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STUDY OF EFFECT OF CLONIDINE PREMEDICATION IN HAEMODYNAMIC CHANGES DURING LAPROSCOPIC CHOLECYSTECTOMY.

Anaesthesiology

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ABSTRACT

Purpose: Laparoscopic cholecystectomy is the treatment of choice for cholelithiasis. The pneumoperitoneum used for laparoscopic procedures leads to significant impairment of cardiopulmonary function. Clonidine has been shown to reduce perioperative haemodynamic instability. The aim of the study was to investigate the clinical efficiency of oral clonidine premedication in prevention of haemodynamic response associated with pneumoperitoneum.

Methods: This randomized double blind study started with institute ethics committee approval. Sixty ASA 1 and ASA 2 patients undergoing elective laparoscopic cholecystectomy with no cardiovascular co-morbidity were enrolled for the study and received either tab clonidine 150 mcg [group C-30] or placebo drug Ranitidine [group P- 30] orally one hour before the induction. Heart rate, systolic blood pressure, diastolic pressure and mean arterial pressure were recorded. The data obtained was analyzed using student's-test, ANOVA and Chi-square test.

Results: There is significant rise in heart rate was observed following pneumoperitoneum in Group P as compared to Group C (99.23±14.02 Vs 81.26±8.40 bpm). Similarly, rise in systolic arterial pressure (143.63±19.60 Vs 119.6±10.06 mm Hg), diastolic arterial pressure (99.23±14.02 Vs 81.26±8.40 mm Hg) and mean arterial pressure (114.13±16.57 Vs 93.83±8.107 mm Hg) was more in Group P following pneumoperitoneum. Nitroglycerine drip was started in 33.3% patients in Group P to control intraoperative hypertension. Incidence of postoperative nausea-vomiting and shivering was also less in Group C.

Conclusion: From our study we found that oral clonidine 150mcg can effectively counteract the cardiovascular changes induced by pneumoperitoneum. , hence it can be recommended as a routine premedication for laparoscopic procedure.

KEYWORDS

Laparoscopic cholecystectomy; Pneumoperitoneum, Haemodynamic response; Clonidine premedication.

I. Introduction

Laparoscopic surgeries are the essence of today's surgical practice. Laparoscopic cholecystectomy is the gold standard treatment of choice for cholelithiasis. There is significant change in the haemodynamics after pneumoperitoneum and position used for laparoscopic surgeries. This in addition to the anesthetic agents put together alters the cardiopulmonary function significantly. Clonidine is a highly selective alpha 2 agonist with central action, used as antihypertensive. In our study we have compared the hemodynamic stability achieved during pneumoperitoneum used for laparoscopic cholecystectomy with the clonidine premedication versus the placebo drug lorazepam.

Aho et al2 used 2 adrenergic receptor agonist for prevention of haemodynamic responses associated with laparoscopic surgery. They found that dexmedetomidine effectively reduces the maximum heart rate response after intubation and pneumoperitoneum. Clonidine inhibits the release of catecholamine and vasopressin and thus modulates the haemodynamic changes induced by pneumoperitoneum.3 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 clonidine in prevention of such haemodynamic changes.

II. Methods

After approval from the Institutional Ethical Committee, randomized prospective study was carried out in 60 patients of ASA 1 or ASA 2 grade scheduled for laparoscopic cholecystectomy. Patients were randomly allocated using computer generated random numbers to either study C (30) or control P (30) group. Group sizes of 30 were determined by power analysis based on standard deviation data from previously published reports Patients recruited were aged between 18 to 70 years,.

Patients with hypertension, ischemic heart disease, aortic stenosis were excluded from the study. Patients concomitantly taking clonidine, methyl dopa, beta blocking drugs, benzodiazepines and MAO inhibitors were also excluded from the study.

All patients received Lorazepam 2 mg orally on the night before surgery. All recruited patients underwent pre-anesthetic evaluation a day prior to the surgery. Laboratory investigations were ordered depending on the individual requirements. The informed and written consent were taken after explaining the procedure of general anesthesia with endo-tracheal intubation and the data gathered being used for study purpose. All our patients were kept pre-operative nil per oral for a period of six hours. On the day of the surgery the patients were given fixed dose tablet clonidine 150mcg or tablet ranitidine 150 mg irrespective of the body weight depending on the group to which they belong, one hour before the induction time in the holding area.

Intravenous access was secured with wide bore cannula in non dominant upper limb. The following standardized anesthetic regimen was followed in both groups; monitors used were non-invasive blood pressure, pulse-oximetry, electrocardiogram, end tidal gas analyser, peripheral nerve stimulator, naso-pharyngeal temperature. Level of sedation (sedation score) was assessed by sedation scale :

(1) awake and agitated
(2) awake and comfortable
(3) asleep but arousable
(4) asleep with sluggish response to persistent call or touch and
(5) no response to call or touch.

Induction with intravenous injection fentanyl 2mcg/kg + intravenous injection propofol titrated to loss of verbal response in both groups. Muscle relaxation was achieved with injection vecuronium 0.12mg/kg in both groups and repeated with twitch response three or more with 0.01mg/kg. Maintenance was done with 50% nitrous oxide in oxygen and isoflurane concentration 0.8% to 1.0% to achieve 1 MAC. The tidal volume (VT) and the ventilatory frequency was adjusted and intermittent positive pressure ventilation (IPPV) was continued by mechanical ventilator to maintain end tidal carbon dioxide between 35-45 mm Hg.

Pneumoperitoneum was created by insufflation of carbondioxide and operation table was tilted about 15º reverse Trendelenburg position.

Position then changed to head up to a maximum of 30° and left tilt to a maximum of 20°.

Intra-operative bradycardia defined as heart rate less than 20% of baseline or absolute heart rate less than 40 beats per minute whichever is less. It was treated by intravenous atropine 20mcg/kg. Intra-operative hypotension was defined as 25% of the baseline or SBP less than 90 mm of Hg. It was treated with injection ephedrine 5mg-10mg intravenous bolus. Intra-operative hypertension was defined as 25 percent of the baseline or SBP more than 200 mm of Hg. It was treated with nitroglycerine infusion 0.5 to 1.0 mcg/kg/min.

The following parameters were observed in both groups: Heart rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP). The parameters were recorded at the following stages of the procedure: Baseline prior to premedication at holding area, Pre induction, 5 minutes after intubation, before pneumoperitoneum, Post pneumoperitoneum: 15 minutes,30 minutes, After Release of Carbon dioxide and After Extubation . The parameters were recorded using multipara monitor .

At the end of the procedure antiemetic injection ondansetron 0.1mg/kg maximum of 4 mg intravenous was given slowly. The residual neuromuscular blockade was reversed with 0.05mg/kg injection neostigmine plus 0.01mg/kg glycopyrollate. Trachea was extubated and patients were transferred to recovery room.

In the post anaesthesia care unit (PACU) they were monitored for any evidence of complications or adverse events. Degree of sedation and intensity of pain were also assessed by using 10 point visual analogue scale (VAS).

The results obtained in the study are presented in tabulated manner. Statistical analysis was done by students 't' test. Chi square test was performed for nonparametric values and corresponding P was computed. P value <0.05 was considered statistically significant.

III. Results

Two patients were withdrawn from the study because the proposed laparoscopic cholecystectomy surgery was converted to open cholecystectomy. Aside from these two patients, 58 patients completed the analysis. Demographic profile and preoperative vital parameters were compared among the two groups of patients and no significant difference was found (Table 1 & 2). Mean intra-abdominal pressure was 12.8±1.47 mm Hg in Group P and 12.5±1.15 mm Hg in Group C. Normocapnia was maintained throughout the procedure. EtCO2 varied from 32.16±3.46 to35.76±5.27 mmHg in Group P and 31.88±2.58 to 34.26±3.22 mm Hg in Group C.

Table 1 Demographic profile (Mean ± SD)

Demographic Profile	Group C	Group P	P Value	Significance
Age (years)	37.23±9.21	36.13±7.97	0.183	NS
Weight (Kg)	57.26±6.02	58.33±7.25	0.111	NS
Sex (M : F)	6 : 24	7 : 23		
ASA Grading	Grade I = 27 Grade II = 4	Grade I = 25 Grade II = 5		

Table 2 Preoperative vital parameters (Mean ± SD)

Vital Parameters	Group C	Group P	P Value	Significance
Pulse Rate (bpm)	78.2±8.81	83.93±10.32	0.358	NS
MAP (mm Hg)	93.9±6.32	92.6±8.99	0.142	NS
SpO2 (%)	97.5±1.27	96.93±1.20	0.1	NS
Sedation Score	1.20±0.42	1.30±0.52	0.064	NS

NS = Not significant

Mean pulse rate varied from 82.44±11.32to 114.11±12.58 bpm in Group P. In Group C it varied from 73.2±7.62 to 94.5±6.83 bpm. Upon statistical comparison in two groups of patients, significant variation was observed throughout the intraoperative period except for the baseline value when no significant difference was observed (Table 3)

Table 3 Changes in pulse rate in two groups

Pulse Rate (bpm)	Group P (Mean±SD)	Group C (Mean±SD)	P Value	Significance
Before Premedication	82.44±11.32	79.1±7.81	0.3540	NS
Before Induction	88.53±14.02	75.16±9.93	0.085	S
After Intubation (5 minutes)	107.76±14.06	87.26±11.34	0.0069	HS
Before Pneumoperitoneum	86.56±16.75	76.26±9.42	0.052	S
After Pneumop eritoneum (15 minutes)	96.06±21.81	75.76±10.07	0.008	HS
After Pneumop eritoneum (30 minutes)	94.73±19.79	75.53±10.15	0.0044	HS
After Release of Carbon dioxide	84.57±15.15	73.2±7.62	0.0026	HS
After Extubation	114.11±12.58	94.5±6.83	0.0048	HS

NS = Not significant; S = Significant; HS = Highly Significant

Changes in the blood pressure when compared in the two groups of patients was found to be statistically highly significant excepting the base line values where no significant difference was found. (Table 4, 5 and 6).

Table 4 Changes in systolic blood pressure in two groups

Systolic Blood Pressure (mm Hg)	Group P (Mean ± SD)	Group C (Mean ± SD)	P Value	Significance
Before Premedication	117.96± 13.07	122.5± 8.45	0.376	NS
Before Induction	122.73± 11.14	112.03± 9.42	0.00017	HS
After Intubation	144.6± 21.54	121.56± 6.58	0.0061	HS
Before Pneumoperitoneum	122.93± 14.46	114.6± 9.64	0.0018	HS
After Pneumoperitoneum (15 minutes)	144.63± 19.60	120.6± 10.06	0.00015	HS
After Pneumoperitoneum (30 minutes)	141.75± 18.52	120.03± 8.22	0.0028	HS
After Release of Carbon dioxide	126.64± 13.77	117.23± 9.48	0.0032	HS
After Extubation	140.35± 9.53	125.13± 8.10	0.018	S

NS = Not significant; S = Significant; HS = Highly Significant.

Table 5 Changes in mean arterial pressure in two groups

Mean Arterial Pressure (mm Hg)	Group P (Mean ± SD)	Group C (Mean ± SD)	P Value	Significance
Before Premedication	91.7± 9.02	95.39± 6.98	0.0883	NS
Before Induction	95± 10.42	85.57± 9.06	0.00059	HS
After Intubation (5 minutes)	113.56± 16.33	93.7± 7.33	0.00018	HS
Before pneumoperitoneum	98.6± 14.74	90.28± 9.26	0.0129	S
After Pneumoperitoneum (15 minutes)	114.13± 16.57	93.83± 8.107	0.00182	HS
After Pneumoperitoneum (30 minutes)	108.60± 15.11	93.64± 8.40	0.033	S
After Release of Carbon dioxide	97.25± 11.34	90.63± 8.96	0.01625	S
After Extubation	108.42± 8.07	97.37± 7.63	0.041	S

NS = Not significant; S = Significant; HS = Highly Significant

Nine patients (30%) in Group P received nitroglycerine infusion (0.5 mcgkg-1 .min-1) for treatment of intraoperative hypertension. It was not required in Group C patients, because they remained haemodynamically stable. Intensity of pain was less in Group C as compared to Group P (VAS 2.1±1.581 Vs 5.014±2.214) during early postoperative period. Incidence of nausea-vomiting, hypertension,

shivering and shoulder pain were 32.64%, 33.60%, 11.2% and 13.9% in the Group P, while only 7.76% patients suffered from nausea vomiting in Group C. Sedation was common in Group C (33.33%). Other complications were not observed in Group C. None of the patient showed any evidence of ischaemia or arrthymia in traoperatively.

Table 6 Changes in diastolic blood pressure in two groups

Diastolic Blood Pressure (mm Hg)	Group P (Mean ± SD)	Group C (Mean ± SD)	P Value	Significance
Before Premedication	78.93± 8.22	81.67± 7.11	0.018	NS
Before Induction	82.1± 9.99	72.93± 9.98	0.00075	HS
After Intubation (5 minutes)	98.76± 13.15	80.83± 8.09	0.0006	HS
Before pneumoperitoneum	83.43± 12.09	77.76± 9.58	0.073	NS
After Pneumoperitoneum (15 minutes)	99.23± 4.02	1.26± 8.40	0.0015	HS
After Pneumoperitoneum (30 minutes)	94.5± 14.82	80.93± 9.15	0.00015	HS
After Release of Carbon dioxide	82.60± 12.18	77.66± 9.79	0.093	NS
After Extubation	92.14± 8.84	83.86± 8.86	0.00138	HS

NS = Not significant; S = Significant; HS = Highly Significant.

IV. Discussion

Pneumoperitoneum during laparoscopy produces significant haemodynamic changes, which can be detrimental especially in elderly and haemodynamically compromised patients. 4 Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum.

This double blind prospective study was carried out in 60 adult patients, to evaluate the effect of clonidine premedication in attenuating haemodynamic stress response associated with pneumoperitoneum.

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. 150 mcg clonidine was administered orally, 60 minutes before surgery in this series. Dose of clonidine varied from 2 to 5 mcg kg-1 in different studies. Higher dose of clonidine (5 mcg kg-1) is usually required for potentiation of postoperative analgesia by intrathecal morphine 5. A small oral dose of clonidine decreased the incidence of perioperative myocardial ischemic episodes without affecting haemodynamic stability. Aho et al2 used 3 mcgkg-1 and 4.5mcgkg-1 clonidine for suppression of haemodynamic response to pneumoperitoneum. Rise in blood pressure and heart rate was less in both the groups but 4.5 mcg kg-1 clonidine produced greater fall in mean arterial pressure before induction. Joris et al3 used very high dose of clonidine (8 mcgkg-1) for reducing thelevel of catecholamine and vasopressin following pneumoperitoneum. Malek et al6 used 150 mcg of clonidine as i.v. infusion and intramuscularly while Sung et al7 and Yu et al8 used 150 mcg of oral clonidine as premedication for maintenance of haemodynamic stability during pneumoperitoneum.

Following pneumoperitoneum with carbon dioxide, patients were hyper ventilated to maintain normocapnia. Every effort was made to maintain intra abdominal pressure(IAP)below14mmHg. Mean intra-abdominal pressure was 12.8±1.47 mm Hg in Group P and 12.5±1.15 mm Hg in Group C.

Haemodynamic changes associated with pneumoperitoneum was first recognized in 1947.9 Diamant et al10 reported 35% decrease in cardiac output in dog with a raised intra abdominal pressure of 40 mm Hg. Ishizaki et al11 tried to evaluate the safe intra-abdominal pressure during laparoscopic surgery. They observed significant fall in cardiac output at 16 mm Hg of intra-abdominal pressure. Haemodynamic alterations were not observed at 12 mm Hg of intra-abdominal pressure. Based on all these observations the current recommendation is to monitor intra-abdominal pressure and to keep it as low as possible.

Cunningham et al12 and Dorsay et al13 assessed the ejection fraction (EF) of left ventricle by trans esophageal echocardiography during pneumoperitoneum. No significant change inejection fraction was reported up to 15 mm Hg of intra-abdominal pressure. Considering all these facts intra abdominal pressure was kept below 14 mm Hg.

In spite of maintaining normocapnia and keeping intra-abdominal pressure below 14mmHg significant rise in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was noticed in Group P. Rise in systolic, diastolic and mean arterial pressure was more than 20% from the baseline. Slight fall in systolic blood pressure, diastolic blood pressure and mean arterial pressure was noticed following premedication with clonidine. Following intubation and pneumoperitoneum, increase in arterial pressure was noticed but it never crossed the base line value. Hence clonidine premedication was able to achieve haemodynamic stability during pneumoperitoneum.

Similar findings were reportedbyAhoet al2, Joris et al3, Maleket al6, Sunget al7,Yuet al8 and Laisalmi et al14.

Aho et al2 observed that 4.5 mcgkg-1 of clonidine significantly decreased the mean arterial pressure before induction of anaesthesia. So they recommended 3 mcgkg-1 of clonidine for perioperative haemodynamic stability. Joris et al3 used higher dose of clonidine for reduction of catecholamine and vasopressin associated with pneumoperitoneum. Clonidine significantly reduced the concentration of catecholamine but not vasopressin and cotisol concentration. Similarly Sunget al7 observed haemodynamic stability during pneumoperitoneum with 150 mcg oral clonidine. Requirement of isoflurane was also less by 30% in the clonidinegroup. Esmolol, labetalol and nifedipine were used Mrinmoy Das et al. Clonidine attenuate haemodynamic response during laparoscopy to control hypertension in control group. FinallyYu et al8 recommended the routine use of clonidine premedication in laparoscopic patients.

The adverse effects in the postoperative period were less in the patients who had clonidine premedication in comparison with placebo premedication. There was incidence of shiveringin 10.70% patients in the placebo group compared to none in the clonidine group.

This finding corroborates the finding of Nicolaou et al, where they concluded that clonidine inhibits cold thermoregulatory response due to an effect on central integration control and output from the thermoregulatory centers.15 Thus he opined that clonidine can be used as an effective agent for inhibition of perioperative shivering which can adversely increase metabolic rate and cardiac work and may also disrupt surgical repair or result in wound dehiscence.

Thirty five percent of patients of the Group P suffered from nausea and / or vomiting, while only 6.89% of the patients receiving clonidine had any such episode. Clonidine increases gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic outflow from the central nervous system. Although many workers have reported the antiemetic property of clonidine, the mechanism by which it acts warrants further investigation.

V. Conclusion

Premedication with 150 mcg oral clonidine, has been found to be relatively safe as well as effective method that provides stable haemodynamics and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. Clonidine also affords an added advantage of reduction in postoperative complications suchasnausea vomiting and shivering.

Hence 150 mcg oral clonidine can reasonably be recommended as premedicant for all laparoscopic procedures in otherwise healthy patients. However further study is required to find out its efficacy in patient with compromised cardiovascular system.

VI. References

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