



Hemodynamic Stress Response during Laparoscopic Cholecystectomy: Effect of Oral Administration of Moxonidine

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Abstract

Background: *In the event of laparoscopic surgeries, pneumoperitoneum can prelude to wide array of pathophysiologic changes in the cardiovascular system which may overture to hypertension and tachycardia. Thus, search for an ideal pharmacological agent to prevent the hemodynamic response is vital.*

Objective: *Thus, the present study was undertaken to evaluate the effect of orally administered moxonidine in attenuating the hemodynamic responses that occur during the laparoscopic surgeries.*

Patients and Methods: *A total of 50 adult ASA I and II patients scheduled for elective laparoscopic surgeries were selected for the study. The patients were divided into two groups moxonidine group (M) and placebo group (P). M group received oral moxonidine 0.3 mg at 8 pm on the day before surgery and at 8 am on the day of surgery. P group received a placebo at the same timing as that of the M group.*

Results: *Following pneumoperitoneum rise in systolic blood pressure (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and heart rate (HR) was higher in P group in comparison to M group which was statistically significant.*

Conclusion: *Significant rise in HR, SBP, DBP, and mean BP was noted in the P group in comparison to moxonidine group. Moxonidine provided better preoperative hemodynamic stability in patients undergoing laparoscopic surgeries.*

Keywords: Laparoscopic surgery, moxonidine, pneumoperitoneum, hemodynamic changes.

Introduction

Laparoscopic cholecystectomy has become gold standard surgery for cholelithiasis ^[1]. Advantages of laparoscopic cholecystectomy are shorter hospital stay, early ambulation, smaller scar, and less compromised postoperative respiratory and

gastro-intestinal functions. However, the procedure is not risk free as it is associated with significant hemodynamic changes due to creation of pneumoperitoneum, potential for systemic absorption of carbon dioxide, and reverse Trendelenberg position. ^[2] The pneumoperitoneum

created for the procedure induce various pathophysiologic changes that makes anesthetic management difficult. These changes include increase in the heart rate, increase in mean arterial pressure, decrease in cardiac output and increase in systemic vascular resistance which can lead to altered tissue perfusion [2]. Postoperative nausea and vomiting is a major drawback of laparoscopic surgery.[3] Various pharmacological agents like nitroglycerine, β blocker, and opioids are used to provide hemodynamic stability during pneumoperitoneum,[4] but they have their own disadvantages.

Moxonidine is a selective imidazoline receptor agonist. Moxonidine stimulates imidazoline type 1(I1) receptors in the cardiovascular regulatory centers of the medulla oblongata, the Rostral Ventrolateral Medulla (RVLM). Selective stimulation of Imidazoline1 (I1) receptor inhibits central sympathetic activity, leading to a reduction in blood pressure. With this backdrop, the present study was scrutinized to evaluate the effect of orally administered moxonidine in the attenuation of the hemodynamic responses seen during laparoscopic cholecystectomy.

Patients and Methods

After institutional review board approval and informed written consent from the patients, this prospective, randomized, double-blind controlled clinical study was carried out in 50 patients of either sex, aged 20–60 years, of ASA physical status I and II, scheduled for laparoscopic cholecystectomy under general anesthesia from January 2014 to October 2015. Exclusion criteria were patients with anticipated difficult airway; body mass index (BMI) >25, history of cardiopulmonary diseases; psychiatric illness; and therapy with α -2 adrenergic agonists, β blocker, methyl dopa, MAO inhibitors, tricyclic antidepressant, and benzodiazepines.

In the pre-anesthetic preparation room, monitoring for heart rate (HR), non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP), peripheral

oxygen saturation (SpO₂), and end-tidal CO₂ (EtCO₂) was instituted. Further, routine investigations like Haemogram, Complete Urine Analysis (CUE), Blood Chemistry (LFT, Serum Electrolytes, Serum Protein) were done. Patients were kept nil by mouth for 8 hours preoperatively. The patients were randomly divided into two groups,

- Group M: Received Moxonidine 0.3 mg at 8 pm the day before surgery and at 8 am on the day of surgery
- Group P: Received placebo at 8 pm the day before surgery and at 8 am on the day of surgery.

Anaesthetic Procedure

Intravenous cannulation was done with 18G cannula after shifting the patients into the waiting area of the operation theatre, and infusion of ringer lactate solution was started. The patients were premedicated with Fentanyl, Glycopyrrolate, Ondansetron, Ranitidine 30 minutes before induction. After shifting to the operation theatre the patients were connected to non-invasive blood pressure monitor, pulse oximeter probe and electrocardiographic leads (limb lead-2).

All patients were pre oxygenated with 100% oxygen for 3 minutes. Induction of anesthesia was carried out with Thiopentone sodium; intubation was facilitated by using Vecuronium bromide. Intubation was achieved with an appropriate size oral cuffed, portex endotracheal tube with the aid of Macintosh laryngoscope blade.

Anesthesia was maintained with Vecuronium bromide and intermittent positive pressure ventilation with nitrous oxide and oxygen in the ratio of 66%: 33% with 0.6% Isoflurane using circle absorber system connected to the Boyle's anesthetic workstation. Pneumoperitoneum (PP) was created and maintained by insufflation of carbon dioxide.

The table was tilted to about 15° reversed Trendelenburg position with left side rotation to facilitate exposure of the gall bladder. Intra-abdominal pressure was maintained between 12–15 mm Hg during the surgery. Throughout the

study period, all the parameters selected (HR, SBP, DBP, MAP, SpO₂ and ETCO₂) were recorded at specified timings. Any change in hemodynamic variables more than 20% on either side of baseline was considered significant.

Any increase in MAP up to 20% from baseline was treated by increasing the concentration of Isoflurane to a maximum 2% or nitroglycerine infusion so as to maintain the MAP within 20% of baseline. Time duration from creation of pneumoperitoneum to the release of pneumoperitoneum was taken as duration of pneumoperitoneum. At the end of surgery, neuromuscular blockade was reversed with neostigmine 60 µg/ kg and glycopyrrolate 10µg/kg intravenously. After satisfying the extubation criteria, trachea was extubated and patients were transferred to post-anesthesia care unit (PACU).

All patients were assessed for changes in hemodynamic parameters (HR, SBP, DBP, MAP) prior to premedication (pre op), before induction, after laryngoscopy and intubation, after pneumoperitoneum, followed by every 10 min for 40 min, then thereafter every 20 min till end of pneumoperitoneum and after extubation. All the observations were standardized to 60 minutes post- pneumoperitoneum so as to maintain uniformity in all the cases.

Statistical analysis

The results were expressed as Mean+ S.D. and they were calculated for all the quantitative variables using SPSS statistical software version. Comparison between two groups at a time (inter-group comparison) was done using Student's unpaired t-test. P <0.05 was considered statistically significant, value < 0.01 was considered highly significant, value > 0.05 was considered insignificant.

Results

There was no significant differences were found with respect to age, weight, and gender (Table 1). The mean pulse rate in the preoperative, at induction, at intubation, before PNP, at 5 min,10

min,20 min,30 min,40 min,60 min after PNP, at the end of PNP, extubation is lower in moxonidine group than placebo group. The results were statically significant (P<0.05) (Table 2).

The systolic blood pressures in the moxonidine group were on the lower side when compared to the placebo group. The pre op SBP in Moxonidine group (119.20+8.63) mm Hg was comparable to that of the placebo group 126.92+7.60 mm Hg; (p value 0.001). [Table 3]. Moxonidine group did not show a significant rise in systolic blood pressure post intubation and after creation of pneumoperitoneum. The SBP in the placebo group was fluctuating throughout the procedure; maintaining on the higher side. The intubation response and the extubation response of SBP were attenuated in the moxonidine group but not in the placebo group. The results were statistically significant. (P < 0.05)

The pre op DBP values were lower in the Moxonidine group (77.44+6.48) mm Hg than that of the placebo group (84.76+7.13) mm Hg; (p value 0.001) [Table 4]. But there were no fluctuation in the diastolic blood pressures intraoperatively among the two groups. The post-operative DBP values did not vary much when compared to the pre-operative DBP values. The results were statistically significant. (P < 0.05).

The preop (94.44+3.36) mm Hg, intraop (97.80+3.88) and post op (95.16+4.24) mm Hg MAP values were around the same range in the Moxonidine group. The MAP in the placebo group was on a higher side compared to the moxonidine group; pre op 98.24+4.59 mm Hg vs. 94.44+3.36 mm Hg, p value: 0.001 and the post op MAP 108.04+4.15vs. 95.16+4.24, p value: 0.001[Table 5]. The results were statistically significant. (P < 0.05).

Table 1: Comparison of Age, Sex, and Weight between Moxonidine and Placebo

Parameter	MOXONIDINE	PLACEBO	P VALUE
Age	41.24±6.17	41±7.35	0.9
Sex (M/F)	12:13	11:14	
Weight	66.32±6.38	66.80±6.08	0.78

Table 2: Comparison of Mean Pulse Rate between Moxonidine and Placebo

	MOXONIDINE MEAN ± SD	PLACAEO MEAN ± SD	P VALUE
Pre op	85.76 +9.76	98.08+8.08	0.0001
At Induction	90+7.37	95.56+7.78	0.01
After Intubation	93.6+5.6	104.44+4.33	0.0001
Before PNP	89.2+4.85	99.32+5.21	0.0001
5 min after PNP	98.32+7.95	106+6.80	0.0006
10 min after PNP	90.36+4.18	112.76+5.91	0.0001
20 min after PNP	87.92+4.86	113.1+1.6	0.0001
30min after PNP	84.68+4.70	110.64+4.23	0.0001
40min after PNP	83.08+3.45	108+4.26	0.0001
60min after PNP	80.56+4.30	103.6+5.53	0.0001
End of PNP	83.56+4.59	100.28+4.62	0.0001
Extubation	84.48+7.51	101.12+8.04	0.0001

Table 3: Comparison of Mean Systolic Blood Pressure between Moxonidine and Placebo

	MOXONIDINE MEAN ± SD	PLACAEO MEAN ± SD	P VALUE
Pre op	119.20+8.63	126.92+7.60	0.0016
At Induction	123.72+6.54	126.48+6.58	0.14
After Intubation	124.20+7.58	130.96+3.98	0.0003
Before PNP	124.32+7.91	129.12+7.03	0.027
5 min after PNP	126.08+6.30	141.28+4.20	0.0001
10 min after PNP	125.28+5.90	134.48+2.82	0.0001
20 min after PNP	124.04+5.42	132.88+3.93	0.0001
30min after PNP	122.44+4.80	131.68+5.24	0.0001
40min after PNP	122.68+6.30	134.72+4.50	0.0001
60min after PNP	123.04+4.65	134.40+4.07	0.0001
End of PNP	122.44+3.74	130.84+4.38	0.0001
Extubation	122.52+4.91	131.12+2.88	0.0001

Table 4: Comparison of Mean Diastolic Blood Pressure between Moxonidine and Placebo

	MOXONIDINE MEAN ± SD	PLACAEO MEAN ± SD	P VALUE
Pre op	77.44+6.48	84.76+7.13	0.0004
At Induction	82.80+3.93	82.44+6.15	0.8
After Intubation	83.20+3.88	89.72+5.00	0.0001
Before PNP	83.1+3.92	84.54+6.16	0.13
5 min after PNP	85.08+2.94	92.52+4.08	0.0001
10 min after PNP	84.60+2.65	92.6+3.48	0.0001
20 min after PNP	83+2.8	90.52+4.46	0.0001
30min after PNP	82.24+2.28	90.72+3.30	0.0001
40min after PNP	81.2+3.49	91.84+3.31	0.0001
60min after PNP	85.64+3.44	89.12+3.77	0.0001
End of PNP	86.2+4.03	92.6+4.91	0.0001
Extubation	83.20+3.88	94.4+7.18	0.0001

Table 5: Comparison of Mean Arterial Blood Pressure between Moxonidine and Placebo

	MOXONIDINE MEAN ± SD	PLACAEBE MEAN ± SD	P VALUE
Pre op	94.44+3.36	98.24+4.59	0.0016
At Induction	97.72 +4.42	98.40+2.71	0.51
After Intubation	97.80+3.88	106.24+4.22	0.0001
Before PNP	100.28+3.58	102.52+3.70	0.03
5 min after PNP	98.8+4.68	105.12+3.3	0.0001
10 min after PNP	96.88+4.92	102.20+3.89	0.0001
20 min after PNP	95.64+5.08	102.44+4.94	0.0001
30min after PNP	95.24+2.82	103.96+3.54	0.0001
40min after PNP	95.24+4.16	103.88+4.28	0.0001
60min after PNP	92.64+4.03	107.16+3.73	0.0001
End of PNP	91.76+4.19	100.28+5.38	0.0001
Extubation	95.16+4.24	108.04+4.15	0.0001

Discussion

Pneumoperitoneum during the laparoscopic surgery can lead to significant hemodynamic changes such as an increase in MAP and SVR and a decrease in cardiac output^[5]. These hemodynamic responses can result in complications such as myocardial ischemia, cerebral hemorrhage, and difficulty in mechanical ventilation of patients. Moxonidine is a centrally acting antihypertensive drug that reduces arterial BP by inhibiting central sympathetic activity^[6]. Its chemical formula is 4-chloro-N-(imidazolidin-2-ylidene)-6-methoxy-2-methyl-5-pyrimidinamine. Its empirical formula is C₉H₁₂CIN₅O and its molecular weight is 241.68^[7]. Moxonidine is an imidazoline compound which acts on IIR in the central nervous system to reduce sympathetic activity and BP.

Farsang, his review of moxonidine, concluded that it suppresses sympathetic tone and effectively reduces BP for at least 24 hrs, and therefore, it can be administered once daily^[8]. Joris *et al.* investigated hemodynamic changes induced by carbon dioxide insufflations in pneumoperitoneum and concluded that vasopressin and catecholamines are probable mediators in increasing the SVR observed during pneumoperitoneum. They concluded that clonidine can modulate the hemodynamic changes due to pneumoperitoneum^[9]. Koivusalo *et al.*, in their study, have shown that postoperative recovery after laparoscopic

cholecystectomy was faster and uneventful when carbon dioxide was not used for pneumoperitoneum. They suggested that mechanical abdominal lift method without carbon dioxide insufflations is better for laparoscopic cholecystectomy may be the method of choice while considering laparoscopic cholecystectomy^[10]. Fenton *et al.*, in their review, observed that moxonidine acts centrally to reduce central and peripheral sympathetic activity, thus decreasing peripheral vascular resistance. In patients with mild to moderate hypertension, moxonidine reduces BP as effectively as most first-line antihypertensive. It improves the clinical and metabolic profile in patients with hypertension and diabetes mellitus^[11]. Malek *et al.* evaluated the effect of moxonidine on the attenuation of hemodynamic response during laparoscopic cholecystectomy in comparison with clonidine. They had concluded that administration of clonidine in premedication before laparoscopic cholecystectomy provides better results; compared to moxonidine^[12]. Sung *et al.* studied the effect of oral clonidine as premedication on preoperative hemodynamic response and post-operative analgesic requirement for patients undergoing laparoscopic cholecystectomy and observed that oral clonidine premedication helped to provide preoperative hemodynamic stability. It reduced the use of isoflurane and requirement of post-operative analgesia^[13]. Das *et al.* studied the

effect of clonidine premedication on hemodynamic changes during laparoscopic cholecystectomy. They concluded that clonidine is safe and effective in providing stable hemodynamics. It protects against stress response due to pneumoperitoneum in patients undergoing laparoscopic cholecystectomy^[14].

Bansal and Hooda concluded in his review of newer drugs in anesthesia that clonidine is not only a good antihypertensive but also it provides perioperative hemodynamic stability and obtunds pressure response to endotracheal intubation^[15].

Banday and Sameer, in his article, reviewed effect of gabapentin and opined that like clonidine, gabapentin also attenuates hemodynamic stress response to direct laryngoscopy and tracheal intubation^[16]. In our study, the overall hemodynamic profile was stable in the moxonidine group when compared to the P group. The fluctuations in mean pulse rate, SBP, DBP, and MAP were significant throughout the intraoperative period in the moxonidine group compared to P group. The results obtained in our study are consistent with the previous studies which used clonidine and dexmedetomidine in reducing stress response due to pneumoperitoneum. Moxonidine has a favorable effect on the clinical and metabolic profile in the body. Hence, it can be used in patients having some derangement in the metabolic profile with regard to blood sugar levels, lipid profile, etc. Moxonidine may have an edge over other centrally acting antihypertensive like clonidine and dexmedetomidine due to their side effects like bradycardia and sedation.

Thus in conclusion, the clinical utility of moxonidine in laparoscopic surgeries is a promising approach in attenuating the hemodynamic response during the intraoperative period. It not only prevents stress response due to endotracheal intubation and extubation but also facilitates smooth recovery from anesthesia.

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