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Haemodynamic Response Associated With Laparoscopic Cholecystectomy: Outcome of Oral Clonidine as a Premedicant and Post Operative Analgesic- A Clinical Study

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Abstract

Background: Laparoscopy provides various advantages than conventional cholecystectomy but may lead to alteration in cardiovascular and pulmonary physiology and stress response. *Objective*: The aim of this study is to assess the outcome of oral clonidine as a premedicant for haemodynamic stability in laparoscopic cholecystectomy and as a postoperative analgesic. *Materials and Methods*: One hundred and fifty adult patients categorized as ASA physical status I or II, time lined for laparoscopic cholecystectomy were chosen and randomly allotted to two groups P & C. Group C (clonidine) received Tab.clonidine 150 μg orally and Group P (placebo) received Tab.ranitidine 150mg orally as premedication 90 minutes before scheduled laparoscopic cholecystectomy. Haemodynamic response in the intraoperative period and postoperative analgesic requirements were recorded. *Results*: Significant haemodynamic variation was noted in the group P as compared to group C. Mean heart rate varied from 74.42±9.13 to 91.84±9.11 (Mean±SD) in group C and 84.64±9.25 to 110±13.95 in group P. Systolic, Diastolic and Mean blood pressures also showed similar variations. Intensity of pain, nausea and vomiting was also less in the group C in the early postoperative period. *Conclusion*: It can be concluded from these results that, premedication with oral clonidine 150 μg provides stable haemodynamics and prevents against stress response due to pneumoperitoneum in laparoscopic cholecystectomy patients and reduces post-operative analgesic requirements.

Keywords: Haemodynamic Response; Laparoscopy; Cholecystectomy; Pneumoperitoneum; Oral Premedication; Clonidine; Post-Operative Pain

Introduction

Minimally invasive surgeries are rapidly replacing traditional open surgeries.Laparoscopic cholecystectomy has radicalized gall bladder surgeries and is now considered as the "gold standard" for treatment of gall bladder diseases [1]. The fact that laparoscopic surgery is associated with diminished pain, cosmetically better scar, decreased hospital stay as well as rapid resumption of regular daily activities has hastened its acceptance. However, laparoscopic procedures translate to new anaesthetic challenges demanding changes in anaesthesia techniques. Haemodynamic effects in laparoscopy are cardinally due to hypercarbia and the raised IAP and are commonly observed initially in the first half an hour of creation of carbon-di-oxide (CO_2) pneumoperitoneum [2]. Decreased cardiac output, increased peripheral vascular resistance, and elevated serum catecholamine level in laparoscopic cholecystectomy (LC) might entail haemodynamic fluctuation which, in turn, compromises tissue perfusion. These effects are further influenced by the CO_2 insufflation rate, patient's age, amount of gas used for insufflation, time taken for the procedure, intraoperative patient positionand associated cardiopulmonary conditions [3,4]. In annexation, diaphragmatic

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dysfunction and ventilator impairment also occur after laparoscopic cholecystectomy (LC) surgery. Elevation in stress hormones, cardiovascular instability, and ventilatory impairment in LC hint that it is not minimally invasive. These haemodynamic changes may have delirious effect especially in those with cardiopulmonary disease.

Clonidine is a centrally acting selective partial α_2 adrenergic agonist that decreases the sympathetic output and acts as an antihypertensive drug [5]. There by it helps in blunting laryngoscopic response, decreases systemic vascular resistance and pulmonary vascular resistance [6-8]. Due to its sedative property it reduces minimal alveolar concentration of inhalational agents also [9,10]. Oral bioavailability is high and due to its lipid solubility clonidine readily penetrates extravascular sites. The present study was conducted to assess the role of oral clonidine in attenuating the haemodynamic response due to CO_2 pneumoperitoneum and also time interval of post-operative analgesia.

Objectives of the Study

To study the effect of oral clonidine in attenuating the haemodynamic response due to CO_2 pneumoperitoneum and duration of post-operative analgesia.

Materials and Methods

Study was conducted in a tertiary care hospital in India. Written informed consent was taken from 150 patients before being included in the study and they were divided into two groups by computer generated randomization during the study period from June 2015 to May 2016.

The study population of 150 patients aged between 18 to 55 years categorized as ASA class 1 and 2, scheduled for elective laparoscopic cholecystectomy were randomly divided into two groups:

Group P (n=75): received Tab. ranitidine 150 mg 90 minutes before induction of anaesthesia

Group C (n=75): received Tab. clonidine 150 μg 90 minutes before induction of anaesthesia

Obese patients, patients with left ventricular failure, IHD, severe AV conduction block, severe valvular disease, uncontrolled hypertension and other severe CVS abnormalities and patients on antihypertensive medications were excluded.

Oral alprozalam 0.5mg was given to all patients on the night before surgery.

On the day of surgery, intravenous line 18G was established and patients were shifted into the operation theatre where the monitors were connected and baseline values of heart rate(HR), blood pressure – systolic (SBP), diastolic (DBP) and mean arterial blood pressure (MAP) and peripheral oxygen saturation (SpO_2) were recorded. The patients were administered general anaesthesia according to a standardized regimen for both the groups which included iv glycopyrrolate 0.01mg.kg^{-1} fentanyl citrate 1.5-2μg.kg^{-1} body weight and were induced with thiopentone sodium 4-7mg.kg^{-1}. Endotracheal intubation was performed using succinylcholine 2 mg.kg^{-1} of body weight. Anaesthesia was maintained with 0.8-1% Isoflurane, 33% oxygen in nitrous oxide, and vecuronium bromide 0.1mg.kg^{-1}. Controlled mechanical ventilation was used to uphold end tidal CO_2 between 35-45 mm Hg. Intra-abdominal pressure (IAP) was maintained <15 mm Hg throughout the surgical procedure. Necessary changes were made after pneumoperitoneum in ventilator settings (tidal volume, respiratory rate) to maintain normocapnia.

During the procedure, any rise in mean arterial pressure more than 20% from the baseline was treated with nitroglycerine drip 0.5-2mcg.kg^{-1}.min^{-1}. The parameters (HR, SBP, DBP, MAP, SpO2 EtCO_2) were recorded at the following points of time:preoperatively, before induction, after intubation, before pneumoperitoneum, after 15 minutes of pneumoperitoneum, after 30 minutes of pneumoperitoneum, 5 minutes after CO_2 ex-sufflation and 5 minutes after extubation. On completion of surgery, isoflurane was discontinued and patients were reversed by appropriate dose of iv.neostigmine and iv glycopyrrolate. Patients were extubated and were transferred to recovery room. Patients were monitored for any evidence of sideeffects or complications in the postanaesthesia care unit (PACU). Magnitude of pain was determined by using 10-point visual analogue scale (VAS) where Zero means no pain and Ten means intolerable pain. Statistical analysis was done by Chi square test and student 't' test were performed and corresponding *P value* was computed. Statistical significance was considered if *P* value <0.05.

Observation and Results

Demographic profile and preoperative vital parameters showed no significant difference between

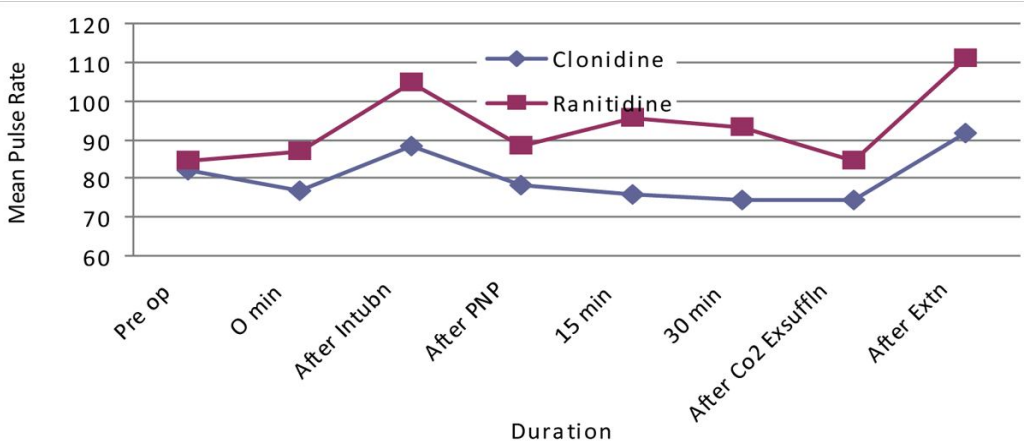
the two groups of patients. Mean intra-abdominal pressure was 13.1±1.47 mmHg in Group P and 12.7±1.15 mm Hg in Group C. All through the procedure normocapnia was maintained. EtCO2 varied from 31.13±3.45 to35.46±5.36mmHg in Group P and 30.66±2.38 to 34.06±3.18 mmHg in Group C.

Mean pulse rate varied from 84.64±9.25 to 110.90±13.95 bpm in Group P. In Group C it varied from 74.42±9.13 to 91.84±9.11 bpm. Both the groups, when compared were statistically significant in the intraoperative period except in the preoperative baseline value.

Table 1: Changes in pulse rate in two groups

Pulse Rate	GROUP C (Mean ± SD)	GROUP P (Mean ± SD)	P value	Significance
Preoperative	81.84 + 12.76	84.64 + 9.25	.212	NS
Before Induction	76.90 + 8.86	86.96 + 9.86	.000	HS
After Intubation	88.44 + 9.77	104.80 + 11.18	0.000	HS
Before Pneumoperitoneum	78.14 + 9.53	88.32 + 13.67	0.000	HS
After pneumoperitoneum (15 minutes)	76.08 + 10.01	95.46 + 11.70	0.000	HS
After pneumoperitoneum (30 minutes)	74.58 + 9.21	93.34 + 11.30	0.000	HS
After CO2 exsufflation	74.42 + 9.13	84.28 +12.89	0.000	HS
After Extubation	91.84 + 9.11	110.90 + 13.95	0.000	HS

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



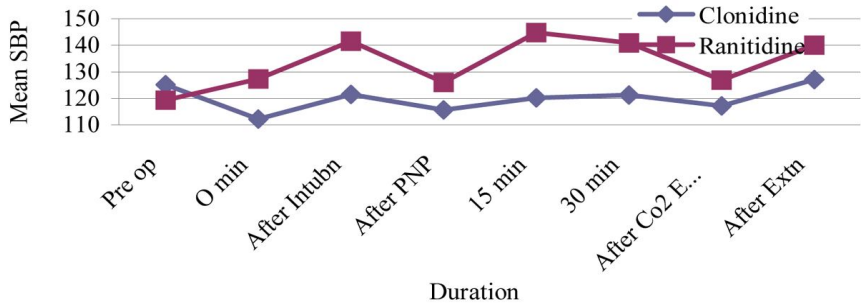
Graph 1: Changes in pulse rate in two groups

Blood pressures in both the groups, when compared were statistically significant in the intraoperative period except in the preoperative baseline value.

Table 2: Changes in systolic blood pressure in two groups

Systolic BP	GROUP C (Mean ± SD)	Group P (Mean ± SD)	P value	Significance
Preoperative	125.04+7.87	119.22±9.72	0.001	NS
Before Induction	112.22±4.34	127.32±12.07	0.000	HS
After Intubation	121.50±3.36	141.62±11.93	0.000	HS
Before Pneumoperitoneum	115.64±2.52	125.98±10.95	0.000	HS
After pneumoperitoneum (15 minutes)	120.16±4.27	144.74±17.87	0.000	HS
After pneumoperitoneum (30 minutes)	121.30±5.16	140.94±12.73	0.000	HS
After CO2 exsufflation	117.10±5.32	126.82±14.28	0.000	HS
After Extubation	127.02±9.46	140.06±15.46	0.000	HS

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

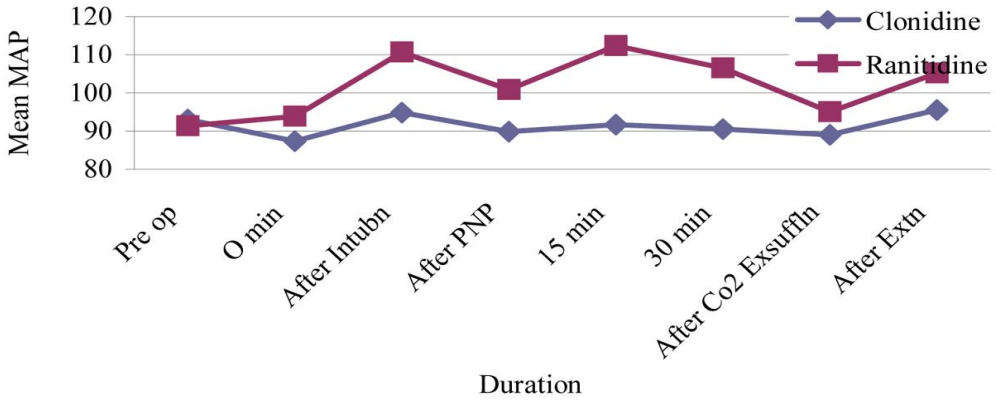


Graph 2: Changes in systolic blood pressure in two groups

Table 3: Changes in Mean Arterial Pressure In Two Groups

Mean Arterial Pressure (mm Hg)	GROUP C (Mean ± SD)	Group P (Mean ± SD)	P value	Significance
Preoperative	92.92±5.27	91.36±7.30	0.224	NS
Before Induction	87.36±5.64	93.86±10.75	0.000	HS
After Intubatiom	94.88±3.63	110.67±10.06	0.000	HS
Before Pneumoperitoneum	89.80±3.35	100.86±9.49	0.000	HS
After pneumoperitoneum (15 minutes)	91.60±4.81	112.32±7.51	0.000	HS
After pneumoperitoneum (30 minutes)	90.50±5.71	106.54±10.57	0.000	HS
After CO2 exsufflation	89.04±3.31	94.96±8.62	0.000	HS
After Extubation	95.52±4.76	105.14±11.51	0.000	HS

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



Graph 3: Changes in mean arterial pressure in two groups

Table 4: Changes in diastolic blood pressure in two groups

Diastolic BP	GROUP C (Mean ± SD)	Group P (Mean ± SD)	P value	Significance
Preoperative	79.54±3.00	79.66±6.61	0.907	NS
Before Induction	71.86±6.04	80.98±9.29	0.000	HS
After Intubatiom	79.94±7.84	93.94±9.56	0.000	HS
Before Pneumoperitoneum	78.02±6.77	82.42±11.85	0.025	HS
After pneumoperitoneum (15 minutes)	80.94±6.27	96.02±10.72	0.000	HS
After pneumoperitoneum (30 minutes)	80.28±7.86	93.46±9.57	0.000	HS
After CO2 exsufflation	77.40±5.10	83.95±8.90	0.000	HS
After Extubation	83.86±6.61	91.96±11.84	0.000	HS

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

Ten patients (33.3%) in Group P received nitroglycerine (NTG) infusion (0.5-2 mcg.kg^{-1}.min^{-1}) for treatment of intraoperative hypertension. It was not required in Group C patients, because they were haemodynamically stable. Magnitude of pain was relatively less in Group C as compared to Group P (VAS 2.16±1.77 Vs 3.34±1.36) in the early postoperative period. Incidence of nausea and vomiting was 35.70% in the Group P, while only 6.89% patients suffered from nausea vomiting in Group C. Incidence of sedation was 33.33% in Group C. None of the patient showed any evidence of intraoperative cardiovascular complications.

Discussion

Pneumoperitoneum during laparoscopy produces significant haemodynamic changes, which can be detrimental especially in elderly and haemodynamically compromised patients [11]. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum. This randomized prospective study comprising of 150 adult patients,was undertaken to assess the effect of oral clonidine as a premedicant in reducing the pneumoperitoneum induced haemodynamic stress response. Clonidine is a α_2 adrenergic agonist belonging to imidazoline group. It is a potent antihypertensive drug. It reduces heart rate and blood pressure by reducing SVR and cardiac output. Oral clonidine 150µg was administered 90 minutes before surgery in this study. The incidences of perioperative cardiovascular ischemic episodes were decreased, with a small oral dose of clonidine,without altering haemodynamic stability [13]. Ahoet al [13] used 3 mg.kg^{-1} and 4.5 mg.kg^{-1} clonidine to decrease the haemodynamic response to CO_2 pneumoperitoneum. Increase in blood pressure and heart rate was less in both the groups whereas more fall in MAP was observed with 4.5g.kg^{-1} clonidine group before induction. A study by Joriset al [14] used clonidine (8mg. kg^{-1}) following CO_2 pneumoperitoneum for decreasing the amount of catecholamine and vasopressin in dogs. Sung et al [16] and Yu et al [17]evaluated premedicant effect of 150 g of oral clonidine for maintaining haemodynamic stability during CO_2 pneumoperitoneum where as Malek et al [15] used 150 mg of clonidine as iv infusion15mins before and150mg of clonidine intramuscularly60-90min before operation to decrease the haemodynamic response to CO_2 pneumoperitoneum.

In our study after CO_2 pneumoperitoneum, controlled ventilation was done to maintain normocapnia. Intraabdominal pressure (IAP) was maintained below 15 mm Hg. Mean intra-abdominal pressure was 13.1±1.47 mmHg in Group P and 12.7±1.15 mm Hg in Group C. Diamant et al [19] showed that with a IAP of 40mm Hg in dogs result in 35% decrease in cardiac output. A study conducted by Ishizaki et al [20] evaluated the IAP in laparoscopic surgeries and found noticeable fall incardiac output at 16mmHg of IAP as compared to lesser fall in cardiac output with 12mmHg. On this basis, the IAP should be kept at the lowest possible limit. A study conducted by Cunningham et al [21] and Dorsay et al [22] showed no noticeable change in ejection fraction with IAP of less than 15 mm Hg.

With reference to the above studies intra-abdominal pressure was kept at 12-14 mm Hg. Despite keeping intra-abdominal pressure at 12-14 mmHg and maintaining normocapnia, there was a noticeable increase in HR, SBP, DBP and MAP in Group P. There was significant increase in SBP, DBP and MAP more than 20% from the baseline. Insignificant decrease in SBP, DBP, and MAP was observed after premedicating with oral clonidine. After intubation and CO_2 pneumoperitoneum, there was a rise in arterial pressure but not above the base line value. Thereby, oral clonidine as a premedicant was suitable to maintain haemodynamic stability after pneumoperitoneum. Nearly same findings were reported by Ahoet al [13], Joriset al [14], Malek et al [15], Sung et al [16], Yu et al [17 and Laisalmi et al [23]. Ahoet al [13] observed that 4.5 mg.kg^{-1} of clonidine significantly reduced the MAP before induction of anaesthesia. So they suggested 3 mg.kg^{-1} of clonidine for maintaining perioperative haemodynamic stability. In another study by Joriset al [14], they used higher dose of clonidine to decrease vasopressinand catecholamine produced due to CO_2 pneumoperitoneum. Though the concentration of catecholamine was notably decreased by clonidine but cortisol and vasopressin concentration remained same. Similar findings were observed by Sung et al [16] for maintenance of haemodynamics during pneumoperitoneum with 150 mg oral clonidine, They also observed that isoflurane requirement was decreased by 30%in the clonidine group. To control hypertension in the control group nifedipine, esmolol and labetalol were administered. Finally, regular use of clonidine as a premedicant in laparoscopic surgeries was recommended by Yu et al [17]. Patients who received clonidine as premedication had less incidence of adverse events like shivering in the postoperative period. Incidence of shivering in placebo group was 10.70% patients as compared to

none in clonidine group. This finding supports the study of Nicolaouet al [24], where they inferred that, cold thermoregulatory response was inhibited by clonidine due to itsaction on the output from thermoregulatory centers and effect on central integration control [24]. They also concluded that, perioperative shivering can be effectively reduced by clonidine, if not treated can adversely escalate the cardiac work and metabolic rate and can also impede surgical repair or results in wound dehiscence. Nausea and / or vomiting were seen in 35% of patients belonging to group P whereas only 6.89% of patients had such episodes in clonidine group. This may be attributed to increase in gastrointestinal motility by clonidine via direct action on the central nervous system,by rise in parasympathetic outflow and reduced sympathetic outflow. In spite of assumptions regarding the antiemetic property of clonidine, the mechanism of action still requires additional research.

Conclusion

In conclusion, oral clonidine 150µg as a premedicant has been observed to be relatively safe as well as an effective method which offers stable haemodynamics and prevents the stress responseinduced by CO_2 pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. Postoperative complications such as nausea, vomiting were also reduced by clonidine thereby offering an additional advantage.

Hence 150 mg oral clonidine can satisfactorilybe recommended in otherwise healthy patients, as a premedicant for most of all laparoscopic procedures. However further study is required, to find out its efficacy in patients with compromised cardiovascular system

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