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Effects of clonidine premedication on hemodynamic changes during laparoscopic cholecystectomy – A randomized control study

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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.

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 tab lorazepam 2mg [group L- 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 reduction of heart rate (16.6003), systolic pressure (22.433) and mean arterial pressure (14.8) ($p < 0.001$) in study group.

Conclusion: From our study we found that oral clonidine 150mcg can effectively counteract the cardiovascular changes induced by pneumoperitoneum.

Key words: clonidine, laparoscopy, heart rate, blood pressure

Introduction

Laparoscopic surgeries are the essence of today's surgical practice. Laparoscopic cholecystectomy is the treatment of choice for cholelithiasis. There is significant change in the homeostasis after pneumoperitoneum [1, 2] and position used for laparoscopic surgeries. This in addition to the anesthetic agents put together alters the cardiopulmonary function significantly. Clonidine [3-7] 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.

Patients and methods

With institute [Kasturba medical college Mangalore, India] ethics committee ap-

proval, the sixty patients who are either ASA 1 or ASA 2 grade, were randomly allocated using computer generated random numbers to either study C (30) or control L (30) group. Patients recruited were aged between 18 to 70 years, undergoing elective laparoscopic cholecystectomy. The sample size was calculated based on mean and standard deviation of earlier studies. Patients with hypertension, ischemic heart disease, aortic stenosis were excluded from the study. 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 endotracheal 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 lorazepam 2mg 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, nasopharyngeal temperature. 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. End-tidal carbon dioxide is maintained between 25 to 35 mm of Hg by adjusting the mechanical ventilator settings in both groups. 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 intra abdominal pressure was kept below 15 mm of Hg using automated electronic insufflator (Storz®). The position of the operating table is made Trendelenberg during verres needle insertion and peritoneal insufflation. Position then changed to head up to a maximum of 30° and left tilt to a maximum of 20°. 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, Post pneumoperitoneum: 5 minutes, 10 minutes 15 minutes, 30 minutes and 60 minutes. The parameters were recorded using Datex Ohmeda Aestiva/Aspire series inbuilt monitor (GE health care®). 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 glycopyrrolate. Patient was extubated when full consciousness and motor function was regained.

The following tests: student's test, chi-square, ANOVA, were employed to assess the data obtained, $p < 0.05$ taken as statistically significant.

Results

The data obtained reveals the following details. Demographic equi-distribution in both the groups can be ascertained by looking at table 1. The data in the table 2 shows the mean difference between the study paramete-

Table 1: Demographic data

Parameter	Group C (mean±SD)	Group L (mean±SD)	t	p
Age (years)	42.1667±9.27021	44.3667±11.06870	1.21400	0.23 ns
Height (cms)	166.7333±7.04142	164.7333±5.98811	1.18500	0.241 ns
Weight (kgs)	68.8000±9.21169	69.3333±8.78609	0.22900	0.819 ns
Male	12	19		0.07 ns
Female	18	11		

SD - standard deviation, cms - centimeter, kgs - kilograms

Table showing the demographic characteristics of the sample population involved in the study

Table 2: Difference between baseline and pre-induction

Group	Parameter	Paired difference		t	p
		Mean	Standard deviation		
Clonidine [C]	HR	16.6003	±15.01126	6.130	<0.001
	SBP	22.4333	±9.88445	12.431	<0.001
	DBP	12.6667	±6.62978	10.465	<0.001
	MAP	14.8000	±6.20567	13.063	<0.001
Lorazepam [L]	HR	0.2667	±11.73246	0.124	0.902
	SBP	0.7000	±2.27657	1.684	0.103
	DBP	0.5333	±1.88887	1.547	0.133
	MAP	0.3667	±1.69143	1.187	0.245

HR - Heart rate, SBP - Systolic blood pressure, DBP - diastolic pressure, MAP - Mean arterial pressure

Data showing the reduction in hemodynamic parameter measured in both groups at baseline and at pre-induction. Study group is showing a statistical significant reduction

ters at the baseline before giving the premedication and pre-induction values. From the data available, decrease in HR, SBP, DBP and MAP can be seen from base line to pre-induction ($p < 0.001$) in the study group C. Figure 1 reveals no change in HR between the groups at baseline, but subsequently clonidine group shows low stable tracing ($p < 0.001$) compared to control group. Figure 2 gives us the data of systolic blood pressure readings, $p = 0.982$ at the baseline, means that there is no difference in between the groups at baseline. Compared to baseline values, pre-induction SBP decreased by 15 to 17 percent in the study group. Similar changes are observed in DBP ($p < 0.001$) and mean arterial pressure ($p < 0.001$) [figures 3 & 4].

Discussion

Pneumoperitoneum used for laparoscopic procedures is a complex patho-physiologic phase with significant hemodynamic variation. Carbon dioxide is most commonly used as it is colourless, non combustible, highly soluble and permeable in tissues thus reducing the risk of gas embolism. The hemodynamic changes associated with pneumoperitoneum are the result of both increased intra-abdominal pressure and hypercarbia [8-17]. Five minutes after the beginning of pneumoperitoneum, there is marked increase of vasopressin and neurophysin. Plasma concentration of vasopressin then decreased; whereas the plasma concentration of neurophysin reaches steady state. The va-

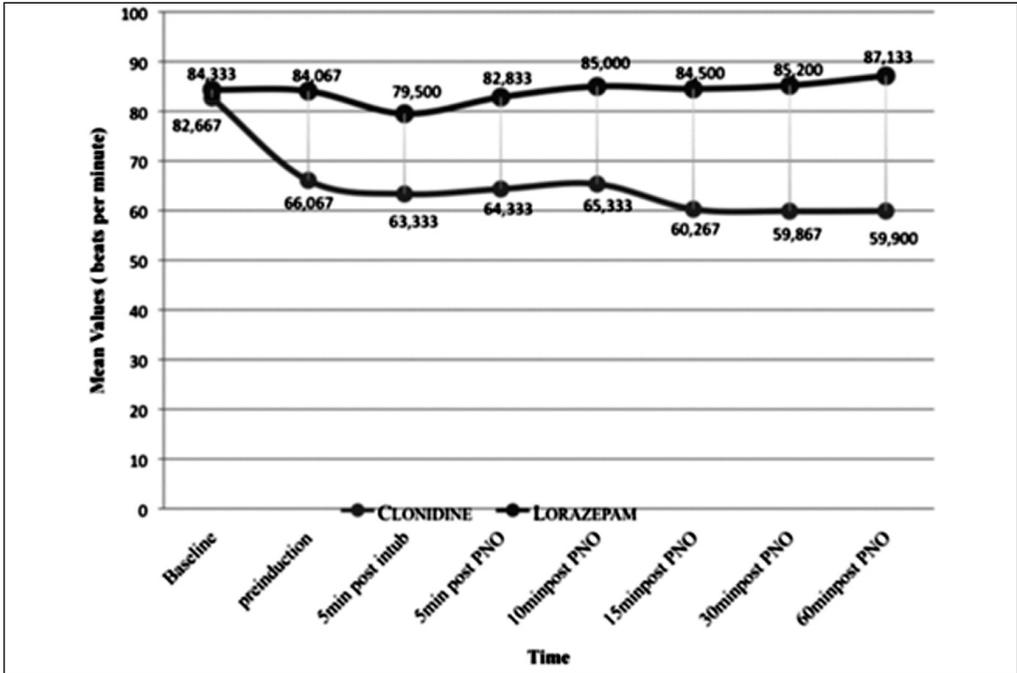


Figure 1: Comparison of heart rate between clonidine and lorazepam group

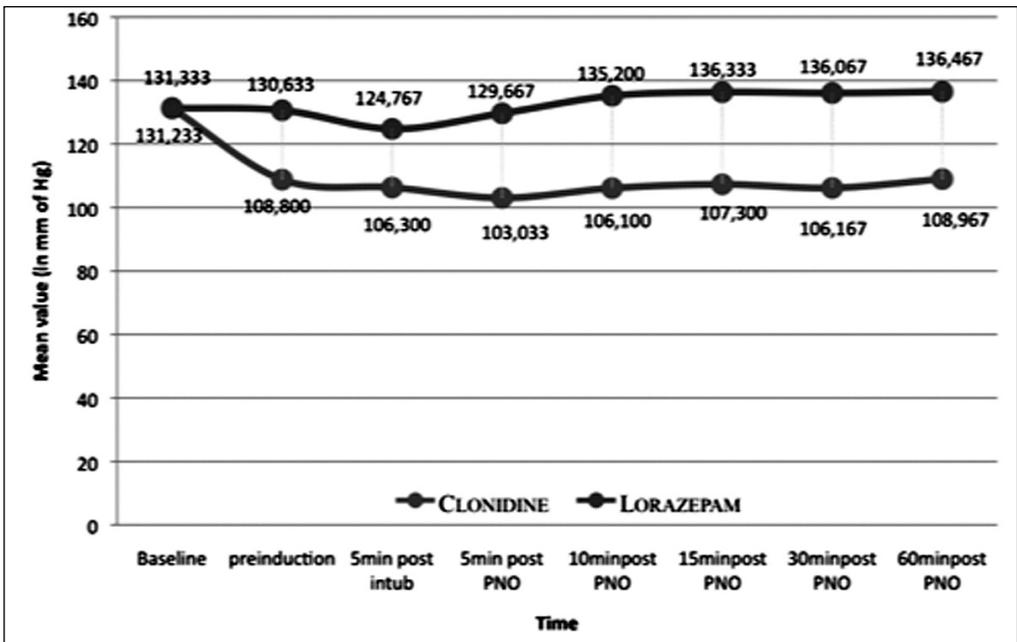


Figure 2: Comparison of systolic blood pressure between clonidine and lorazepam group

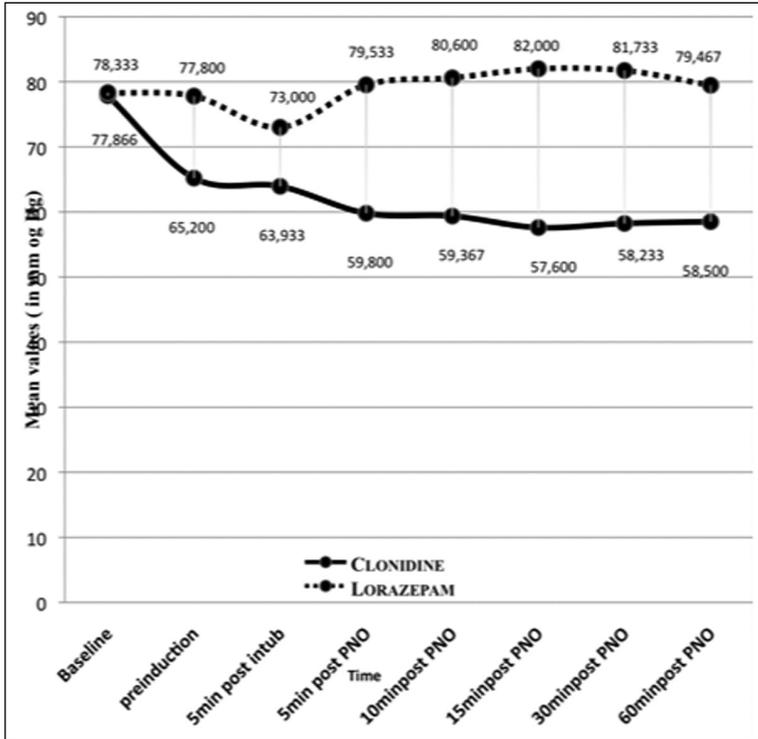


Figure 3: Graph showing the comparison between the study group and control group diastolic blood pressure.

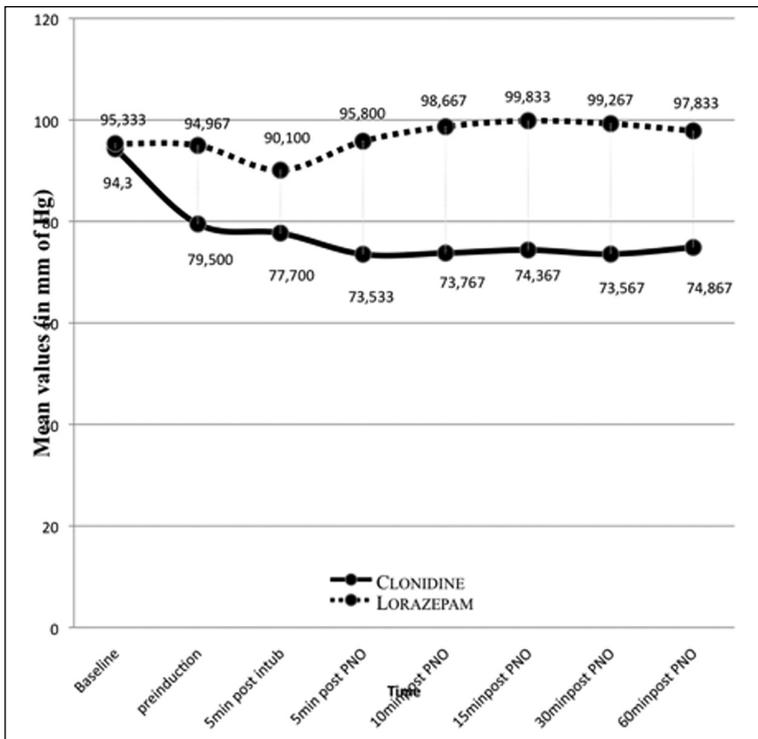


Figure 4: Comparison between the study and control group – mean arterial pressure

sopressin levels were in line with the changes in SVR. Plasma concentrations of epinephrine, norepinephrine and renin also increased during laparoscopy [17]. To attenuate this hemodynamic response, a wide variety of agents are being used both during premedication and induction. Research fellows have tried beta blockers, alpha 2 agonists, magnesium sulphate, opioids, vasodilators, and gasless approach to negate the hemodynamic variations. Alpha 2 agonists have been a topic of discussion since early 80s. The Euro anesthesia [18] 2003 summit has discussed the pharmacology of alpha 2 agonists and anesthesia extensively. Compared to other agents the safety margin for clonidine is ideal 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 [18-20]. Stimulation of these receptors results in the suppression of efferent sympathetic pathways and the subsequent decrease in blood pressure and vascular tone in the heart, kidneys, and peripheral vasculature.

Clonidine premedication dose ranges from 2 to 5 mcg/kg in different studies [21-23]. Sharma [13] and colleagues demonstrated increase in intra-abdominal pressure and volume after pneumoperitoneum. Intra-abdominal pressure of approximate 14 mm Hg raises systemic vascular resistance, heart rate, vena cava pressures and mean arterial pressure, at the same time stroke volume falls. These effects are exaggerated by head up position. In our study the intra-abdominal pressure was kept below 15 mm of Hg. Safran [11] showed that mild hypercarbia 45-50 mm of Hg produces no significant effects. But moderate to severe levels of 50-70 mm of Hg have direct myocardial depressant and vasodilatory effect. There is a moderate decline in cardiac output, stroke volume, systolic blood pressure, and PH due to retained CO₂ and dependent on the volume insufflated. Hence in our study the end tidal carbon dioxide maintained between 25mm of Hg to 35 mm of Hg.

In our study we found that after clonidine premedication the mean heart rate difference between baseline and pre-induction was 16.6003 ($p < 0.001$), systolic blood pressure 22.433 ($p < 0.001$), diastolic blood pressure 12.667 ($p < 0.001$) as well as mean arterial pressure reduced by 14.8 ($p < 0.001$) [Table 2]. In the study done by Aho et al [21] two different strength 3.0mcg and 4.5 mcg per kg intramuscular injection clonidine was given 30 to 45 minutes prior to induction. They noticed significant fall in mean arterial pressure with 4.5mcg dose before induction. Also there was no change in heart rate after premedication. But they noticed decreased heart rate in both groups in recovery room. Taittonen [22] in their study documented 11 percent and 15 percent reduction in systolic arterial pressure and diastolic pressure respectively during perioperative period. They used 4.5mcg /kg clonidine intramuscularly 45-50 minutes before induction. In our study we observed about 14 percent systolic arterial pressure and 16 percent diastolic pressure reduction with average fixed oral dose of 150mcg [except in one patient (body weight 94kgs)] given one hour before induction.

Joris [23,24] et al showed that capnoperitoneum leads to increase in the heart rate and blood pressure due to stretching of peritoneum. The same investigator did two sequential studies to know the hemodynamic changes during laparoscopy and their endocrine correlation along with effect of clonidine premedication (8mcg/kg; IV). Clonidine significantly reduced MAP and HR compared with placebo, but did not significantly affect the release of vasopressin, observed immediately after peritoneal insufflation. Conversely, plasma concentrations of epinephrine and norepinephrine were significantly reduced in the clonidine group. Also clonidine had no effect on cortisol release. In our study also it was evident that hemodynamic stability is much better with clonidine premedication. What we observed was, in the study group there was progressive decrease in heart rate post pneumoperitoneum in the first 30 minutes then followed by a steady state with no

further reduction. None of our patients met the criteria fixed for intra-operative bradycardia which is to be treated. Henceforth clonidine in lower doses per se should not cause alarming low levels of heart rate. When mean arterial pressure is considered the graph-4 is showing almost a straight line indicating the insignificant fluctuation followed by pneumoperitoneum ($p < 0.001$) in comparison to placebo. None of our patients had intra-operative hypotension. Similar studies like Sung [25] observed hemodynamic stability during pneumoperitoneum with 150 mcg oral clonidine. Requirement of isoflurane was also less by 30% in the clonidine group. In another similar study Mrinmoy Das [26] et al used 150mcg oral clonidine which is approximately 2.7mcg/kg. Whereas in our study we used the same strength 150mcg oral clonidine which is approximately 2.0mcg/kg and the control, what we achieved during pneumoperitoneum was mean heart rate(63+/-7), SBP(103+/-4), DBP(60+/-3), MAP(74+/-3). This was much stable and lower than their study. Malek [27], Laisalmi [28] and Yu [29] also reported similar findings of better hemodynamic stability with clonidine premedication. Yuvesh Passi [30] and colleagues used clonidine 150mcg orally. The result of this study is no different from ours; in addition they also highlighted the decreased incidence of postoperative nausea and vomiting. We have taken one hour post pneumoperitoneum as the time limit to assess the effects of clonidine on hemodynamic changes induced by pneumoperitoneum. Henceforth we recommend routine use of Clonidine premedication to laparoscopic surgeries.

Speculation

There are many studies involving drugs to attenuate the hemodynamic turbulence due to pneumoperitoneum. Of all the drugs alpha 2 agonists seem to be more logical. Many earlier studies have been done using clonidine as well as dexmedetomidine. To date no consensus agreement has been reached on what

dose and route should be adequate to prevent the side effects, as well as achieving the desired result. Hence this study was undertaken. Moreover utilisation of clonidine also reduces anesthetic consumption. The future will be the era of alpha 2 agonists.

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