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Effects of Oral Clonidine Premedication on Haemodynamic Responses During Laparoscopic Cholecystectomy –a Randomized Control Study

KEYWORDS: clonidine, laparoscopy, pneumoperitoneum, heart rate, blood pressure

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ABSTRACT ***Purpose:*** *Laparoscopic cholecystectomy is the treatment of choice for cholelithiasis. The pneumoperitoneum used for laparoscopic procedures results in significant hemodynamic and respiratory responses which might be harmful especially in cardiac patients. Clonidine has anti-hypertensive properties and augments the effects of anesthesia, thus it is a potentially an ideal agent to contain the stress response to pneumoperitoneum. We undertook this study to evaluate the clinical efficacy of oral clonidine premedication in patients undergoing laparoscopic cholecystectomies.*
Methods: *100 patients of ASA grade I–II, scheduled for elective laparoscopic cholecystectomy under general anaesthesia were randomly allocated to receive premedication with either oral clonidine 150 µg (Group I, n = 50) or placebo (Group II, n = 50) 90 minutes prior to induction. The patients were managed with a standard general anaesthetic. The two groups were compared with respect to haemodynamic parameters, pain and sedation scores and incidence of adverse effects like nausea-vomiting, shivering, hypotension, bradycardia etc.*
Results: *Haemodynamic parameters i.e. pulse rate, systolic blood pressure, mean arterial pressure and diastolic blood pressure were significantly lower and stable in the clonidine group as compared to placebo group. Patients receiving oral clonidine premedication had less anxiety and no incidence of post –operative shivering. Clonidine also decreased need of postoperative analgesics and incidence of postoperative nausea / vomiting.*
Conclusion: *From our study we found that clonidine in dose of 150 mcg can be used effectively and safely in ASA class I & II patients to control the hemodynamic changes which occur during laparoscopic cholecystectomy.*

Introduction:
Laparoscopic cholecystectomy was introduced by Phillipe Mouret in 1987.[1] It offers many benefits than conventional cholecystectomy so it has now become the "gold standard" for treatment of cholelithiasis. However, this procedure is not free from risks[2-4]. Pneumoperitoneum produced during laparoscopic cholecystectomy itself leads to many problems. It causes pathophysiological changes of RAAS (Renin angiotensin aldosterone system), respiratory system, circulatory system, haemodynamic changes, acid base balance, stress response changes, nausea-vomiting, shivering and shoulder pain.

Clonidine, a centrally acting alpha$_2$-agonist that is an imidazoline derivative is a selective alpha-2 adrenergic agonist with a ratio of 200:1 (alpha-2: alpha1). It is a potent antihypertensive drug. The plasma level of clonidine peaks in approximately 3 to 5 hours and the plasma half-life ranges from 12 to 16 hours.[5] Clonidine has been known to attenuate stress-induced sympathoadrenal responses and minimizing haemodynamic changes after tracheal intubation, noxious stimuli from surgery and associated with pneumoperitoneum is an important goal for anaesthetic care in patients undergoing laparoscopic cholecystectomy. Clonidine has also been studied to result in decreased anxiety[6], salivation[7], pain[2,8,9] shivering[2], nausea and vomiting [2,10] related to surgery and anaesthesia. These properties can make it beneficial drug in laparoscopic cholecystectomy. Hence this study has been designed as prospective blind randomized controlled study to evaluate the effects of clonidine premedication on haemodynamic changes during laparoscopic cholecystectomy.

Methods and Materials
This prospective, randomized, double blind study was conducted in the Department of Anaesthesiology and Critical Care at Command Hospital (WC) Chandimandir. After the approval of study by the Institutional Ethics Committee, written and informed consent was obtained from the patients. A total number of 100 ASA grade I–II patients undergoing laparoscopic cholecystectomy under general anaesthesia were included in the study and randomly divided into two groups:

Group I (n=50) - the study group. These patients were given 150 mcg of oral clonidine 90-120 minutes before the expected time of surgery.

Group II (n=50) - the placebo group. These patients were given oral placebo 90-120 minutes before expected time of surgery.

Morbidly obese patients, Patients with history of hypertension, ischemic heart disease, aortic stenosis, left ventricular failure and AV block and patients already taking drugs like Clonidine, Methyldopa, beta-blockers, Benzodiaz-

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epines, MAO Inhibitors, Calcium channel blockers, Antipsychotics, Tricyclic Antidepressants,alpha2 –antagonists were excluded from the study. The patients were kept fasting overnight and given Tab diazepam 5 mg orally on the night before surgery.

In operation theatre after intravenous cannulation and attaching monitors, patients were premedicated with intravenous glycopyrrolate 0.2 mg, ondansetron 0.1 mg/kg, and fentanyl 1.50 mcg/kg. Induction was done with propofol 2mg/kg. Patients were intubated with vecuronium 0.1mg/kg bolus, and vecuronium was repeated intraoperative as per requirement. Positive pressure ventilation was provided by volume controlled ventilator. Tidal volume and ventilator frequency were adjusted to maintain $EtCO_2$ between 35-40mm Hg. Anaesthesia was maintained with oxygen in nitrous oxide with sevoflurane. Intra abdominal pressure was maintained below 14mm Hg throughout the surgery. Any rise in blood pressure above 20% base values was treated with intraoperative infusion of nitroglycerine to maintain normotension.

At the end of the procedure neuromuscular blockade was reversed with appropriate doses of neostigmine and glycopyrrolate intravenously. Data was analysed using appropriate statistical tests. The student 't' test was used for testing the significance of pulse rate, systolic, diastolic and mean blood pressure between the two groups. ANOVA test was applied to compare parametric values within the Groups. For analyzing the significance of nonparametric values Chi Square test and Mann-Whitney test was applied.

Results:

The two randomized groups were found similar in respect of age, gender, height, weight, BMI and ASA grades.

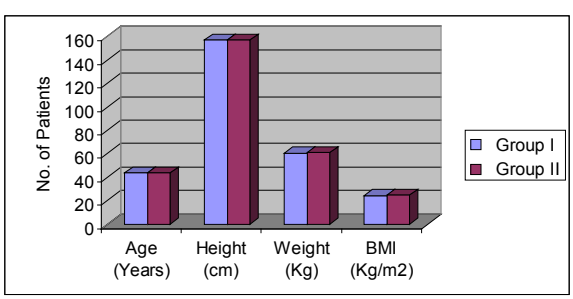

Fig. 1 Demographic Profile

Preoperative vital parameters were comparable among the patients of the two groups.

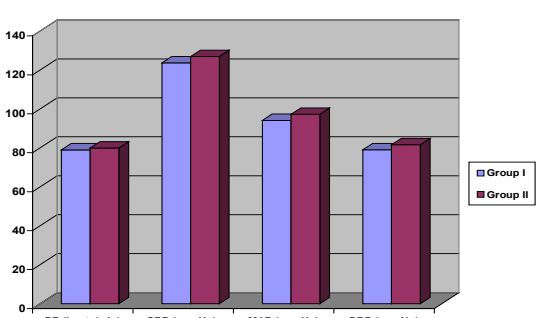

Fig. 2 Preoperative Vital Parameters

Eight patients were withdrawn from the study because the proposed laparoscopic cholecystectomy surgery was converted to open cholecystectomy. Aside from these 08 patients, 92 patients completed the analysis.

Haemodynamic parameters i.e. pulse rate, systolic blood pressure, mean arterial pressure and diastolic blood pressure were significantly lower and stable in the Group I as compared to Group II. Significantly less number of patients in Group I required NTG infusion than in Group II.

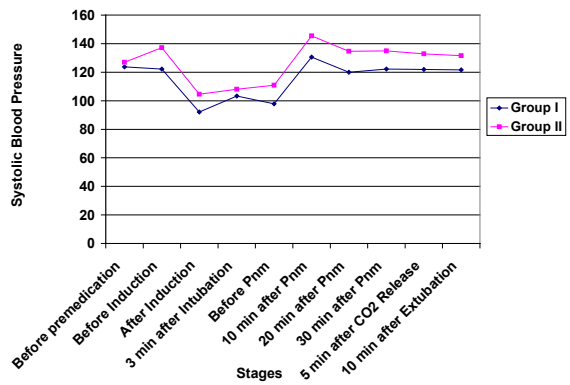

Fig. 3 Changes in pulse rate between and within the Groups

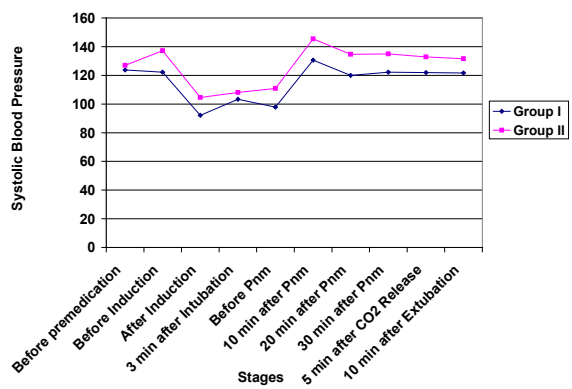

Fig. 4: Changes in Systolic Blood Pressure between and within the Groups

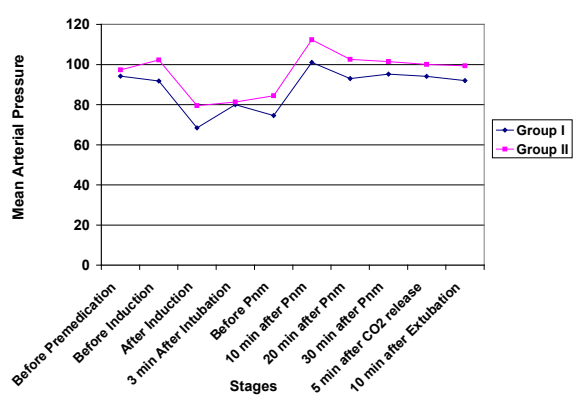

Fig. 5: Changes in Mean Blood Pressure between and within the Groups

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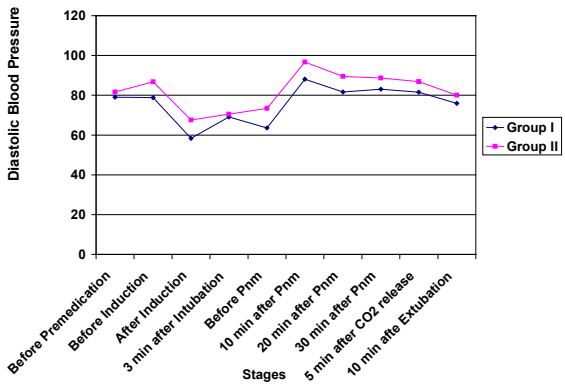

Fig. 6: Changes in diastolic Blood Pressure between and within the Groups

Anxiety level of the patients in the Group I was significantly lower as compared to the patients in the Group II. The patients in the Group I had higher sedation score but they were easily arousable.

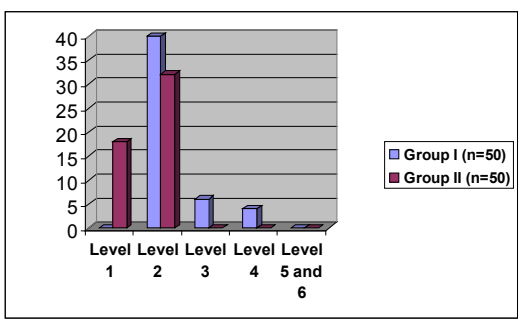

Fig. 7: Preoperative Sedation/Anxiety

In Group I, 4 patients had bradycardia, and which responded to atropine and 9 patients had hypotension, which was treated by reducing concentration of sevoflurane and rushing fluids. Dry mouth is the side effect of clonidine which was complained only by 2 patients in Group I in this study.

Table-1: Comparison of side effects in two groups

Side effects	Group I (n=50)	Group II (n=50)
Bradycardia	04	00
Hypotension	09	00
Dry Mouth	02	00

Pain score was significantly lower in the patients of the Group I as compared to the patients in the Group II. Lesser number of patients in the Group I requested for postoperative analgesic before 8 hrs of postoperative period.

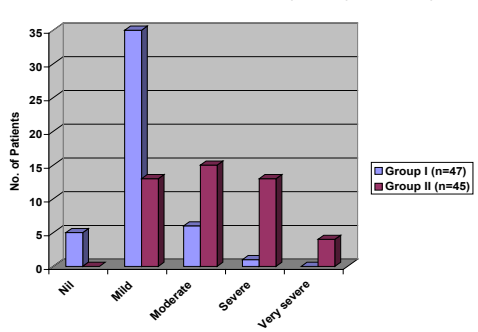

Fig. 8: Severity of Pain

Nausea-vomiting was found in lesser number of patients (18%) in patients of the Group I as compared to the patients (30%) in Group II. Shivering was observed in none of the patients in Group I but it was seen in 10% of the patients in Group II.

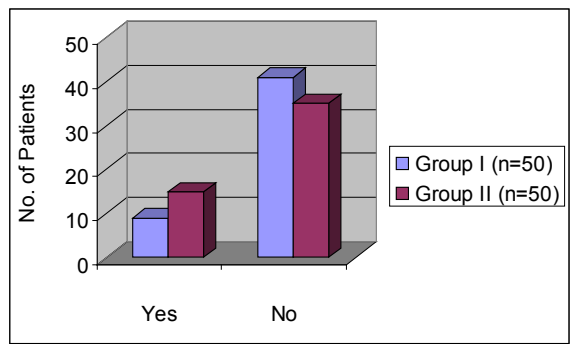

Fig. 9: Postoperative Nausea – Vomiting

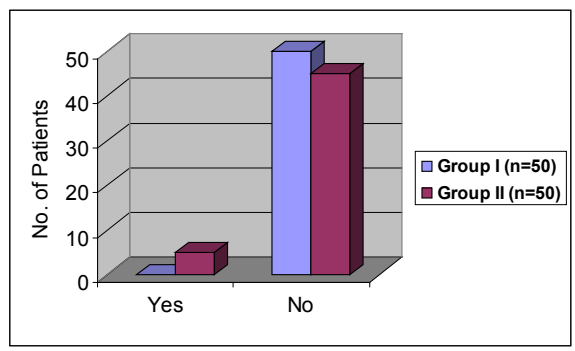

Fig. 10: Shivering in two groups

Discussion:

Laproscopic cholecystectomy is associated with significant hemodynamic changes. These changes result from the combined effects of pneumoperitoneum, patient position, anaesthesia, and hypercapnia from the absorbed CO_2, reflex increases of vagal tone and arrhythmias.

To attenuate these haemodynamic responses, a wide range of substances have been used including b-blocker, gabapentin, pregabaline, magnesium, alfa2 agonist, opoids etc. Compared to other agents, safety margin and effects of clonidine are well suited for its use in anesthesia. Clonidine acts as an agonist at pre-synaptic alpha-2 receptors in the nucleus tractus solitarius of the medulla oblongata. Stimulation of these receptor results in suppression of efferent sympathetic pathways resulting in fall in the heart rate and blood pressure [2,11-16]

In our study clonidine 150 ug/kg effectively attenuated the haemodynamic responses of pnemoperitoneum during laproscopic cholycystectomy. Haemodynamic parameters i.e. pulse rate, systolic blood pressure, mean arterial pressure and diastolic blood pressure were significantly lower and stable in the clonidine (Group I) as compared to placebo (Group II). Mrinmoy Das et al[2] in their study involving 60 patients observed Significant rise in heart rate following pneumoperitoneum in patients receiving ranitidine 150 mg as compared to those receiving clonidine 150ug (99.23±14.02 Vs 81.26±8.40 bpm).

In pre-operative period, a significant fall in systolic and diastolic blood pressure and heart rate was observed in patients 90 minutes after receiving oral clonidine. This is presumably due to decreased level of anxiety in patients receiving cloni-

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dine. Higher level of sedation and lower level of anxiety were noted in patients who received oral clonidine as premedication in comparison to patients who received placebo. No patient in either group was deeply sedated or unarousable. Mrinmoy Das et al[2] used 150 mcg Clonidine orally 90 minutes before induction and found more sedation in clonidine Group (33.33%). Raval DL and Mehta MK[17] studied on 100 patients and found that oral Clonidine in a dose of 4 mcg/kg effectively produces marked sedation and anxiolysis. Wright et al [33] in a study with 0.3 mg Clonidine observed significantly greater level of sedation in clonidine group after 75-105 minutes.

Alpha$_2$ adrenergic receptor activation produces a potent analgesic responses which involves systemic, spinal, supraspinal and peripheral sites.[18] In the present study Intensity of pain was less in clonidine group as compared to plecebo group (ARS) during early postoperative period. 17 patients in placebo group had severe and very severe pain and requested for postoperative analgesic before 8 hrs after surgery whereas only one patient in clonidine group requested post-operative analgesia before 8 hours after surgery ($p<0.05$). Similarly, Mrinmoy Das et al[2] found that intensity of pain was less in clonidine group as compared to placebo group (VAS 1.9±1.688 Vs 5.214±2.114) during early postoperative period. In our study, 18% patients in clonidine group and 30% patients in placebo group II suffered from nausea-vomiting in post-operative period showing that clonidine have favourable effect on post-operative nausea-vomiting. Mrinmoy Das et al[2], Javaherfroosh F et al[10] also reported less incidence of both nausea and vomiting with clonidine.

Clonidine inhibits cold thermoregulatory response due to an effect on central integration control and output from the thermoregulatory centers. In the present study incidence of shivering was not found in any of the patients receiving clonidine but it was seen in 10% patients in placebo group. Hence, the study concludes Clonidine can control shivering very effectively. Mrinmoy Das et al[2] in a study found shivering in 0% patients in clonidine group and in 10.7% patients in placebo group. Nicolaou et al[21], also found decreased incidence of shivering with clonidine. He opined that clonidine can be used as an effective agent for inhibition of peri-operative shivering which can adversely increase metabolic rate and cardiac work and may also disrupt surgical repair or result in wound dehiscence.

In the present study bradycardia was seen in 8% patients in clonidine group and was treated with atropine. Hypotension was seen in 18% patients in clonidine group especially after induction and it was treated by reducing sevoflurane level and rushing fluid.

Goel S and Sinha M[22] observed bradycardia in 6% patients in clonidine group who were easily treated with glycopyrrolate 0.2 mg. Javaherfroosh F et al[10] observed no case of hypotension or bradycardia in either of clonidine or placebo group.

In this series 150 mcg clonidine tablet was administered orally, 90-120 minutes before surgery. Dose of clonidine varied from 2 to 5 mcg/kg in different studies. Mrinmoy Das et al[2] used 150 mcg clonidine orally 90 min before induction. Aho et al [11] used 3 mcg/kg and 4.5 mcg/kg 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 clonidine produced greater fall in mean arterial pressure before induction. Carabine et al [23] have shown that using 0.2 mg of clonidine was associated with minimal cardiovascular effects and good anxiolytic action. However on using a higher dose of 0.3 mg, the decrease in heart rate and arterial blood pressure was found to be significant as compared to other treatment groups.

Hence we conclude that clonidine in dose of 150 mcg can be used effectively and safely in ASA class I & II patients to control the haemodynamic changes which occur during laparoscopic cholecystectomy. Clonidine also helps in reducing preoperative anxiety and shivering. It decreases need of postoperative analgesics and incidence of postoperative nausea / vomiting. No significant symptoms and signs of toxicity are seen with the use of clonidine.

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