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Effect of Oral Clonidine Premedication on Perioperative Haemodynamic Response and Postoperative Analgesic Requirement for Patients Undergoing Laparoscopic Cholecystectomy

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Abstract
Objectives: *Clonidine is a centrally acting sympatholytic agent with antihypertensive activity. It blunts stress response, provides analgesia, sedation and augments effects of anesthesia. Hence it was hypothesized to be an ideal agent to prevent stress response associated with laparoscopic surgeries and provide post-operative analgesia.*
Patients and Methods: *120 adult patients of ASA physical status I and II scheduled to undergo elective laparoscopic cholecystectomy under general anesthesia were randomly allocated to receive oral clonidine (150 mcg) premedication (Group I, n=60) or placebo (Group II, n=60) 90 mins prior to induction. Intra-operatively they were managed by standard anesthetic agents. The two groups were compared in terms of hemodynamic parameters, sevoflurane concentrations at predetermined intervals during surgery, post-operative time to analgesic request and cumulative analgesic requirements.*
Results: *Mean heart rate, blood pressure and sevoflurane concentration requirements at 1 and 5 mins after intubation, skin incision, start of pneumoperitoneum, 15 and 30 mins after pneumoperitoneum and 15 mins after release of pneumoperitoneum were significantly lower in clonidine group than in placebo group. Time to request of analgesic in clonidine group (150.72 ± 38.47) was significantly higher than that in placebo group(128 ± 28.5 minutes), (p= 0.0004). Total post-operative tramadol requirement in excess of 2 doses was only in 15% of patients in clonidine group vs 60% of patients in placebo group.*
Conclusions: *Administration of oral clonidine premedication resulted in better hemodynamic stability and reduction of intra-operative anesthetic requirement and post-operative analgesia.*
Keywords: *laparoscopic, clonidine, hemodynamic, stress, postoperative, pain*

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I. Introduction

Innovation of Laparoscopic surgery heralded a new era in surgical advancement widely known as minimally invasive surgical procedures. In 1910 Hans Christian Jacobaeus of Sweden, reported the first laparoscopic operation in humans[1]. Laparoscopic techniques gained popularity as they are less painful and allow faster return to normal functional status and has demonstrably better quality-of-life outcomes than conventional open surgery[2]. Philippe Mouret performed the first laparoscopic cholecystectomy in 1987[3]. It was found that Laparoscopic cholecystectomy is superior in maintaining homeostasis and respiratory parameters intraoperatively and postoperatively [4,5] than conventional open surgery.

Laparoscopic procedures require insufflation of CO_2 into the peritoneal cavity, making ports through which instruments are negotiated into the distended abdomen and various changes in patient position according to the type of surgery. Associated neurohumoral factors─ increase in intraabdominal pressure(IAP), pooling of blood in peripheries, stress hormone responses (cortisol, epinephrine and nor-epinephrine) [6, 7, 8] contribute to the resultant hemodynamic fluctuations[9]. Additionally, raised IAP and altered position make ventilation of a patient in laparoscopic surgery difficult [6].

Clonidine is an α_2 adrenergic agonist. It is a central sympatholytic agent with $t_{1/2}$ of 9-12 hr[10]. Clonidine premedication blunts the stress response to surgical stimuli and reduces perioperative hemodynamic instability in multiple surgeries including laparoscopic cholecystectomy[11-14]. Being an analgesic via central[15] and peripheral pathways[16], it reduces the narcotic analgesic requirement for postoperative analgesia[17-19].

These favorable properties suggest that Clonidine premedication could be an effective and safe modality to optimize the tenuous hemodynamics of the patient undergoing laparoscopic cholecystectomy and thereby reduce the intraoperative anesthetic and postoperative analgesic requirements.

II. Materials and Methods

TRIAL DESIGN

After obtaining approval from the hospital research and ethical committee and written informed consent from the patients, 120 adult patients scheduled to undergo laparoscopic cholecystectomy were enrolled for a prospective, randomized, single-blind, placebo-controlled study. The patients were then randomly allocated into two groups of 60 patients each by computer generated random number table :-

Group I patients(60) were administered oral clonidine(150 μg) 90 min before induction of anesthesia.

Group II patients(60) were administered oral vitamin C tablets(placebo) 100 mg 90min before induction of anesthesia.

Inclusion criteria:-

Patients who were included in the study were adult patients of ASA physical status I and II aged 20years to 60 years scheduled for laparoscopic cholecystectomy surgery. 120 such patients were selected and randomly allocated into two groups as described above.

Exclusion criteria:-

Patients not fulfilling the selection criteria, lack of patient consent, known allergy to clonidine, hypertensive and/or diabetic patients, with history of bronchial asthma, severe coronary insufficiency, myocardial infarction, on β-blockers, MAO inhibitors, tricyclic antidepressants, already on clonidine therapy or opioid dependent patients were not included in the study.

During pre-anaesthetic assessment, a detailed history was obtained and thorough physical examination of each patient was carried out to optimize them prior to surgery. History of comorbidities, if any, was recorded.

On arrival in the operating room, all patients' baseline pulse oximetry, ECG, non-invasive blood pressure, heart rate were recorded and a wide bore peripheral intravenous line was established.

Intra–operatively heart rate, non-invasive blood pressure, calculated mean blood pressure (MAP), oxygen saturation by plethysmograshy, end tidal carbon dioxide ($EtCO_2$), concentration of sevoflurane in inspired and expired gas were monitored and recorded at fixed intervals as described subsequently.

The patients were pre-medicated with intravenous glycopyrrolate (0.004mg/Kg), midazolam 0.07mg/Kg and fentanyl 2 mcg/Kg 30 mins before induction. General anesthesia was induced with propofol (2-2.5 mg/Kg) and atracurium (0.5 mg/Kg) was used as the muscle relaxant. Anesthesia was maintained with sevoflurane in 40%O_2 and air mixture. Controlled mechanical ventilation was regulated to maintain endtidal CO_2 between 35-45 mmHg. The mean arterial blood pressure (MAP) was maintained at 20% above or below the pre-operative value by adjusting the concentration of sevoflurane.

In case of more severe haemodynamic fluctuations, medical intervention other than adjustment of sevoflurane was applied. For bradycardia (heart rate lower than 60 bpm), atropine 0.6 mg i.v. was administered. Hypotension (MAP<60 mmHg) was managed with fluid challenges and/or i.v mephentermine (6 mg) bolus. Hypertension (MAP> 110 mmHg) was treated with inj. nitroglycerine 0.5-5μg/kg/min i.v.

Haemodynamics and sevoflurane concentration was recorded prior to induction, 1 min after endotracheal intubation, 5 min after endotracheal intubation, at skin incision, at start of pneumoperitoneum, 15min after institution of CO_2 pneumoperitoneum, 30min after institution of CO_2 pneumoperitoneum and15 min after release of pneumoperitoneum.

Postoperative pain intensity was assessed using a 10-cm visual analog scale (VAS) where zero denoted no pain and 10 denoted intolerable pain. Sedation was assessed using Ramsay sedation score from 1 to 6. Occurrence of any adverse events like nausea, vomiting, hypotension, hypertension, sedation and CO_2 retention was recorded.

VAS, sedation score and adverse events were recorded at 30 min, 60 min, 90 min and 120 min postoperatively. Time to the first request of analgesic (TAR) signifying the period of time elapsed from the end of surgery until the point when first dose of analgesia was given at patient's request (VAS≥ 3) was recorded. Rescue analgesia was given in the form of a combination of inj. diclofenac sodium 75 mg i.v. over 30 min 12 hourly and inj. tramadol(l mg/kg) i.v as requested by patient (i.e. at VAS ≥ 3). Patients were kept pain free in either group. The total dose of post-operative analgesic requirement was also recorded.

The statistical significance for categorical variables was determined by chi-square test. Fisher exact test was used in case one or more expected cell count was less than 5. For continuous variables two sample t-test was applied. Non paramertric "Mann whitney" test was used for data that did not follow a normal distribution. Results were expressed as Mean ± SD (standard deviation). A P value < 0.05 was considered statistically significant. For statistical analysis of data which are not normally distributed like the time to the first dose of

post-operative analgesic, 24-h cumulative analgesic requirement, VAS and sedation score 'Wilcoxon Mann Whitney' test, which is a non-parametric test, was applied. Adverse effects were analysed by Fisher's exact test. Taking $\alpha = 0.05$, for detecting mean time of requirement of analgesic from the end of surgery (185.6 ± 34.13 minutes in group I vs. 100.40 ± 24.33 minutes in group II), taking sample size of 60 in each group, the power of study is approximately 74%.

III. Results

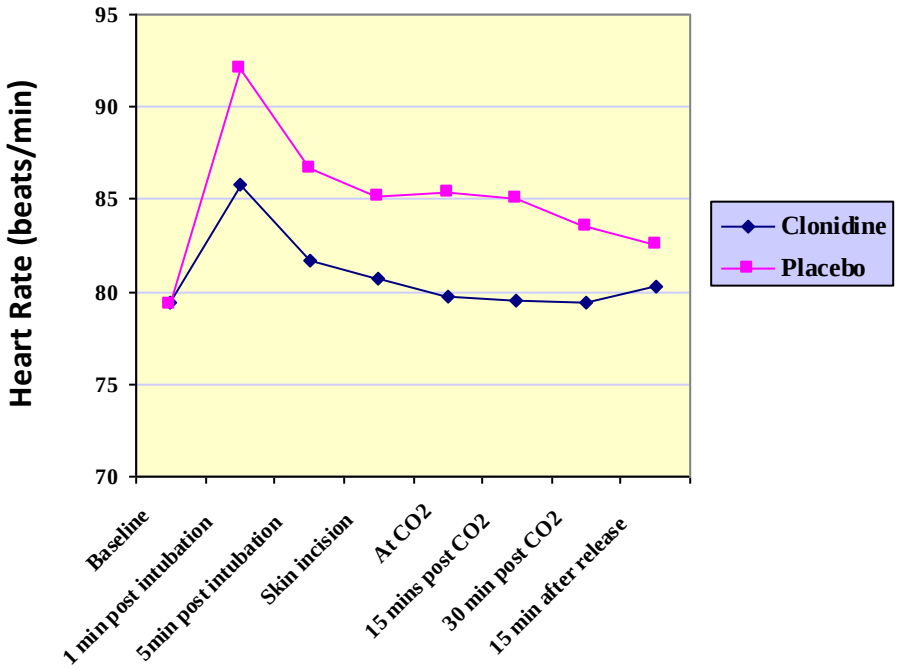
The demographic data of the two groups were compared. Sex was analysed by chi-square test. Age, weight and height were subjected to statistical analysis using two sample t-tests. There were no significant differences between the Clonidine and placebo groups in terms of age, sex, height and weight [Table 1].(P>0.05 in all four parameters).

Table 1: Demographic data

	Group I (Clonidine)	Group II (Placebo)	P value
Sex(M/F)(n/%)	15(33%)/45(67%)	17(39%)/43(71%)	0.83
Age (yr)(mean ± SD)	35.97 ± 10.56	34.2 ± 5.15	0.24
Height (cm)(mean ± SD)	163.82 ± 5.28	162.61 ± 5.28	0.21
Weight (Kg) (mean ± SD)	61.5 ± 6.07	62.72 ± 5.1	0.24

The haemodynamic parameters namely heart rate, mean arterial pressure (MAP) and sevoflurane requirement were also analyzed using two sample t-tests. The basal heart rate was similar in both groups. There was a rise in pulse rate after intubation in both the groups but more in placebo group than in Clonidine group. Throughout the intraoperative period the heart rate remained higher in the placebo group than in the Clonidine group. Mean heart rate in the Clonidine group ranged from 79.38 ± 9.81 to 85.8 ± 8.33 per minute, whereas it ranged between 79.3 ± 6.8 to 92.1 ± 9.4 per minute in the placebo group. Significantly higher heart rate was recorded in the placebo group at 1 minutes and 5 minutes after intubation, at skin incision, following start of pneumoperitoneum and 15 min and 30 minutes after initiation of pneumoperitoneum . The mean heart rates became comparable again 15 minutes after release of pneumoperitoneum. [Graphical representation is presented in Figure 1]

Figure 1: Comparison of heart rate of Clonidine group vs Placebo



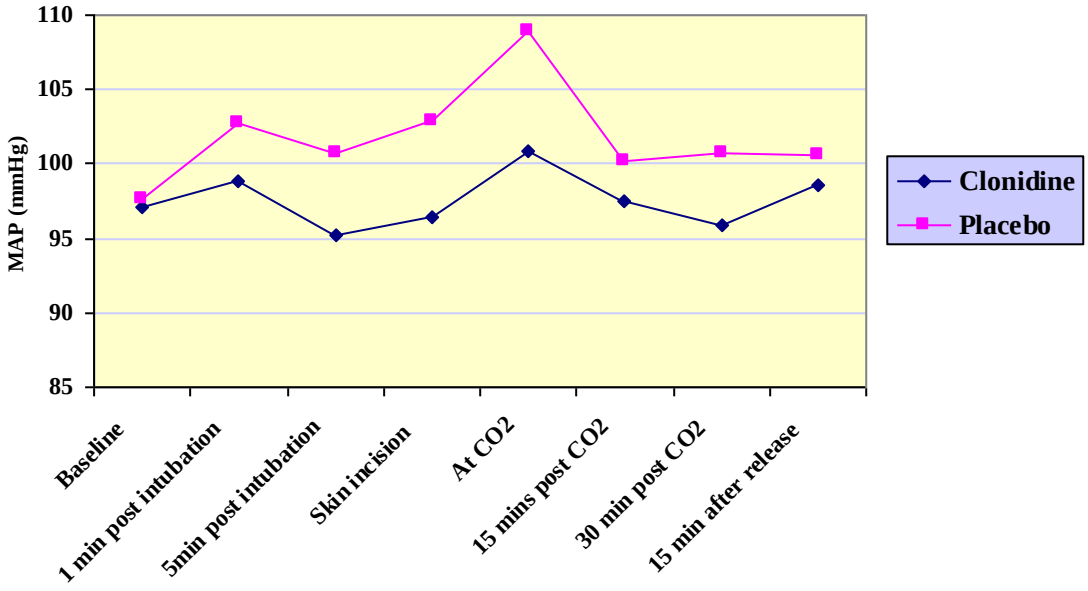
The baseline mean arterial pressures (MAP) of the two groups were not significantly different. Throughout the perioperative period, the MAP of Clonidine group was consistently lower than those who received placebo. In Group I MAP was in the range of 95.17±7.27mmHg to 100.1 ±7.24mmHg while in Group II it was in the range of 97.6 ±6.85mmHg to 108.9 ±6.45mmHg. The maximum rise in MAP was noted at 1

minute after intubation and at the start of pneumoperitoneum in both groups. The difference of the MAP between the two groups was statistically significant ($p<0.05$) at 1 minutes and 5 minutes after intubation, at skin incision, following start of pneumoperitoneum, 15 min and 30 minutes after initiation of pneumoperitoneum. The MAP became comparable again after 15 minutes of releasing pneumoperitoneum [Table 2]. Graphical representation is presented in Figure 2.

Table 2: Mean arterial blood pressure

	Group I	Group II	P value
Prior to induction (mean ± SD)	97.1 ± 6.69	97.6 ± 6.85	0.68
1 min after intubation (mean ± SD)	98.87 ± 6.79	102.68 ± 6.6	0.002
5 min after intubation (mean ± SD)	95.17 ± 7.27	100.78 ± 6.66	<0.0001
Skin incision (mean ± SD)	96.48 ±7.31	102.88 ± 6.59	<0.0001
Start of pneumoperitoneum (mean ± SD)	100.1 ± 7.24	108.9 ± 6.45	<.0001
15 min after pneumoperitoneum (mean ± SD)	97.54 ± 6.7	100.14 ± 6.6	0.03
30 mins after pneumoperitoneum (mean ± SD)	95.92 ± 6.81	100.68 ± 6.6	.0002
15 after release pneumoperitoneum (mean ± SD)	98.64 ± 6.77	100.6 ± 6.69	0.11

Figure 2: Comparison of mean blood pressure of Clonidine group vs Placebo

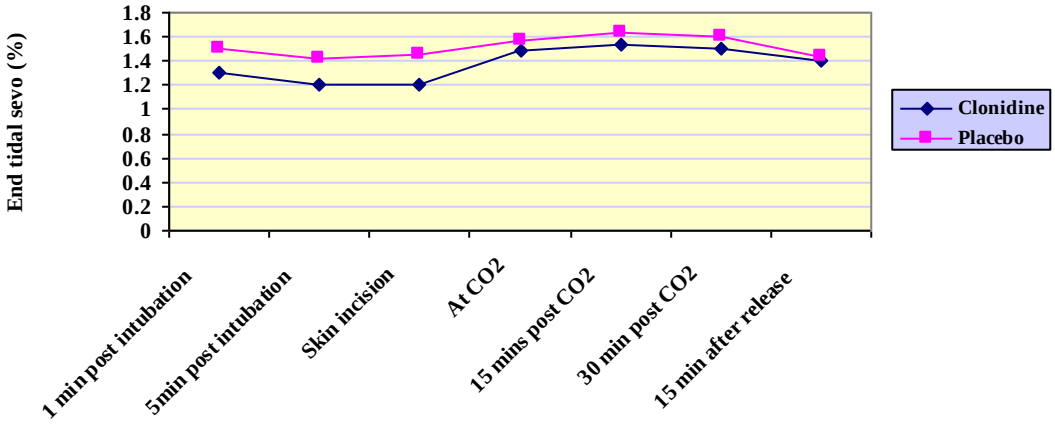


Mean sevoflurane requirement to maintain anesthesia of placebo group was higher than that of Clonidine group throughout the intraoperative period. Significantly higher sevoflurane requirement was recorded at 1 minutes and 5 minutes after intubation and at skin incision time. [Table 3] The rest of the recordings were not statistically significant. Graphical representation of the sevoflurane requirement has been presented in Figure 3.

Table 3 : End tidal Sevoflurane concentration

	Group I (Clonidine)	Group II (Placebo)	P value
1 min after intubation (mean ± SD)	1.3 ± 0.33	1.5 ± 0.24	0.0004
5 min after intubation (mean ± SD)	1.2 ±0.28	1.42 ±0 .22	0.0009
Skin incision (mean ± SD)	1.2 ± 0.28	1.46 ±0.21	0.0002
Start of pneumoperitoneum (mean ± SD)	1.49 ±0.27	1.57 ±0.25	0.08
15 min after pneumoperitoneum (mean ± SD)	1.54 ±0.25	1.64 ±0.28	0.057
30 mins after pneumoperitoneum (mean ± SD)	1.5 ±0.25	1.6 ±0.26	0.06
15 after release pneumoperitoneum (mean ± SD)	1.4 ±0.25	1.44 ±0.19	0.32

Figure 3: Comparison of sevoflurane (percent expired concentration) between group I (Clonidine) and group II (Placebo)



VAS and sedation scores were recorded at 30 min intervals till 2 h postoperatively. Time to the first request of analgesic (TAR) after surgery was significantly longer in the clonidine group (150.72 ± 38.47 mins) than in the placebo group (128 ± 28.5 minutes)(p=0.004)

Total dose of rescue analgesic to keep VAS<3 was monitored in the clonidine group and placebo group [Table 4].The requirement of diclofenac sodium in the clonidine group (71%) was significantly lower than that of placebo group (90%) [p=0.019]. The total diclofenac requirement in excess of 2 doses in 24 hrs was also significantly lower in the clonidine group (20%) than placebo group (41.7%) [p=0.017]. [Figure 4]

Tramadol requirement was also reduced in the clonidine group [Table 5]. Number of patients who did not require even one dose of tramadol was significantly greater in the clonidine group(46.7%) than the placebo group (15%) [p= 0.0003]. Significantly less number of patients in clonidine group required two or more dose of tramadol to alleviate postoperative pain in the first 24 hrs (15% vs 60%) [p< 0.0001]. [Figure 5]

Table 4: Diclofenac sodium requirement :-

	Clonidine group	Placebo group
No Diclofenac	17	6
1 dose of Diclofenac	31	29
≥2 doses of Diclofenac	12	25

Figure 4: Diclofenac requirement postoperative 24 hrs

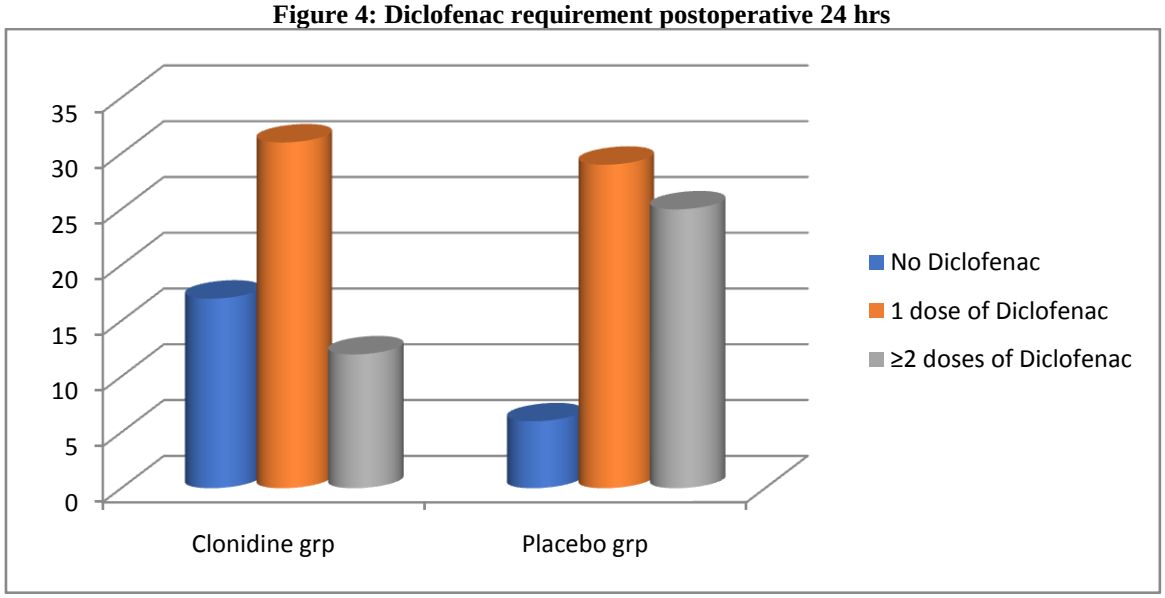
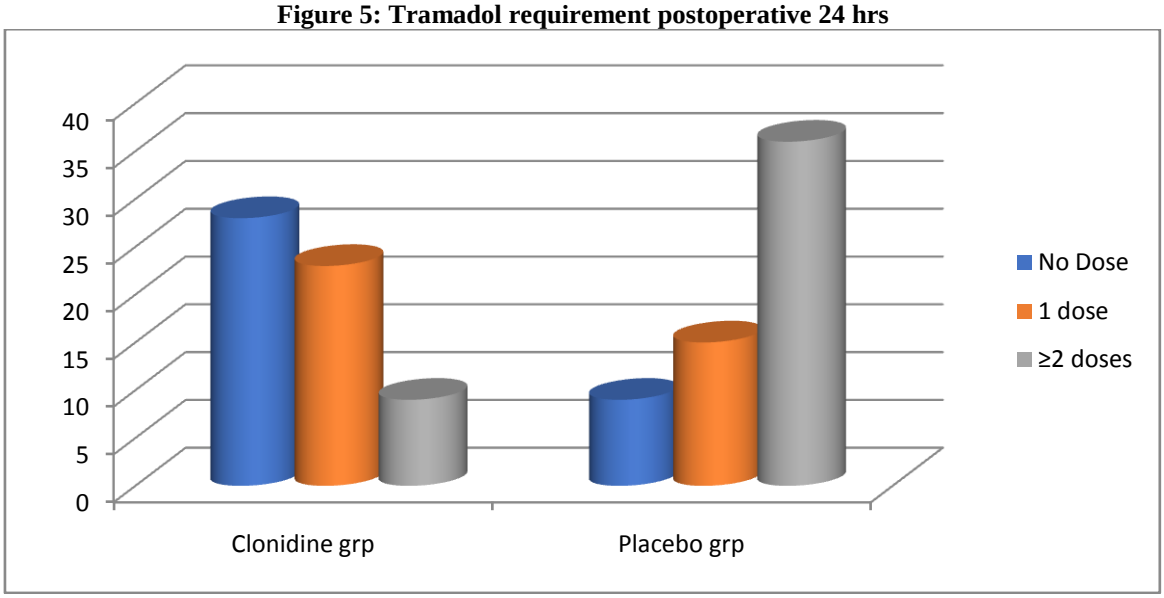


Table 5: Tramadol requirement :-

	Clonidine group	Placebo group
No Tramadol	28	9
1 dose of Tramadol	23	15
≥2 doses of Tramadol	9	36

Figure 5: Tramadol requirement postoperative 24 hrs



Bradycardia and hypotension were found only in the Clonidine group but incidence was not significantly greater than the Placebo group (p>0.05).Bradycardia was treated with iv Atropine and intravenous crystalloid fluid bolus was administered to manage the episodes of hypotension. Incidence of postoperative nausea and vomiting was less in the Clonidine group compared to the control group though not statistically significant (p>0.05). Incidence of postoperative shivering was also higher in the placebo group than in the Clonidine group though statistically insignificant (*P*=0.09). [Table 8]. No incidence of in respiratory depression or hypercarbia was noted in the Clonidine premedicated group. No other adverse effects were noticed.

Table 6: Adverse events

	Clonidine	Placebo	P value
Bradycardia	3	0	0.24
Hypotension	4	1	0.36
PONV	1	6	0.11
Shivering	2	8	0.09

IV. Discussion

Laparoscopic surgeries present a unique challenge to the anesthesiologist in terms of maintaining a stable intraoperative hemodynamic profile of the patient. Choice of anesthetic technique for upper abdominal laparoscopic surgery is mostly limited to general anesthesia with muscle relaxation, tracheal intubation and controlled mechanical ventilation[20]. Raised intra abdominal pressure due to CO_2 insufflation into the peritoneum and various positions used in laparoscopic surgeries lead to inferior vena cava compression, peripheral pooling of blood [21] and increase in venous resistance [22, 23] which thereby compromise venous return and cardiac output [24, 25, 26]. Neurohumoral stress factors like catecholamines, renin, angiotensin II and vasopressin[7, 27] released during laparoscopic cholecystectomy increase systemic vascular resistance and blood pressure[6]. Additionally, stress response to pneumoperitoneum due to stretching of parietal peritoneum further complicates the labile hemodynamics of laparoscopic surgeries [9, 25]. Laparoscopic cholecystectomy is often performed safely as an ambulatory procedure[28]. Therefore it requires a reliable, sustained and safe pain management practice to allow discharge of the patient from post anesthesia care unit.

Clonidine, an α_2 adrenoreceptor agonist, is rapidly and completely absorbed after oral administration and reaches peak plasma concentrations within 60-90 min [10]. This study was conducted on 120 adult patients of ASA physical status I and II undergoing elective laparoscopic cholecystectomy to evaluate the potential of oral clonidine (150mcg), taken 90 minutes before surgery, to maintain a stable intraoperative hemodynamic profile and provide safe and sustained post-operative analgesia.

The study population was randomly divided into two groups such that the demographic parameters like age, sex, weight and height were similar in both the groups. One group was administered oral Clonidine (150

mcg) while the other received a placebo. After comprehensive analysis of the results, it was found that while the baseline heart rate and blood pressure of the two groups were comparable, the cardiovascular response (rise in HR and MAP) to laryngoscopy, intubation and surgical stress was significantly blunted in the clonidine premedicated group. Sudden increases of heart rate associated with pneumoperitoneum, a regular phenomenon observed in the control group was also reduced significantly by clonidine premedication. The MAP values became comparable again after 15 minutes of release of pneumoperitoneum. The end tidal sevoflurane concentration required to maintain anesthesia and restrict fluctuations of hemodynamic parameters was significantly lower in Clonidine premedicated group than in the control group at 1 and 5 mins post intubation and at skin incision.

In a study conducted on adult patients undergoing laparoscopic cholecystectomy Das M. et al observed that premedication with oral Clonidine 150 mcg was an effective method to provide stable haemodynamics against stress response triggered by pneumoperitoneum[13]. Clonidine premedication was found to reduce catecholamine release and attenuate hemodynamic changes during laparoscopy[12]. Sung et al recorded significantly lower need for intraoperative isoflurane in patients premedicated with clonidine along with greater hemodynamic stability and reduced postoperative analgesic requirement[29]. A reduced requirement of propofol to maintain anesthesia and better hemodynamic control with clonidine premedication was also reported when propofol with epidural anesthesia was used for laparoscopic cholecystectomy [30]. On BIS monitoring in laparoscopic cholecystectomy with sevoflurane adjusted to maintain BIS between 40 and 50, IV clonidine pretreatment(3 mcg/Kg)15 minutes before induction provided better perioperative hemodynamic stability than placebo[19].

In the present study, time of the first request of analgesic (TAR) was prolonged in patients receiving clonidine premedication (150.72 ± 38.47 mins) in comparison with the placebo group (128 ± 28.5 mins). More patients in the clonidine group required either no dose (46.6% vs 15%) or only one dose of rescue analgesic (tramadol) (38.3% vs 25%) during the first post-operative 24-h period. Significantly more patients in the placebo group required ≥2 doses of tramadol in the same period (60% vs 15%). Similarly, more patients in the clonidine group required no diclofenac sodium (28.3% vs 10%) or only one dose of diclofenac sodium (51% vs 48%) during the post-operative 24-h period. Significantly greater number of patients in placebo group required ≥2 doses of diclofenac than the clonidine group patients (41% vs 20%). The difference in cumulative postoperative analgesic requirement between clonidine and placebo group was found to be significant.

Pain following laparoscopic cholecystectomy can be attributed mostly to visceral pain [31] and incisional pain [32], irritation of the peritoneum from blood, bile spillage and residual CO_2 used for creation of the pneumoperitoneum [33]. Clonidine exerts its analgesic action by blocking the central pain pathways[15, 16]. Clonidine premedication before laparoscopic cholecystectomy significantly reduced plasma renin activity after pneumoperitoneum thereby providing a stable hemodynamics and decreasing the requirement of perioperative opioids[18]. Singh S and Arora K[3] demonstrated that oral Clonidine premedication prolonged the time interval to the first request of analgesia postoperatively compared to placebo. Total analgesic (Meperidine and Diclofenac) requirement was found to be significantly reduced in the clonidine premedicated group. K. Gupta et al [14] reported an attenuation of hemodynamic response of laryngoscopy and intubation along with reduced requirement of opioid analgesic in the perioperative period on premedication with oral clonidine and pregabalin compared to placebo.

Adverse events noted were bradycardia in 3 patients of the clonidine group which was promptly treated with atropine.No patient of the placebo group had bradycardia. Hypotension was seen in 4 patients of Clonidine group and 1 patient of placebo group immediately after initiation of CO_2 insufflation. It was treated with bolus intravenous crystalloids. However, the frequency of these events was not significantly different between the two groups. Lesser incidence of postoperative shivering was seen in the patients of the Clonidine group than the placebo group (2 vs 8). Postoperative nausea and vomiting noted was also lesser in the Clonidine group than the placebo (1 vs 6) premedicated patients. However, these results were not significantly different between the two groups and larger randomized controlled studies will be required to reach a definite conclusion.

The present study has the limitation of being restricted to ASA I and II adults only, excluding those with risk factors for cardiac diseases. Larger randomized control studies including patients with cardiovascular comorbidities undergoing laparoscopic cholecystectomy will be required before clonidine can be considered as a premedication for such patients.

In conclusion it was found that premedication with oral Clonidine (150 mcg) 90 mins before induction is a simple and cost effective modality to achieve hemodynamic stability and reduce intraoperative anesthetic requirement during laparoscopic cholecystectomy. Additionally, it helps to significantly reduce the postoperative analgesic requirement.

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