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Original Research Article

Effect of oral clonidine premedication on hemodynamic responses during laparoscopic cholecystectomy

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ABSTRACT

Background: Laparoscopic cholecystectomy has rapidly revolutionized gall bladder surgeries and has now become the gold standard for the treatment of cholelithiasis. Even though it has several advantages, creation of pneumoperitoneum for the surgical procedure can have several adverse haemodynamic and respiratory consequences. Thus, the present study was designed to evaluate the type and extent of haemodynamic changes associated with laparoscopic surgery and also to find out the efficacy of oral clonidine premedication in attenuation of such haemodynamic changes.
Methods: In this prospective, randomized, double blinded comparative study, 60 patients between 18-60 years age group, belonging to ASA 1 and ASA 2 categories scheduled for elective laparoscopic cholecystectomy under general anaesthesia were categorized into 2 groups as Group C and Group P with 30 patients in each group. Patients in Group C received premedication with oral clonidine 150µg and Group P received Tab. Vitamin C, 90 minutes prior to surgery. The two groups were compared with respect to haemodynamic parameters and sedation scores.
Results: There was significant increase in all the haemodynamic variables in group P as compared to group C where the variables remained close to baseline values and patients in Group C had mild to moderate sedation without causing respiratory depression.
Conclusions: Oral premedication with clonidine effectively attenuates the haemodynamic response to pneumoperitoneum and also provides sedation without respiratory depression, thus reducing anaesthetic requirement.

Keywords: Clonidine, General anaesthesia, Haemodynamic response, Laparoscopic cholecystectomy, Sedation score

INTRODUCTION

The Laparoscopic surgery also called as minimally invasive surgery (MIS), band aid surgery, keyhole surgery or pinhole surgery is a modern surgical technique in which operations in the abdomen are performed through small incisions (usually 0.5-1.5cm) as compared to larger incisions needed in traditional surgical procedures. In the last few years, laparoscopic surgery has got tremendous popularity because of its several advantages over the conventional laparotomy technique. These include shorter hospital stay, more rapid return to normal activities, less pain, smaller incisions and less postoperative ileus. The prerequisite for laparoscopic surgery is a working space allowing endoscopic access to the peritoneal cavity after insufflation of a gas to create

space between the anterior abdominal wall and the viscera. This space is necessary for the safe manipulation of instruments and organs.

Laparoscopic surgery can also be extraperitoneal, can be gasless with abdominal wall retraction and more recently it may be hand assisted. The preferred anaesthetic technique for upper abdominal laparoscopic surgery is mostly controlled ventilation general anaesthesia with endotracheal tube placement because of patient's discomfort associated with creation of pneumoperitoneum, extent of position changes associated with the procedure and to minimize the risk of acid aspiration if reflux occurs.[1,2]

Although laparoscopic cholecystectomy offers many benefits than conventional cholecystectomy, the use of pneumoperitoneum in combination with position changes causes stress hormone responses which may cause significant haemodynamic and respiratory changes.[3,4] Creation of pneumoperitoneum with carbon dioxide (CO2) insufflation induces a cardiovascular response characterized by abrupt tachycardia, hypertension and increased myocardial oxygen requirements. Carbon dioxide is readily absorbed from the peritoneal cavity into the circulation resulting in hypercarbia and acidosis.[5,6] There are reports of life threatening consequences due to hypercarbia, respiratory acidosis and cardiovascular collapse.[7,8]

Abdominal insufflation causes increase in femoral venous pressure and venous stasis which predisposes to deep vein thrombosis.[9] Increased peripheral vascular resistance, elevated serum catecholamine level, and decreased cardiac output in Laparoscopic cholecystectomy might entail haemodynamic fluctuations which in turn compromise tissue perfusion. Also, many patients complain of shoulder pain after conventional carbon dioxide pneumoperitoneum.[10]

In addition, ventilatory impairment and diaphragmatic dysfunction also occur after laparoscopic cholecystectomy. As the period of operative insufflations of carbon dioxide increases, the risk of cardiovascular and respiratory complications also increases. To counteract these influences of pneumoperitoneum on various systems, various modalities have been considered. These include:

Non-pharmacological methods

- Gasless technique (Abdominal wall lift method)
- Helium and Argon have been tried to replace CO2 for creating pneumoperitoneum.[11,12]

Pharmacological methods

- ß blockers (propanolol)
- Opioids
- Vasodilators (nitroglycerine)
- Magnesium sulphate.[13-15]

α2 adrenergic receptors which are present at central and peripheral sites, serve to modulate a wide variety of physiological and behavioral functions including pain transmission and autonomic outflow. Activation of the α2 adrenergic receptors would reduce peripheral sympathetic outflow, inhibit the release of substance P from the primary afferents of dorsal horn, and suppress the noxiously evoked activity of wide dynamic range neurons which are important for the centripetal transmission of nociceptive impulses.

Clonidine, an imidazoline derivative, is a selective α2 adrenoceptor agonist and has a half-life of 8 to 12 hours. It exerts central sympatholytic effects, reduces peripheral sympathetic discharge and potentiates parasympathetic nervous system. These characteristics suggest that clonidine may be useful in the anaesthetic management of patients undergoing laparoscopic cholecystectomy. Accordingly, we designed this study to observe and evaluate the type and extent of haemodynamic changes associated with laparoscopic cholecystectomy and also to evaluate the effectiveness of oral clonidine premedication in reduction of perioperative stress response, on suppression of hemodynamic upheaval, and on modulation of postoperative pain.

METHODS

The study was a prospective, randomized, double-blinded, comparative study conducted after obtaining institutional ethical committee approval. It was conducted in 60 patients belonging to ASA1 and ASA2 Physical Status of either sex, between 18-60 years age group scheduled for elective laparoscopic cholecystectomy under General Anesthesia. Patients with known severe renal disease, hypertension, ischaemic heart disease, disabling neuro-psychiatric disorders, ASA III and IV physical status, with the history of chronic alcohol consumption, drug abuse and those who are concomitantly taking clonidine, methyldopa, beta blockers, benzodiazepenes, MAO inhibitors were all excluded from the study.

All the patients undergoing elective laparoscopic cholecystectomy were assessed as per the routine preoperative protocol, nil oral status and preoperative investigations were carried out as per the standard guidelines. The study was explained to the patient and informed written consent was obtained from the patient and one relative. Premedication with Tab. omeprazole 20mg was administered orally the night before surgery. Patients were categorized into 2 groups as Group C and Group P, after establishing an intravenous line in the pre-operative room.

Randomization done based on the reference number and randomization table. Patients in Group C received premedication with clonidine 150µg and Group P

received. Vitamin C 100mg, orally 90 minutes prior to surgery. Baseline parameters - heart rate, blood pressure (systolic blood pressure, diastolic blood pressure, mean arterial pressure), respiratory rate and oxygen saturation were noted in the preoperative period for all the patients considered for study. Induction was done with intravenous administration of Fentanyl citrate 2µg/ kg and propofol 1%, 2mg/kg titrated to the response, with simultaneous close watch on pulse and respiration. Inj. Atracurium Besylate 0.5mg/kg was used for neuromuscular blockade. Airway secured with a portex cuffed endotracheal tube of appropriate size and Anaesthesia was maintained with 50% nitrous oxide in oxygen and sevoflurane as the inhalational agent.

Clinically significant haemodynamic changes were managed with intermittent doses of Opiods and inhalational agent. Ventilation was controlled mechanically and ventilator settings adjusted to maintain normocapnia (ETCO2 30 - 37 mmHg) throughout the surgical procedure. Intra-abdominal pressure was maintained between 13 to 15 mmHg after creation of pneumoperitoneum. Heart rate (HR), non-invasive blood pressure (NIBP), five lead electrocardiogram (ECG), oxygen saturation, end tidal carbon dioxide (ETCO2), minimal alveolar concentration of sevoflurane (MAC), end tidal nitrous oxide (ETN2O), inspiratory nitrous oxide (INSN2O), inspired oxygen fraction (FiO2) were monitored intraoperatively. Neuromuscular blockade was reversed with a combination of intravenous neostigmine 0.05mg/kg and glycopyrrolate 0.008 mg/kg.

Extubation was done after adequate reversal of neuromuscular blockade as determined by the clinical signs, adequate unassisted spontaneous breathing (tidal volume >400 ml/min) and eye opening on command. Patients were monitored postoperatively in recovery room for one hour. Occurrence of complications such as bradycardia and hypotension during the observation period were noted in both the groups.

Parameters assessed were

A. Sedation: 90 minutes after premedication and post operatively

- Degree of sedation - Score
- Asleep - 3
- Drowsy, quiet and easily arousable - 2
- Awake but uncommunicative - 1
- Awake and talkative - 0

B. Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure at following points of time during the surgery:

- Baseline
- 2 prior to induction
- Immediately after intubation
- Three minutes after intubation
- Before pneumoperitoneum
- 10 minutes after pneumoperitoneum
- 10 minutes after the release of carbon dioxide
- 10 minutes after extubation.

Statistical analysis

Data analysis was done by repeated measures ANOVA in each group separately for heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure outcomes. We used Bonferroni's adjustment for multiple comparisons. Since we had seven a-priori comparisons, we used $P < 0.007$ (0.05/7) as the cut-off value for considering statistical significance so as to ensure overall alpha error of less than 0.05. In addition, we conducted two-way ANOVA with repeated measures on one factor (time) to compare the above outcomes at all time points. Again, since there were 8 a-priori comparisons, we used $P < 0.006$ (0.05/8) as the cut-off value for determining statistical significance according to Bonferroni's correction for multiple comparisons.

RESULTS

A comparaive study consisting of 60 patients of which 30 patients belonged to group C and 30 patients in group P. There was no statistically significant difference in the groups in erms of age, gender, ASA physical status (Table 1, 2 and 3) and baseline haemodynamic variables (heart rate systolic blood pressure, diastolic blood pressure, ean arterial pressure).

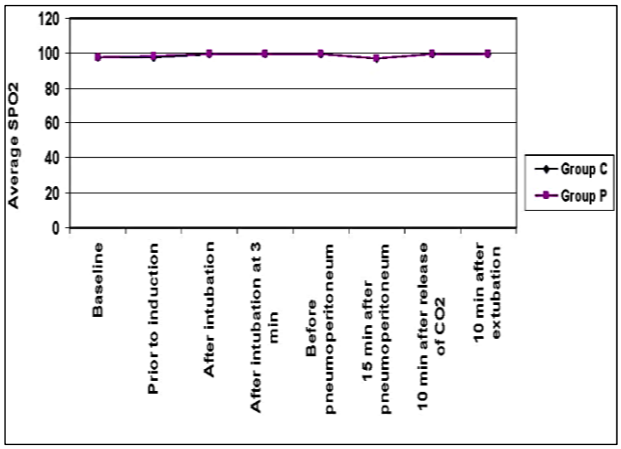

Figure 1: Comparison of SPO2 in study groups.

The above Figure shows that the SPO2 was maintained within a narrow range with mean values between 97 and 99.83 in both the group.

The oxygen saturation (SpO2) and End tidal CO2 (EtCO2) were maintained within a narrow range with P>0.05 throughout the observation period (Figure 1 and 2).

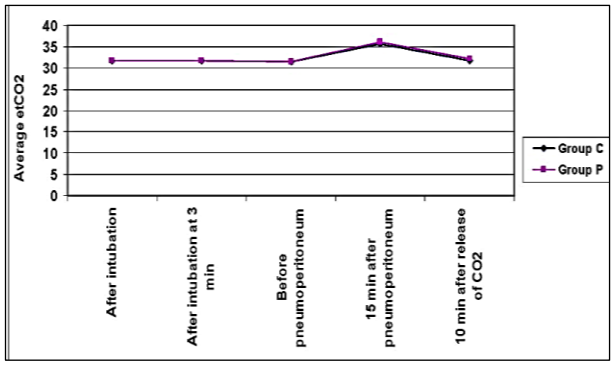

Figure 2: Comparison of EtCO2 in study groups.

The Figure 2 shows EtCO2 values during the observation period were maintained between 30 mmHg and 37 mmHg in both the groups. Thus, both the groups were comparable with P>0.05

Thus, both the groups were statistically comparable. The haemodynamic parameters and respiratory rate were monitored and assessed at different points of time in the observation period. Comparing between groups, at all time points after baseline, the heart rate was significantly lower and closer to baseline levels in clonidine group compared to placebo (P < 0.001 for each comparison) as seen in Table 4.

Table 1: Comparison of age in study groups.

Parameters	Group C	Group P	Z-Value	P-Value
	Mean±SD (n=30)	Mean±SD (n=30)		
Age (years)	40.07±8.56	40.67±7.99	0.28	>0.05

SBP was significantly higher in the placebo group before intubation, after intubation, before and after pneumoperitoneum and after release of CO2 (P < 0.001 for each comparison) as seen in Table 5.

Table 2: Sex wise distribution of cases in study groups

Sex	Group C	Group P	Total
Male	10 (16.67)	9 (15)	19 (31.67)
Female	20 (333.33)	21 35)	41 (68.33)
Total	30 (50)	30 (50)	60 (100)

But, it remained similar in both the groups again after extubation. DBP was significantly higher in the placebo group compared to clonidine group (P < 0.001 for each comparison) before and after intubation, before and after pneumoperitoneum and after extubation. But, it remained similar in both groups after release of CO2 (P = 0.10) as seen in Table 6.

Table 3: ASA grade wise distribution of cases in study groups.

ASA grade	Group C	Group P	Total (%)
I	22 (36.67)	20 (33.33)	42 (70)
II	8 (13.33)	10 (16.67)	18 (30)
Total	30 (50)	30 (50)	60 (100)

Table 4: Comparison of heart rate in study groups.

HR (beats/min)	Group C		Group P		P value (comparison between two groups)
	Mean±SD	P Value*	Mean±SD	P Value*	
Baseline	78±5.09	-	78.9±5.42	-	>0.05
Prior to induction	73.8±7.16	<0.001**	79.3±8.47	0.57	<0.001**
After intubation	84±8.47	<0.001**	97.50±11.73	<0.001**	<0.001**
After intubation at 3 min	78.73±6.96	0.35	86.43±10.58	<0.001**	<0.001**
Before pneumoperitoneum	74.03±5.64	<0.001**	78.53±7.41	0.70	0.002**
10 min after pneumoperitoneum	78.5±5.51	0.40	99.7±10.78	<0.001**	<0.001**
10 min after release of CO2	73.33±4.93	<0.001**	79.37±6.64	0.44	<0.001**
10 min after extubation	82.17±7.96	0.001**	99.1±15.54	<0.001**	<0.001**

At all-time points after baseline, except after release of CO2, the MAP was significantly lower in clonidine group compared to placebo group (P < 0.001 for each comparison) as seen in Table 7.

Table 5: Comparison of systolic blood pressure in study groups.

SBP (mmHg)	Group C		Group P		P value (comparison between two groups)
	Mean±SD	P Value*	Mean±SD	P Value*	
Baseline	121.57±4.52	-	122.63±5.49	-	>0.05
Prior to induction	115.03±4.57	<0.001**	120.53±8.47	0.02	<0.001**
After intubation	124.33±4.94	0.01	140.4±9.64	<0.001**	<0.001**
After intubation at 3 min	119.1±3.79	0.001**	133.2±8.63	<0.001**	<0.001**
Before pneumoperitoneum	114.37±4.43	<0.001**	122.9±6.35	0.75	<0.001**
10 min after pneumoperitoneum	121.1±5.83	0.60	141.9±8.32	<0.001**	<0.001**
10 min after release of CO2	114.03±5.19	<0.001**	121.33±7.39	0.32	<0.001**
10 min after extubation	121.9±3.92	0.66	124.9±4.22	0.09	0.20

Table 6: Comparison of diastolic blood pressure in study groups.

DBP (mmHg)	Group C		Group P		P value (comparison between two groups)
	Mean±SD	P Value*	Mean±SD	P Value*	
Baseline	76.2±4.49	-	76.1±4.93	-	>0.05
Prior to induction	73.03±4.47	<0.001**	78.27±6.71	0.01	<0.001**
After intubation	83.93±5.33	<0.001**	96±8.56	<0.001**	<0.001**
After intubation at 3 min	79.6±3.53	<0.001**	89.8±7.44	<0.001**	<0.001**
Before pneumoperitoneum	78.06±3.71	0.03	84.8±4.97	<0.001**	<0.001**
10 min after pneumoperitoneum	83.2±5.07	<0.001**	101.63±6.24	<0.001**	<0.001**
10 min after release of CO2	77.33±5.05	0.28	79.93±5.58	0.004**	0.10
10 min after extubation	79.73±3.87	0.001**	90.9±6.66	<0.001**	<0.001**

Table 7: Comparison of mean arterial pressure in study groups.

Mean BP (mmHg)	Group C		Group P		P value (comparison between two groups)
	Mean±SD	P Value*	Mean±SD	P Value*	
Baseline	91.32±4.31	-	91.61±4.59	-	>0.05
Prior to induction	87.03±4.19	<0.001**	92.36±6.83	0.01	<0.001**
After intubation	97.4±4.20	<0.001**	110.8±8.32	<0.001**	<0.001**
After intubation at 3 min	92.77±3.15	0.04	104.3±7.20	<0.001**	<0.001**
Before pneumoperitoneum	90.17±3.59	0.12	97.5±4.74	<0.001**	<0.001**
10 min after pneumoperitoneum	95.83±4.68	<0.001**	114.1±6.01	<0.001**	<0.001**
10 min after release of CO2	89.57±4.52	0.06	93.73±5.72	0.004**	0.009
10 min after extubation	93.79±3.52	0.006	105.6±6.59	<0.001	<0.001**

*Within group comparison, campared with baseline value; ** Statistically significant after Bonferroni's adjustment for multiple comaparisons.

Table 8: Pre-operative Sedation score in study groups.

Sedation score	Group C	Group P	Total
0	9	26	35
1	19	4	23
2	2	0	2
Total	30	30	60

Table 9: Post-operative sedation score in study groups.

Sedation score	Group C	Group P	Total
0	12	22	34
1	18	8	26
Total	30	30	60

Sedation was assessed on a four-point scale in both the groups (Table 8 and 9) and we found that - In group C, 19 patients had score of 1 and 2 patients had score of 2 as compared to 4 and 0 respectively in group P in the preoperative period and 18 patients had score of 1 in group C as compared to 8 in group P when observed upto 1 hour in the postoperative period. Median sedation score was found to be 1 in Group C and 0 in Group P at both points of time.

Using Mann-Whitney U test (P<0.05) we found that there is a significant difference between Group C and Group P with respect to sedation score.

Respiratory rate was comparable in both the groups at baseline, prior to induction and 10 minutes after extubation with P> 0.05 as seen in Table 10.

Table 10: Comparison of respiratory rate in study groups.

Respiratory rate	Group C	Group P	Z Value	P Value
	Mean±SD (n=30)	Mean±SD (n=30)		
Baseline	13.53±1.07	13.5±1.17	0.12	>0.05
Prior to induction	13.57±1.01	13.87±1.14	0.99	>0.05
10 min after extubation	13.27±1.01	13.2±1.06	0.25	>0.05

DISCUSSION

Laparoscopic cholecystectomy has rapidly revolutionized gall bladder surgeries and has now become the gold standard for the treatment of cholelithiasis. Even though, it has several advantages, induction and maintenance of pneumoperitoneum required for the surgical procedure has several adverse haemodynamic and respiratory consequences. Various pharmacological agents were chosen to prevent such changes associated with pneumoperitoneum. Clonidine, an imidazoline derivative, a selective α2 adrenoceptor agonist, exerts central sympatholytic effects and has a half-life of 8-12 hours. It increases perioperative circulatory stability in patients undergoing laparoscopic cholecystectomy, blunts the stress response to surgical stimuli and reduces the analgesic, anaesthetic requirement in the perioperative period. Considering all these observations, the present study was designed to evaluate the type and extent of haemodynamic changes associated with laparoscopic surgery and also to find out the efficacy of oral clonidine premedication in attenuation of such haemodynamic changes.

In present study, the study groups were similar in terms of patient characteristics, baseline haemodynamic variables and anaesthetic protocol followed. Ventilatory settings were adjusted to maintain SpO2 and EtCO2 within a narrow range in both groups. Therefore, monitoring the haemodynamic variables (heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure) helped to evaluate the type and extent of changes associated with pneumoperitoneum and positional changes in laparoscopic cholecystectomy and also to evaluate the effectiveness of clonidine in attenuation of such responses. In our study, there was significant increase in all the above haemodynamic variables in group P, maximum after pneumoperitoneum as compared to group C where the variables remained close to baseline values. Also, there was early return of the variables to the baseline values in group C as compared to group P. Attenuation of haemodynamic responses were highly significant and consistent with clonidine group compared to placebo group at all intervals of monitoring.

There was no change in respiratory rate in the preoperative or postoperative period in both the groups. Thus, we can conclude that clonidine does not cause respiratory depression. There was a significant difference between the two groups in sedation score with clonidine showing mild to moderate sedation prior to induction and mild sedation in post-operative period as compared to placebo. This sedation was helpful in perioperative period to alleviate anxiety.

Among the two study groups superiority of clonidine over placebo for providing sedation without respiratory depression and thus reducing anaesthetic requirement and attenuation of sympathetic response to pneumoperitoneum was evident and statistically highly significant.

Carabine et al, did a dose response study in which clonidine was administered in doses of 0.1mg, 0.2mg, 0.3mg. Clonidine 0.2mg produced a significant reduction in anxiety.[16] Sedation increased with increasing dose. Also, the decrease in arterial pressure and heart rate with clonidine 0.3mg were significant as compared with other groups.

Das et al carried out a prospective randomised study to investigate the clinical efficiency of oral clonidine premedication in prevention of haemodynamic response associated with pneumoperitoneum.[17] Group I received clonidine 150µg and Group II received ranitidine 150µg orally 90 minutes prior to induction of anaesthesia. They found significant rise in heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure in group II which was more than 20% from the baseline. Increase in blood pressure was noted in group I also, following intubation and pneumoperitoneum but it never crossed the baseline value. They concluded that oral clonidine premedication is safe and effective that provides stable haemodynamics and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy with

an added advantage of reduction in post-operative complications such as nausea, vomiting and shivering. The trends in our study corroborated with the above study.

Sung CS et al studied the clinical efficacy of oral clonidine premedication in anaesthesia and analgesia in patients undergoing laparoscopic cholecystectomy.[18] They observed haemodynamic stability during pneumoperitoneum with 150µg oral clonidine and reduced requirement of isoflurane by 30%.

Singh et al designed a study to evaluate the effects of oral clonidine premedication on haemodynamic response and modulation of post-operative pain in patients undergoing laparoscopic cholecystectomy.[19] They administered 150µg oral clonidine as premedicant in patients undergoing laparoscopic cholecystectomy and found that it improved perioperative haemodynamic stability and reduced in intra operative anaesthetic and post-operative analgesic requirements. Study findings were in concordance with the above studies.

CONCLUSION

Oral clonidine is a simple and cost-effective form of premedication with ease of administration in patients undergoing laparoscopic cholecystectomy. It effectively attenuates the haemodynamic response to pneumoperitoneum and results in better haemodynamic stability.

Oral clonidine also produces dose dependent sedation, it can be considered as an anaesthetic adjuvant as it alleviates perioperative anxiety leading to decreased amount of anaesthetic requirement during perioperative period.

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