EFFECT OF INTRAVENOUS CLONIDINE AS PREMEDICATION ON HAEMODYNAMIC RESPONSE DURING LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

BACKGROUND

Laparoscopic approach has revolution in the surgical field, first introduced by Phillippe Mouret for laparoscopic cholecystectomy in 1987.¹ During laparoscopic cholecystectomy due to pneumoperitoneum, position of patient may adversely affect the haemodynamic and ventilator parameters. During laparoscopic cholecystectomy, there were chances of haemodynamic instability and cardiovascular changes right from the pre-operative to post-operative period too. Both mechanical and neurohumoral factors, increased intra-abdominal pressure contribute to haemodynamic instability and Catecholamines mediate increase in Systemic Vascular Resistance (SVR) during PNO. It stimulates a series of hormonal and metabolic changes that constitute stress response. Clonidine is centrally acting selective partial α_2 adrenoceptor agonist that acts by reducing responsiveness of peripheral vessels to vasoactive substances and to sympathetic stimulation having sedative, anxiolytic, stress reducing, anaesthetic and analgesic properties.

The present study was designed to evaluate the effect of intravenous clonidine as premedication on reduction of perioperative stress response, maintaining haemodynamic stability and on modulation of postoperative pain in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

MATERIALS AND METHODS

After approval from the Institutional Ethics Committee of Agartala Govt. Medical College and GBP Hospital, patient with ASA physical status I and II scheduled to undergo laparoscopic cholecystectomy from Jan. 2012 to Dec. 2012, where 100 patients are divided into two groups (Group C - have received intravenous clonidine 1.5 microgram/kg body wt. before induction and Group S - have received intravenous saline before induction). Heart rate, mean arterial pressure, systolic and diastolic BP, oxygen saturation percentage and end tidal CO₂ measured.

RESULTS

Hence mean HR, systolic BP, diastolic BP were comparable among the groups during pre-operative, after infusion of drug, after induction, 5 mins. after release of pneumoperitoneum and post-operatively 5 mins. after extubation and statistically significant difference was found at most of the time in mean HR between the two groups after intubation, 1 min, 10 mins., 20 mins., 30 mins. and 40 mins. of creating pneumoperitoneum. Post-operative analgesia by VAS scores are significantly lower in clonidine group ($p < 0.05$) without the use of analgesic for up to 4 hours, whereas in control group with the use of analgesic VAS scores are higher.

CONCLUSION

Intravenous clonidine at 1.5 $\mu\text{g/kg}$ as premedication maintains heart rate, mean arterial blood pressure as it gives more haemodynamic stability, which also reduces VAS scores and prolongs the requirement of first postoperative analgesic.

KEYWORDS

Clonidine, Premedication, Haemodynamic, Laparoscopic Cholecystectomy.

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BACKGROUND

Phillippe Mouret introduced laparoscopic cholecystectomy in 1987.^{1,2} The operation table is tilted to 15° reverse Trendelenburg position. Creation of pneumoperitoneum with CO₂ and positional changes adversely affect the haemodynamic and ventilatory parameters. During laparoscopic cholecystectomy, there is reduced venous

return; Left Ventricular End Diastolic (LVED) pressure is reduced, intrathoracic pressure is increased, right atrial and Pulmonary Artery Occlusion Pressure (PAOP) increased during insufflations. There is increase in Mean Arterial Pressures (MAP), Heart Rate (HR) And Increased Systemic Vascular Resistance (SVR) and pulmonary vascular resistance.³ Intra-abdominal Pressure (IAP) should be maintained at 6 - 12 mmHg, which should not be allowed to exceed 15 mmHg. After PNO, necessary changes in ventilator settings like tidal volume and respiratory rate should be done to maintain normocapnia.³

Both mechanical and neurohumoral factors contribute to haemodynamic instability, increased intra-abdominal pressure leads to release of norepinephrine, epinephrine and cortisol.^{4,5,6} Catecholamines mediate increase in Systemic Vascular Resistance (SVR) during PNO.

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Pain after laparoscopic cholecystectomy may be quite severe, particularly in early postoperative period either from incision or visceral manipulation and traction on nerve, vascular injury, peritoneal inflammation, presence of gas in abdomen, release of inflammatory mediators.

Clonidine is centrally acting selective partial α_2 adrenoceptor agonist. The drug acts by reducing responsiveness of peripheral vessels to vasoactive substances and to sympathetic stimulation. Clonidine has been shown to have sedative, anxiolytic, anaesthetic and analgesic properties. It reduces the requirement of anaesthetic and analgesic agents and also attenuates the stress responses associated with anaesthesia and surgery, thus conferring haemodynamic stability.^{7,8,9} These characteristics suggest that clonidine may be useful in the anaesthetic management of patients undergoing laparoscopic cholecystectomy.

The present study was designed to evaluate the effect of intravenous clonidine as premedication on reduction of perioperative stress response, maintaining haemodynamic stability and on modulation of postoperative pain in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

Aims

To evaluate the effects of intravenous clonidine as premedication on haemodynamic response during laparoscopic cholecystectomy.

Objectives

1. To stabilise the haemodynamic fluctuations during laparoscopic cholecystectomy using intravenous clonidine as premedication.
2. To compare the haemodynamic status of control subjects with the study subjects.
3. To evaluate the effect of intravenous clonidine on postoperative analgesic requirement.

MATERIALS AND METHODS

The present study was carried out after approval from the Institutional Ethics Committee of Agartala Govt. Medical College and GBP Hospital. A written consent form was obtained from all patients included in the study.

Study Area

GB Panth Hospital, Department of Anaesthesiology, laparoscopic surgical operation theatre.

Study Population

This study was carried out in patient with ASA physical status I and II scheduled to undergo laparoscopic cholecystectomy.

Exclusion Criteria

Patients with history of hypertension, ischaemic heart disease, terminal valvular insufficiency, AV conduction block, increased intracranial pressure, asthma, patient on MAO inhibitor, methyldopa, beta blockers, benzodiazepine was excluded from the study.

Study Period - Jan. 2012 to Dec. 2012.

Sample Size - 100 patients were divided into two groups.

Study Design

Randomised double-blind prospective study between two groups of patients scheduled to undergo laparoscopic cholecystectomy.

Sample Design

100 ASA physical status I and II, aged 18 - 60 yrs. undergoing elective laparoscopic cholecystectomy were randomly assigned to one of the two groups containing 50 patients.

Group C - Have received intravenous clonidine 1.5 microgram/kg body wt. before induction.

Group S - Have received intravenous saline before induction.

Parameters to be Studied

The following Parameters were taken into consideration for study.

Demographic Variables

- a. Age in years.
- b. Sex (male/female)
- c. Body weight (kg).
- d. Height (cm).

Vitals

1. Heart rate (beats per minute).
2. Mean arterial pressure (mmHg by non-invasive tech).
3. Systolic and diastolic BP (mmHg by non-invasive tech).
4. Oxygen saturation percentage.
5. End tidal CO₂.

All these readings were taken at following Intervals

- Pre-operative.
- After infusion of study drug.
- 1 min. after induction.
- 1 min. after intubation.
- 1 min. after pneumoperitoneum.
- 10 mins. after pneumoperitoneum.
- 20 mins. after pneumoperitoneum.
- 30 mins. after pneumoperitoneum.
- 40 mins. after pneumoperitoneum.
- 5 mins. after release of pneumoperitoneum.
- 5 mins. after extubation.

Statistical Sample Analysis

We calculated a sample size of 100 patients by using Software Statistical Version 6 (Tulsa, Oklahoma StatSoft Inc., 2001).

Blinding Method

The patients were unaware of which of the study drugs they received. The anaesthesiologist who was not otherwise participating in the trial prepared the study drugs into a ready-to-use form and administered to the patients.

RESULTS

Demo-graphic Parameter	Group Mean $\pm$ SD	Statistical Test Results	Statistical Significance
Age (Years)	Group C: 37.74 $\pm$ 11.69 Group S: 40.22 $\pm$ 5.61	Unpaired t-test P = 0.179	Not Significant
Height (cm)	Group C: 154 $\pm$ 8.15 Group S: 153.44 $\pm$ 6.8	Unpaired t-test P = 0.711	Not Significant
Weight (kg)	Group C: 57.32 $\pm$ 6.77 Group S: 55.7 $\pm$ 6.44	Unpaired t-test P = 0.223	Not Significant
Duration of Surgery (min.)	Group C: 43.96 $\pm$ 4.08 Group S: 43.42 $\pm$ 6.94	Unpaired t-test P = 0.647	Not Significant
Sex (Male: Female)	Group C: 39: 11 Group S: 35: 15	Chi-square test P = 0.3618	Not Significant
ASA Physical Status (I:II)	Group C: 38: 12 Group S: 38: 12	Chi-square test P = 1.00	Not Significant

Table 1. Table comparing Demographic Profile of the Study Groups

The above table shows that all the demographic parameters were comparable among the groups.

Variables	Group C N = 50 (mean±SD)	Group S N = 50 (mean±SD)	Statistical Test Results	Signi- ficance
Baseline/Before Premedication	83.26± 9.89	79.6± 9.4	Unpaired t-test P = 0.061	Not Significant
After Infusion of Study Drug/ Saline	83.22± 11.54	80.44± 11.97	Unpaired t-test P = 0.240	Not Significant
After Induction	82.44± 12.54	78.78± 10.90	Unpaired t-test P = 0.116	Not Significant
1 min After Intubation	86.92± 12.46	91.96± 12.36	Unpaired t-test P = 0.045	Significant
1 min After Pneumo- peritoneum	89.64± 15.69	96.12± 13.80	Unpaired t-test P = 0.031	Significant
10 mins. After Pneumo- peritoneum	89.24± 14.19	96.94± 13.00	Unpaired t-test P = 0.006	Significant
20 mins. After Pneumo- peritoneum	90.34± 15.10	98.08± 13.46	Unpaired t-test P = 0.008	Significant
30 mins. After Pneumo- peritoneum	88.72± 14.51	94.7± 11.42	Unpaired t-test P = 0.024	Significant
40 mins. After Pneumo- peritoneum	87.38± 13.05	94.86± 10.99	Unpaired t-test P = 0.003	Significant
5 mins. After Pneumo- peritoneum Release	86.16± 12.29	90.30± 10.50	Unpaired t-test P = 0.073	Not Significant
5 mins. After Extubation (P.O.)	81.24± 8.19	81.00± 6.00	Unpaired t-test P = 0.868	Not Significant

Table 2. Table comparing Heart Rate in (Beats/Minute) among the Study Groups at Specified Points of Time during Surgery (N = 100)

Applying the 2-tailed unpaired t-test (assuming equal variance) between the mean of HR of each group $p < 0.05$ was found at after intubation 1, 10, 20, 30, 40 mins. after creating pneumoperitoneum and $p > 0.05$ was found preoperatively, after infusion of clonidine or normal saline after induction of 5 mins. after release of pneumoperitoneum and postoperatively 5 mins. after extubation. Hence, mean HR were comparable among the groups during pre-operative after infusion of drug, after induction, 5 mins. after release of pneumoperitoneum and postoperatively 5 mins. after

extubation and statistically significant difference was found at most of the time in mean HR between the two groups after intubation, 1 min., 10 mins., 20 mins., 30 mins., 40 mins. of creating pneumoperitoneum.

Variables	Group C N = 50 (Mean ± SD)	Group S N = 50 (Mean ± SD)	Statistical Test Results	Significance
Baseline/Before premedication	125.42± 11.66	122.30± 7.27	Unpaired t-test P = 0.112	Not Significant
After Infusion of Study Drug/Saline	119.26± 13.48	122.10± 7.30	Unpaired t-test P = 0.193	Not Significant
After Induction	117.36± 14.06	118.02± 9.93	Unpaired t-test P = 0.787	Not Significant
1 min After Intubation	132.62± 15.59	139.16± 14.85	Unpaired t-test P = 0.014	Significant
1 min after Pneumo- peritoneum	132.16± 14.84	147.92± 12.54	Unpaired t-test P = 0.000	Significant
10 mins. After Pneumo- peritoneum	135.22± 12.58	148.38± 13.12	Unpaired t-test P = 0.000	Significant
20 mins. After Pneumo- peritoneum	136.02± 12.84	148.96± 13.34	Unpaired t-test P = 0.000	Significant
30 mins. After Pneumo- peritoneum	134.02± 13.75	143.38± 9.80	Unpaired t-test P = 0.000	Significant
40 mins. After Pneumo- peritoneum	133.98± 13.87	139.30± 8.37	Unpaired t- test P = 0.022	Significant
5 mins. After Pneumo- peritoneum Release	130.86± 11.76	135.16± 7.62	Unpaired t-test P = 0.032	Significant
5 mins. After Extubation (P.O.)	123.50± 5.23	124.96± 3.02	Unpaired t-test P = 0.091	Not Significant

Table 3. Table comparing Systolic Blood Pressure (mmHg) among the Study Groups at Specified Points of Time during Surgery (N = 100)

Applying the 2-tailed unpaired t-test (assuming equal variance) between the mean of SBP of each group, $p < 0.05$ was found after intubation, 1 min. after pneumoperitoneum, 10 mins. after pneumoperitoneum, 20 mins. after pneumoperitoneum, 30 mins. after pneumoperitoneum, 40 mins. after pneumoperitoneum and 5 mins. after release of

pneumoperitoneum and $p > 0.05$ was found preoperatively, after infusion of drug, after induction and postoperatively 5 mins. after extubation. Hence, during preoperative after infusion of drug, after induction and postoperative mean SBP were comparable among the groups and statistically significant difference was found at most of the time in mean SBP between the two groups after intubation, during various stages of pneumoperitoneum and 5 mins. after release of pneumoperitoneum.

Variables	Group C N = 50 (mean ±SD)	Group S N = 50 (mean ±SD)	Statistical Test Results	Significance
Baseline/Before Premedication	83.06± 6.74	82.90± 5.70	Unpaired t-test P = 0.899	Not Significant
After Infusion of Study Drug/Saline	81.66± 10.11	82.74± 5.41	Unpaired t-test P = 0.507	Not Significant
After Induction	81.18± 12.03	80.32± 6.50	Unpaired t- test P = 0.658	Not Significant
1 min After Intubation	89.12± 8.86	94.56± 5.41	Unpaired t-test P = 0.001	Highly Significant
1 min. after Pneumo- peritoneum	90.36± 11.40	100.46± 7.70	Unpaired t-test P = 0.000	Highly Significant
10 mins. After Pneumo- peritoneum	90.88 ± 9.38	99.96± 8.99	Unpaired t-test P = 0.000	Highly Significant
20 mins. after Pneumo- peritoneum	91.72± 8.30	100.22± 6.56	Unpaired t-test P = 0.000	Highly Significant
30 mins. After Pneumo- peritoneum	89.86± 8.77	97.88± 6.39	Unpaired t-test P = 0.000	Highly Significant
40 mins. After Pneumo- peritoneum	90.20± 8.76	95.86± 5.68	Unpaired t-test P=0.000	Highly Significant
5 mins. After Pneumo- peritoneum Release	86.98± 7.09	91.62± 6.36	Unpaired t-test P = 0.001	Significant
5 mins. After Extubation (P.O.)	83.08± 3.54	84.94± 3.18	Unpaired t-test P = 0.006	Significant

Table 4. Table comparing Diastolic Blood Pressure (mmHg) among the Study Groups at Specified Points of Time during Surgery (N = 100)

Applying the 2-tailed unpaired t-test (assuming equal variance) between the mean of DBP of each group, $p < 0.05$ was found at after intubation, during different time intervals after creating pneumoperitoneum, 5 mins. after release of pneumoperitoneum and postoperatively 5 mins. after extubation and $p > 0.05$ was found preoperatively, after infusion of drug and after induction. Hence, during pre-operative, after infusion of drug and after induction mean DBP were comparable among the groups and statistical significance was found at most of the time in mean DBP between the two groups after intubation, during different time intervals after creating pneumoperitoneum, 5 mins. after release of pneumoperitoneum and postoperatively 5 mins. after extubation.

Variables	Group C N = 50 (mean± SD)	Group S N = 50 (mean± SD)	Statistical Test Results	Significance
Baseline/before Premedication	97.08± 7.86	96.02± 5.80	Unpaired t-test P = 0.445	Not Significant
After infusion of Study Drug/Saline	93.66± 8.59	95.86± 5.40	Unpaired t-test P = 0.129	Not Significant
After Induction	93.62± 11.62	93.02± 7.38	Unpaired t-test P = 0.759	Not Significant
1 min. after Intubation	103.26± 10.22	108.90± 7.57	Unpaired t-test P = 0.002	Significant
1 min. after Pneumo- peritoneum	104.76± 11.78	116.12± 9.08	Unpaired t-test P = 0.000	Significant
10 mins. after Pneumo- peritoneum	105.64± 9.94	115.98± 9.79	Unpaired t-test P = 0.000	Significant
20 mins. after Pneumo- peritoneum	106.96± 9.53	116.40± 8.05	Unpaired t-test P = 0.000	Significant
30 mins. after Pneumo- peritoneum	104.40± 9.92	113.08± 7.13	Unpaired t-test P = 0.000	Significant
40 min after Pneumo- peritoneum	104.66± 9.88	110.18± 5.62	Unpaired t-test P = 0.001	Significant
5 mins. after Pneumo- peritoneum Release	101.24± 9.86	105.96± 6.09	Unpaired t-test P = 0.001	Significant
5 mins. after Extubation	96.50± 3.86	98.32± 2.82	Unpaired t-test P = 0.008	Significant

Table 5. Table comparing Mean Arterial Pressure (mmHg) among the Study Groups at Specified Points of Time During Surgery (N = 100)

Applying the 2-tailed unpaired t-test (assuming equal variance) between the mean of MAP of each group $p < 0.05$ was found at after intubation, during different time intervals after creating pneumoperitoneum, 5 mins. after release of pneumoperitoneum and postoperatively 5 mins. after extubation and $p > 0.05$ was found preoperative, after infusion of drug and after induction. Hence, during pre-operative, after infusion of drug, after induction and MAP were comparable among the groups and statistically significance was found at most of the time in mean MAP between the two groups after intubation, during different time intervals after creating pneumoperitoneum and 5 mins. after release of pneumoperitoneum and postoperatively 5 mins. after extubation.

Time Interval	Group C N = 50 (mean±SD)	Group S N = 50 (mean±SD)	Statistical Test Results	Significance
5 mins. to 2 hrs.	3.00±00	5.12±0.799	Unpaired t-test P = 0.000	Highly significant
2 hrs. to 4 hrs.	3.46±0.503	3.76±0.431	Unpaired t-test P = 0.002	Significant
4 hrs. to 8 hrs.	3.92±0.724	4.96±0.880	Unpaired t-test P = 0.000	Highly Significant
8 hrs. to 12 hrs.	3.40±0.495	3.46±0.503	Unpaired t-test P = 0.549	Not Significant

Table 6. Table comparing Post-Operative VAS Scores among Group C and Group S

The table shows that VAS scores are significantly lower in clonidine group ($p < 0.05$) without the use of analgesic for up to 4 hours, whereas in control group with the use of analgesic VAS scores are higher.

Time Interval	Group C (N = 50)		Group S (N = 50)		Statistical Test Results
	Number	%	Number	%	
5 min. to 2 hrs.	0	00%	100	100%	Chi-square = 57.44 DF = 2 P < 0.001
2 hrs. to 4 hrs.	6	12%	29	38%	
4 hrs. to 8 hrs.	31	62%	36	72%	

Table 7. Table comparing Postoperative Analgesia in Group C and Group S

Requirement of first dose of analgesic was prolonged in clonidine group for up to 4 hrs. post-operatively ($p < 0.001$). Inj. Diclofenac sodium was used as rescue analgesic in both the groups.

DISCUSSION

Laparoscopic cholecystectomy is the gold standard surgical procedure for treatment of chronic cholecystitis. Laparoscopic surgery has proved immensely as a standard surgical procedure in gynaecological and surgical fields. To reduce the incidence and severity of these potentially hazardous changes in haemodynamic status during laparoscopy, several interventions have been tried. These interventions include fluid loading or tilting the patient slight head-down position before peritoneal insufflations, use of compression device in lower extremities, use of vasodilating anaesthetic agent like isoflurane or other vasodilating substance like nitroglycerin and nicardipine and use of α_2 adrenergic agonists like clonidine (or dexmedetomidine and β -blocking agents and remifentanyl alternative techniques of CO₂ pneumoperitoneum such as use of inert gases like helium, argon or gasless laparoscopy.

Clonidine, an imidazoline derivative is a selective α_2 adrenergic agonist. It is a potent antihypertensive drug. It produces a fall in the heart rate and blood pressure associated with decreased SVR and cardiac output. Studies using oral clonidine (150 μ g) administered 60 to 90 mins. before induction of anaesthesia have shown promising results in minimising the haemodynamic changes during laparoscopic surgery. Although, the bioavailability of clonidine after oral administration is over 90%, it requires 2 to 4 h to develop its peak effect necessitating its ingestion at least 2 h prior to induction to have clinically desirable actions. As intravenous clonidine has an onset of action within 15 mins. (with a peak at 30 mins.), its administration half an hour before induction of anaesthesia is a better option.

In this perspective, a randomised, double-blind, prospective, placebo-controlled study was conducted at Agartala Govt. Medical College and GBP Hospital, Agartala in which 100 patients were randomly allocated into 2 groups. One group (Group C) received clonidine intravenously and the other group (Group S) received normal saline intravenously. The haemodynamic changes during perioperative period were recorded.

A study^{10,11} reported significant rise in MAP in Group P (Placebo) as compared to Group C (clonidine 150 mcg) after intubation (113.56±16.33 mmHg vs 93.70±7.33; $p < .001$), after PNO at 15 mins. as (114.13±16.57 mmHg vs 93.83±8.10; $p < 0.001$), at 30 mins. (108.60 ± 15.11 mmHg vs 93.64±8.40; $p = 0.033$). In our study, similar significant rise in MAP was noted in Group S as compared to Group C at intubation (108.90 ± 7.57 mmHg vs 103.26±10.22 mmHg; $p = 0.002$) after PNO at 10 mins. (115.98±9.79 mmHg vs 105.64±9.94 mmHg; $p < 0.001$), at 20 mins. (116.40±8.05 mmHg vs 106.96±9.53 mmHg; $p < 0.001$) and at 30 mins. (113.08±7.13 mmHg vs 104.40±9.92 mmHg; $p < 0.001$).

The study also reported significant rise in HR in Group P compared to Group C after intubation (107.76 ± 14.06 bpm vs 87.26 ± 11.34 bpm; $p = 0.006$), after PNO at 15 mins. as (96.06 ± 21.81 bpm vs 75.76 ± 10.07 bpm; $p = 0.008$), at 30 mins. (94.76 ± 19.79 bpm vs 75.70 ± 10.20 bpm; $p = 0.004$), which were comparable to present study that is at intubation (91.96 ± 12.36 bpm vs 86.92 ± 12.46 bpm; $P = 0.045$), after PNO at 15 mins. (96.94 ± 13.00 bpm vs 89.24 ± 14.19 bpm; $P = 0.006$), at 20 mins. (98.08 ± 13.46 bpm vs 90.34 ± 15.10 bpm; $P = 0.008$), and at 30 mins. (94.7 ± 11.42 bpm vs 88.72 ± 14.51 bpm; $P = 0.024$).

In the same study, significant rise in HR was observed in control group compared to clonidine group (before PNO; 70 bpm vs 62 bpm), at (15 mins. after PNO; 82 bpm vs 70 bpm) and at (30 mins.; 83 bpm vs 78 bpm) ($p < 0.001$). In our study also mean HR was significantly raised in Group S, that is before PNO (91.96 ± 12.36 bpm vs 86.92 ± 12.46 bpm; $P = 0.045$), after PNO at 10 mins. (96.94 ± 13.00 bpm vs 89.24 ± 14.19 bpm; $P = 0.006$), at 20 mins. (98.08 ± 13.46 bpm vs 90.34 ± 15.10 bpm; $P = 0.008$), and at 30 mins. (94.7 ± 11.42 bpm vs 88.72 ± 14.51 bpm; $P = 0.024$).

In another study,⁹ significant rise in MAP was observed in control group compared to clonidine group (8 mcg/kg) (Pre-induction; 98 mmHg vs 75 mmHg), at (15 mins. after PNO; 90 vs 72 mmHg), at (30 mins. 89 mmHg vs 70 mmHg): ($p < 0.001$). In our study also mean MAP raised significantly in Group S as compared to Group C, that is before PNO (108.90 ± 7.57 mmHg vs 103.26 ± 10.22 mmHg; $p = 0.002$), after PNO at 10 mins. (115.98 ± 9.79 mmHg vs 105.64 ± 9.94 mmHg; $p < 0.001$), at 20 mins. (116.40 ± 8.05 mmHg vs 106.96 ± 9.53 mmHg; $p < 0.001$), and at 30 mins. (113.08 ± 7.13 mmHg vs 104.40 ± 9.92 mmHg; $p < 0.001$).

In the same study, significant rise in HR was observed in control group compared to clonidine group (at pre-induction 74 bpm vs 66 bpm), (at 15 mins. after PNO; 76 bpm vs 63 bpm) and at (30 mins.; 89 bpm vs 7p bpm). In our study also mean HR was significantly raised in Group S, that is before PNO (91.96 ± 12.36 bpm vs 86.92 ± 12.46 bpm; $P = 0.045$), after PNO at 10 mins. (96.94 ± 13.00 bpm vs 89.24 ± 14.19 bpm; $P = 0.006$), at 20 mins. (98.08 ± 13.46 bpm vs 90.34 ± 15.10 bpm; $P = 0.008$), and at 30 mins. (94.7 ± 11.42 bpm vs 88.72 ± 14.51 bpm; $P = 0.024$).

In the present study, VAS scores were significantly lower in clonidine group in the first 12 hours, 5 to 15 mins. 3.00 ± 00 ($P = 0.000$), 15 mins. to 2 hrs. 3.48 ± 0.505 ($P = 0.004$), 2 hrs. to 4 hrs. 4.04 ± 0.786 ($P = 0.000$), 4 hrs. to 12 hrs. 3.40 ± 0.495 ($P = 0.549$).

Up to 4 hrs. post-operatively, VAS scores were significantly lower without the use of analgesic for the first 4 hrs. compared to control group with the use of diclofenac sodium as analgesic. These findings suggest that clonidine group of patients did not require analgesic for up to 4 hrs. P.O.

A study¹² where patients were pre-medicated with clonidine 150 mcg orally displayed greater haemodynamic stability perioperatively with VAS scores statistically significant and the postoperative analgesic requirement was significantly less (1.5 ± 1.3 vs 2.2 ± 1.3) dose and the time for the first dose of analgesic was prolonged (411 ± 565 vs 264 ± 441 mins.) in clonidine group $p < 0.005$, whereas in our study VAS scores were significantly lower in Group C with statistical significance $p < 0.001$ up to 12 hrs. and the time for

first analgesic was prolonged up to a minute postoperatively ($p < 0.001$).

A study¹³ to assess the effects of clonidine 100 mcg on postoperative pain and morphine consumption after abdominal hysterectomy showed that total morphine consumption and VAS scores were lower in clonidine group up to 48 hrs. compared to control group and morphine consumption was less in clonidine group 20 ± 1.28 vs 26.9 ± 2.8 ($p < 0.05$); comparable to our study VAS scores were significantly lower in Group C with () up to 12 hrs. and up to 24 hrs. and time for first postoperative analgesic was prolonged up to a minute post-operatively.

In another study,¹⁴ twenty ASA physical status 2 or 3 patients recovering from abdominal surgery were allocated randomly to receive either epidural fentanyl (100 micrograms in 10 mL isotonic saline; EF group) or epidural fentanyl (same dose) plus epidural clonidine (150 micrograms; EF + C group) in isotonic saline solution. Pain was evaluated at 15 mins. for 2 hours and 30 mins. for 4 hours. Maximum pain relief was 68.2 (24.1%) of initial VAS scores in clonidine group compared to 14.7 (25.2%) in saline group and duration of analgesia was 210 ± 87 mins. in clonidine group compared to 45 ± 27 mins. in saline group. In our study, VAS scores were significantly lower up to 12 hrs. with statistical significance ($p < 0.001$).

Overall, the present study showed that administration of IV clonidine at $1.5 \mu\text{g/kg}$ as premedication in patients undergoing laparoscopic cholecystectomy provides stable perioperative haemodynamics, protection against adverse haemodynamic response triggered by pneumoperitoneum reduction in post-operative pain and requirement of analgesic.

CONCLUSION

From the results of the present study following conclusion may be drawn with the use of intravenous clonidine at $1.5 \mu\text{g/kg}$ as premedication.

1. Maintains heart rate during pneumoperitoneum.
2. Mean arterial blood pressure is maintained with clonidine as it gives more haemodynamic stability.
3. Reduces VAS scores and prolongs the requirement of first post-operative analgesic.

REFERENCES

- [1] Vecchio R, MacFayden BV, Palazzo F. History of laparoscopic surgery. Panminerva Med 2000;42(1):87-90.
- [2] Hodgson C, McClelland RM, Newton JR. Some effects of peritoneal insufflation of carbon dioxide at laparoscopy. Anaesthesia 1970;25(3):382-90.
- [3] Antony C, Noreen D. Intraabdominal laparoscopic surgery: anaesthetic implication in wylie and Churchill Davidsons. A practice of anesthesia. 7th edn. London; Hodder Arnold Publications 2003.
- [4] Koivusalo AM, Lindgren L. Effects of CO₂ pneumoperitoneum for laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2000;44(7):834-41.
- [5] Joris JL, Noirot DP, Legrand MJ, et al. Hemodynamic changes during laparoscopic cholecystectomy. Anaesth Analg 1993;76(5):1067-72.

- [6] Karayiannakis AJ, Makri GG, Mantzioka A, et al. Systemic stress response after laparoscopic or open cholecystectomy: a randomized trial. *Br J Surg* 1997;84(4):467-71.
- [7] Ghignone M, Calvillo O, Quintin L. Anaesthesia & hypertension: the effect of clonidine on perioperative hemodynamics & isoflurane requirements. *Anaesthesiology* 1987;67(1):3-10.
- [8] Quintin L, Duke PC, Kehler CH, et al. Effect of clonidine on narcotic requirement & hemodynamic response during induction of fentanyl anaesthesia & endotracheal intubation. *Anesthesiology* 1986;64(1):36-42.
- [9] Joris J, Chinche JD, Lamy M. Clonidine reduced hemodynamic changes induced by pneumoperitoneum during laparoscopic cholecystectomy. *Br J Anaesthesiology* 1995;74(suppl):A124.
- [10] Sung CS, Lin SH, Chan KH, et al. Effect of oral clonidine premedication on perioperative hemodynamic response & post-operative analgesic requirement for patients undergoing laparoscopic cholecystectomy. *Acta Anaesthesiol Sin* 2000;38(1):23-9.
- [11] Ruffolo R. Physiology and biochemistry of the peripheral autonomic nervous system. In: Wingard L, Brody T, Larner J, et al. (edtr). *Human Pharmacology: Molecular-to-Clinical*, St. Louis: Mosby-Year Book; 1991:77.
- [12] Farquhar-Smith WP. Anatomy, physiology and pharmacology of pain. *Anaesthesia and Intensive Care Medicine* 2008;9(1):3-7.
- [13] Joris JL, Chiche JD, Canivet JL, et al. Haemodynamic changes induced by laparoscopy and their endocrine correlates: effects of clonidine. *J Am Coll Cardiol* 1998;32(5):1389-96.
- [14] Odeberg S, Ljungqvist O, Svenberg T, et al. Haemodynamic effects of pneumoperitoneum and the influence of posture during anaesthesia for laparoscopic surgery. *Acta Anaesthesiol Scand* 1994;38(3):276-83.