaesthesiologists have come up with various techniques or drugs which help maintain the haemodynamic stability during the procedure. Although both regional and general

anaesthesia can be administered for the surgery, general anaesthesia remains the gold standard practice. Centrally acting alpha agonist drugs have been proved time and again to produce an effect which lies close to the normal physiology. Clonidine, dexmedetomidine, magnesium sulfate and other drugs have been compared numerous times for the same and though there is not a clear winner yet, it is important to appreciate and dig deeper into one of these drugs and exactly study the effect of it during laparoscopic cholecystectomy.

In order to achieve haemodynamic stability during laparoscopic cholecystectomy, we have explored and studied the effects of three distinct oral clonidine dosages.

Aim and Objectives

To compare three different doses of oral clonidine in attenuating haemodynamic responses to pneumoperitoneum in patients undergoing laparoscopic cholecystectomy

Primary objective:

To compare and evaluate pneumoperitoneum induced changes in heart rate and blood pressure after premedication with oral clonidine

Secondary objectives:

To compare

1. Adverse effect of clonidine like bradycardia and hypotension
2. Requirement of additional opioids perioperatively
3. Postoperative sedation and pain scores
4. Incidence of postoperative nausea, vomiting and shivering

Materials and Methods

This study was a single centred, prospective, double blind randomised control trial for a period of 1.5 years from May 2021 to January 2023, where 90 patients scheduled for laparoscopic cholecystectomy were included.

Inclusion criteria

1. ASA PS I or II
2. Either gender
3. BMI ≤ 30 kg/m^2
4. Age 18 - 60 years

5. Scheduled for laparoscopic cholecystectomy

Exclusion Criteria

1. Refusal to consent for the study
2. History of allergy to clonidine
3. Concomitant use of MAO inhibitors, antihypertensives or opioids
4. Pregnancy
5. Patients with heart disease

There were two observers in our study. Observer 1 (nonblinded) conducted **preanaesthetic** assessment. Observer 2 was an experienced anaesthesiologist blinded to group allocation who performed intubation and recorded the study parameters. Observer 1 carried out the preanaesthesticcheckup and only those fulfilling the eligibility criteria were asked to participate in the study. Consent was obtained from every participant after explaining the trial in the language best understood by them. Patients were premedicated with tab. pantoprazole 40 mg and tab. metoclopramide 10 mg in the morning at 6 am on the day of surgery.

Patients were allocated into three groups based on a computer-generated randomisation table.

1. **Group C 50 - Received 50 mcg of Clonidine**
2. **Group C 100 - Received 100 mcg of Clonidine**
3. **Group C 150 - Received 150 mcg of Clonidine**

Participants in the study were blinded as they would not be aware of the dose of the tablet administered to them. Sixty to ninety minutes before to the commencement of general anaesthesia, clonidine was administered orally with sips of water. Prior to giving oral clonidine, baseline heart rate (HR), mean arterial pressure (MAP), systemic blood pressure (SBP), diastolic blood pressure (DBP), and SpO_2 levels were noted.

Intra-operatively, **as per standard institutional practice**; after confirming NPO, standard ASA monitors were attached with peripheral nerve stimulator (PNS) and pre-induction vitals were recorded. IV fentanyl (2 mcg/kg body wt) was administered. Patients were pre-oxygenated for 3 minutes till ETO_2 >95%, following which IV propofol (2 mg/kg body wt) was used as an induction agent. After check ventilation, patients received IV vecuronium bromide 0.1 mg/ kg body wt. followed by 3 minutes of bag and mask ventilation using oxygen along with 1.2% isoflurane Patient were intubated using appropriate sized portex cuffed endotracheal tube when the train-of-four count was zero. After securing the tube, the maintenance of anaesthesia was done with oxygen and air in ratio of 50:50 along with 1.2% Isoflurane. Intra-operatively, maintenance dose of IV vecuronium bromide was used when required.

Carboperitoneum was created in neutral position following which the table was inclined 10-15 degrees in reverse Trendelenberg position with left lateral tilt. Intra-abdominal pressure (IAP) was maintained below 14 mm Hg throughout the surgery. After insufflation tidal volumes and respiratory changes were made in order to maintain permissive hypercapnia with end tidal carbon dioxide level between 35-45 mmHg.

Systemic arterial pressure (systolic, diastolic and mean), heart rate, peripheral oxygen saturation (SpO_2), end tidal carbon dioxide concentrations ($ETCO_2$) were be noted at the following points of time during surgery:

a. Baseline, before premedication
b. After premedication
c. Prior to induction
d. Before pneumoperitoneum
e. After peritoneal insufflations at 1, 5, 15, 30, 45, 60 minutes
f. After exsufflation
g. After extubation

Additional use of opioids or analgesics, if any during surgery was noted.

Muscle relaxation action was then reversed using IV neostigmine 0.05 mg /kg and glycopyrrolate 0.01 mg/kg body weight and patients were extubated after achieving satisfactory extubation criteria, followed by transfer to the recovery room.

Postoperatively, all episodes of nausea and vomiting (PONV) and drowsiness experienced by the patient during the first 2 hours after anaesthesia were recorded. Rescue antiemetic (IV ondansetron 4mg) was used if patient had nausea or vomiting, and the number of doses required was documented. Post-operative pain and sedation of the patient was monitored for 2 hours using the visual analogue scale (VAS) and the Ramsay sedation score respectively. Any deviation from the aforementioned protocol due to clinical judgment from the anaesthesiologist/surgeon was considered a deviation and excluded from our study.

Ramsay sedation score:

1 – Patient is anxious, agitated, restless

2 - Patient is co-operative, oriented and tranquil

3 - Patient responds to oral commands only

4 - Patient asleep but easily arousable by tactile stimulus

5 - Patient asleep and difficult to arouse by tactile stimulus

6 - Patient deeply sedated, no response to stimulus

We had defined the potential risks and rescue medications in the study as follows:

Table 1: Rescue medications

Bradycardia (HR < 50 beats/min)	IV atropine 0.6 mg bolus
Hypotension (MAP < 60 mm Hg)	IV mephentermine 3 mg bolus + IV fluid bolus (150 - 200 mL)
Tachycardia (HR > 25% of baseline)	Bolus dose of IV fentanyl 25 mcg
Hypertension (MAP > 25% of baseline)	IV propofol 20 - 30 mg bolus
Excessive sedation	Oxygen supplementation and observation till patient fully awake
Nausea +/- vomiting	IV ondansetron 0.1 mg/kg

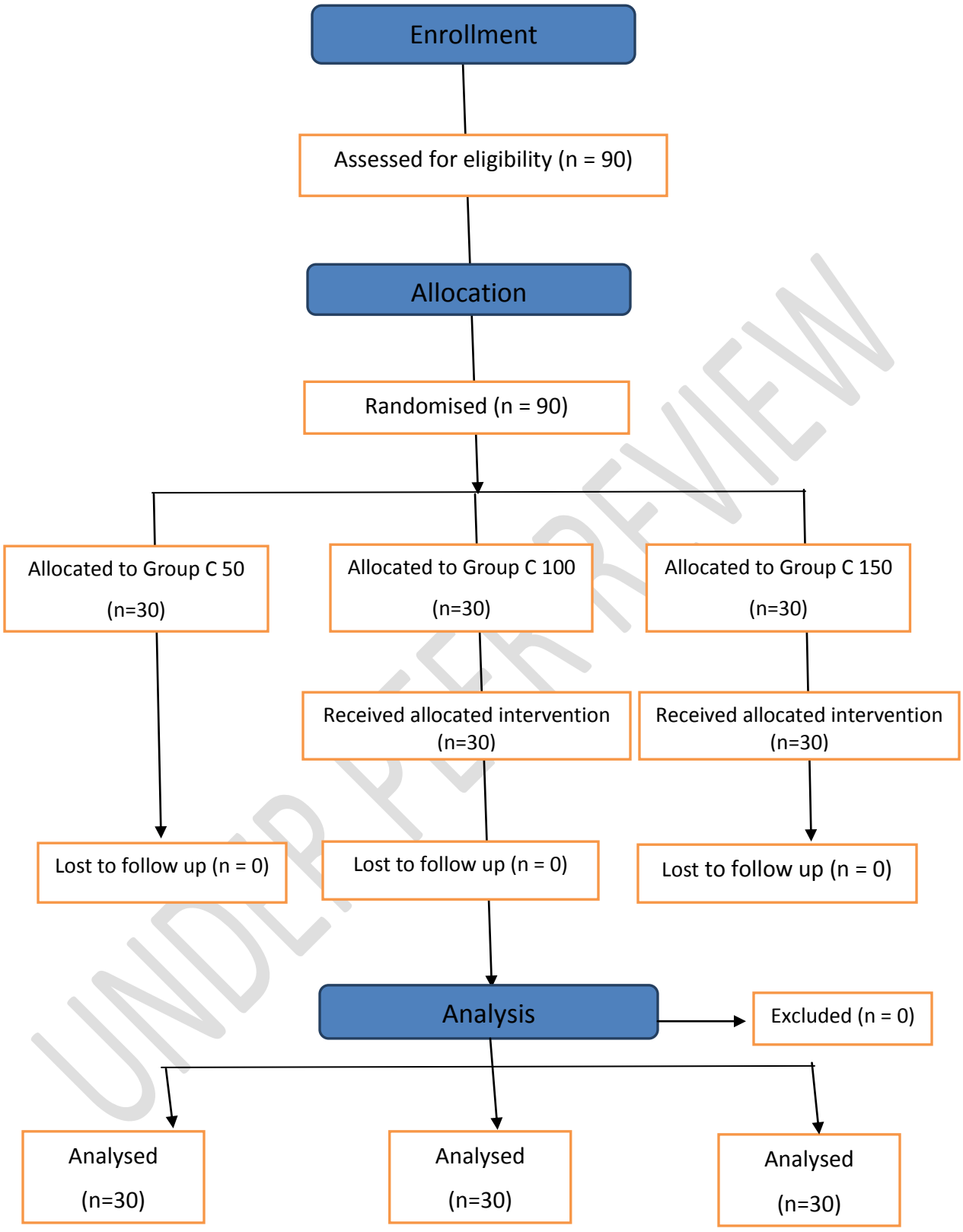

Figure 1: CONSORT flow diagram of participants

RESULTS

Ninety patients were included in the study. Thirty patients in each group.

Table 2: Demographic data

	Group C 50 (n =30)	Group C 100 (n =30)	Group C 150 (n =30)
Age (years) (Mean ± SD)	44.7 ±9.03	41.1 ±8.91	41.1 ±10.1
Gender (M/F)	12/18	19/11	16/14
BMI (kg/m^2) (Mean ± SD)	24.6 ±3.12	24.2 ±4.13	24.5 ±3.57
ASA PS I/II	20/10	11/19	18/12

ASA PS: American Society of Anesthesiologists physical status

BMI: Body Mass Index

Table 3: Changes in Heart rate (beats/min)

Variables	**Group C 50 (n=30) Mean ±SD**	**Group C 100 (n=30) Mean ±SD**	**Group C 150 (n=30) Mean ±SD**	**p value**
Preinduction	65.1 ±8.46	67.3 ±12.9	65 ±9.49	0.626
Before pneumoperitoneum	70.4 ±10.4	69.6 ±7.28	67.9±8.96	0.55
After pneumoperitoneum	73.7 ±12.9	70.6 ±11.5	63.3 ±12.4	0.003* C50 vs C100= 1.00# C 100 vs C 150=0.085# C 50 vs C150=0.003#
5 min	76.2 ±10.6	73 ±14.3	70.3 ±9.88	0.12
15 min	76.3 ±11.9	70.5 ±9.79	69.2 ±11.2	0.029* C50 vs C100= 0.149# C 100 vs C 150=1.00# C 50 vs C150= 0.038#
30 min	73.9 ±12.7	73.7 ±10.7	74.1 ±11.0	0.989

45 min	73.5 ±12.0	74.9 ±12.6	70.6 ±11.4	0.380
60 min	72.9 ±10.3	75.0 ±10.5	71.7 ±11.1	0.498
After exsufflation	74.8 ±10.2	74 ±11.9	74.3 ±9.79	0.946

* ANOVA test, # Independent sample t-test, SD= standard deviation

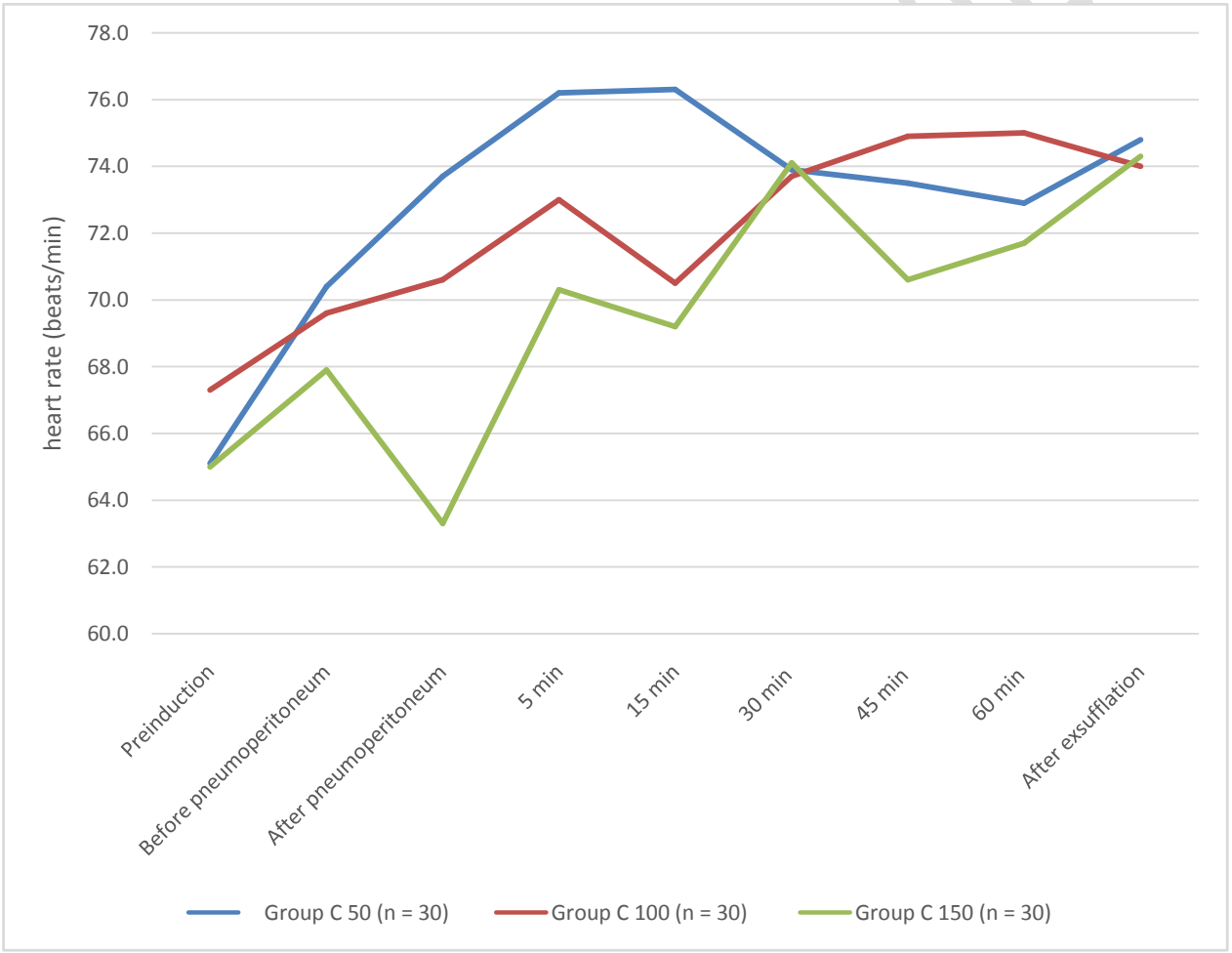

Figure 2: Trends in heart rate

Table 4: Changes in Systolic BP (mmHg)

Variables	Group C 50 Mean ±SD	Group C 100 Mean ±SD	Group C 150 Mean ±SD	p value
Preinduction	127 ±21.3	119 ±19.2	120 ±22	0.26
Before pneumoperitoneum	133 ±24.4	129 ±27.7	126 ±24.7	0.601
After pneumoperitoneum	124 ±23.1	121±5.8	113 ±25.3	0.238
5 min	129 ±18.7	125 ±23.8	124 ±22.1	0.643
15 min	130 ±19.6	128 ±21.9	128 ±15.4	0.900
30 min	130 ±17.5	135 ±18.9	129 ±20.0	0.442
45 min	132 ±15.8	133 ±16.8	129 ±18.3	0.715
60 min	134 ±15.7	133 ±17.9	130 ±18.2	0.578
After exsufflation	137 ±15.5	135 ±17.7	129 ±16.9	0.170

* ANOVA test

Table 5: Changes in Diastolic BP (mmHg)

Variables	Group C 50 Mean ±SD (n = 30)	Group C 100 Mean ±SD (n = 30)	Group C 150 Mean ±SD (n = 30)	p value
Preinduction	71.6 ±17.7	68.5 ±18.8	68.2 ±19.2	0.750
Before pneumoperitoneum	67 ±17.3	61.7 ±17.2	63.9 ±18.7	0.529
After pneumoperitoneum	65.3 ±15.3	60.0 ±15.9	57.8 ±15.3	0.188
5 min	68.2 ±13.9	66.3 ±10.5	66.8 ±11.3	0.835
15 min	64.4 ±9.77	67.2 ±13.6	66.0 ±13.3	0.690
30 min	68.7 ±12.0	67.5 ±12.6	66.5 ±11.3	0.781
45 min	68.1 ±10.4	67.9 ±11.1	67.3 ±12.3	0.956
60 min	72.7 ±9.76	69.0 ±11.1	69 ±10.0	0.317
After exsufflation	70.5 ±10.8	70.5 ±12.3	69.0 ±11.0	0.851

* ANOVA test

Table 6: Changes in Mean BP (mmHg)

Variables	Group C 50 Mean ±SD (n = 30)	Group C 100 Mean ±SD (n = 30)	Group C 150 Mean ±SD (n = 30)	p value
Preinduction	90.2 ±16.3	85.3 ±17.2	85.6 ±19.0	0.509
Before pneumoperitoneum	89.0 ±18.4	84.2 ±18.3	84.6 ±19.2	0.571
After pneumoperitoneum	84.7 ±16.9	80.3 ±17.1	76.2 ±17.5	0.179
5 min	88.5 ±13.7)	85.8 ±13.0)	85.9 ±12.2)	0.680
15 min	86.3 ±10.4)	87.5 ±11.7)	86.8 ±12.5)	0.925
30 min	89.1 ±12.7)	90.0 ±13.5)	87.4 ±12.8)	0.730
45 min	89.3 ±10.5)	89.6 ±12.0)	88.0 ±12.7)	0.854
60 min	93.1 ±9.43)	90.4 ±12.2)	89.2 ±11.1)	0.409
After exsufflation	92.6±9.69)	92.0 ±12.5)	89.0 ±9.99)	0.396

* ANOVA test

Table 7: Adverse events

	Group C 50 (n = 30)	Group C 100 (n = 30)	Group C 150 (n = 30)
Bradycardia	2	3	7
Hypotension	3	9	12
Tachycardia	18	16	7

Adverse effect of bradycardia was seen maximally in group C 150 in 7 out of 30 patients (23%) and 12 out of 30 patients in group C 150 had hypotension (40%)

Table 8: Postoperative sedation and pain scores

Variables	Group C 50 (n = 30)	Group C 100 (n = 30)	Group C 150 (n = 30)
Excessive sedation (Ramsay sedation score>4)	3	6	12
Requiring additional opioid in postop period	1	-	-
Number of patients requiring rescue drug for PONV	1	1	3

In group C 150, 40% of patients had excessive sedation and 10% of patients required rescue medication for post-operative nausea and vomiting.

Discussion

The gold standard treatment for cholelithiasis is laparoscopic cholecystectomy. Similar to this, the most popular and recommended technique for these surgeries continues to be general anaesthesia with endotracheal intubation and controlled ventilation. Even though it is a minimally invasive procedure, there is no such thing as a minimal anaesthesia. The cardiovascular system is affected by pneumoperitoneum, which initially causes a drop in heart rate and cardiac output followed by a rise in heart rate and SVR. This may have harmful consequences, especially for people with heart conditions.[4]

The role of clonidine, both oral and intravenous, has been studied several times before in its role to attenuate pneumoperitoneum responses at various time points throughout the surgery.[16] In this study, we wanted to investigate the optimal dose of clonidine which would achieve the best haemodynamic stability with the least adverse effects perioperatively.

This prospective double-blind trial enrolled 90 adult patients, (30 in each group received 50 mcg, 100 mcg and 150 mcg of oral clonidine), to assess how clonidine premedication affects the surgery's varied timings of the haemodynamic stress response brought by pneumoperitoneum (Figure 1, Table 2).The findings in this study support the beneficial effects of clonidine and highlight the adverse effects of the same.

An alpha-2 agonist, clonidine alters intraoperative cardiovascular and endocrine responses positively to surgical stimuli of laryngoscopy and laparoscopy and reduces central sympathetic output.[4] It has been demonstrated that clonidine lowers plasma catecholamine levels and sympathetic nervous system activity. It is known to cause sleepiness and reduce the need for anaesthetic medications.[10]

The current study showed that administration of 150 mcg oral clonidine (Group C 150) 90 min prior to induction there was a significant drop in heart rate just after pneumoperitoneum and a significant drop after 15 min of pneumoperitoneum compared to 50 mcg (Group C 50) of oral clonidine (Figure 2, Table 3). Changes in systolic or diastolic blood pressure in the three groups were comparable during the procedure (Table 4, 5 & 6).

Passi et al., compared 150 mcg oral clonidine with a placebo group which resulted in significant haemodynamic stability in the clonidine group.[12]

Mrinmoy das et al.[7] using oral clonidine 150 mcg dose as premedicant they found better haemodynamic stability and fewer postoperative cases of nausea vomiting and shivering. But in our study, we had recorded a higher number of patients (10%) suffering from side effects such as PONV and sedation compared to Group C 100 where only 3% of patients' suffered from these events (Table 8). As expected more sedation (Ramsay sedation score ≥ 4)was documented in Group C 150 post operatively (Table 8). Same was also observed by *Yu. et al.*[18] They administered atropine to all patients along with clonidine to negate the adverse effect of clonidine such as bradycardia and hypotension, which was quite evident in our study. In Group C 150 intraoperatively 7 out of the 30 patients had an episode of bradycardia and 12 out of the 30 patients had hypotension (40%, Table 7). Similarly 18 patients in Group C 50 and 16 patients in Group C 100 had tachycardia during different time points in the procedure. Rescue medications were administered to treat it (Table 1). Postoperatively we also observed less opioid consumption (Table 8). Only 1 in 90 patients had an additional requirement, which was comparable to the trial by *kularni et al.*[3] None of the patients had postoperative shivering.

Thus, clonidine can be considered as safe and cost effective drug to attenuate the haemodynamic changes associated with the creation of carboperitoneum for major laparoscopic surgery. A dose of 100 mcg of oral clonidine is found to be optimal in laparoscopic cholecystectomy as it causes fewer adverse effects and provides better haemodynamic stability throughout the surgery compared to doses of 50 and 150 mcg.

Limitations of the trial:

1. A lack of control group in the present trial. Enrollment of control group would have measured the comparable effect and overall attenuation of haemodynamic responses in a better way.
2. High-risk patients with comorbidities were excluded, hence a larger study population may be needed to draw definitive conclusions.

Conclusion

- Premedication with oral clonidine is a safe and effective method that provides haemodynamic stability against the neuroendocrine responses due to carboperitoneum in patients undergoing laparoscopic cholecystectomy
- Escalation of doses from 100 microgram to 150 microgram increases adverse effects and does not enhance efficacy

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