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ORIGINAL ARTICLE

EFFECT OF ORAL MOXONIDINE IN THE ATTENUATION OF THE HEMODYNAMIC RESPONSES SEEN DURING LAPAROSCOPIC CHOLECYSTECTOMY: A CLINICAL STUDY

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ABSTRACT: BACKGROUND: Pneumoperitoneum required for laparoscopic surgeries results in various pathophysiologic changes in the body, especially in the cardiovascular system. Moxonidine is a selective Imidazoline I_1-receptor agonist with an I_1:α_2 affinity ratio of 40:1 to 70:1. Through an action in the Rostral Ventrolateral Medulla (RVLM), where the I_1 receptors are situated, it reduces sympathetic outflow and lowers peripheral vascular resistance. BP reduction is not accompanied by any significant change in heart rate or cardiac output. **AIMS AND OBJECTIVES:** The aim of our study was to evaluate effect of orally administered Moxonidine in attenuating the hemodynamic responses that occur during laparoscopic cholecystectomy. **MATERIALS AND METHODS:** 50 adult ASA I and II patients scheduled for elective laparoscopic cholecystectomy were selected for this prospective randomized double blinded comparative study. They were randomly allocated to two groups; Moxonidine group and Placebo group. Moxonidine group received oral Moxonidine 0.3 mg at 8 PM the day before surgery and at 8 AM on the day of surgery. Placebo group received a placebo at the same timing as that of the Moxonidine group. **RESULTS:** When vital parameters were compared significant rise in heart rate, systolic, diastolic and mean blood pressure was noted in the Placebo group following pneumoperitoneum, where as in Moxonidine group the rise was not more than 20% of baseline. **CONCLUSION:** In conclusion, Moxonidine when administered preoperatively provides perioperative hemodynamic stability in ASA I and II patients undergoing laparoscopic cholecystectomy. It's other benefits such as absence of reflex tachycardia, preservation of hepatic and renal function makes it a good choice for laparoscopic procedure.

KEYWORDS: Laparoscopic cholecystectomy, Pneumoperitoneum, Hemodynamic response, Moxonidine, Imidazoline receptor, Rostral Ventrolateral Medulla.

INTRODUCTION: No other surgery has been so profoundly affected by the advent of laparoscopy as cholecystectomy. In fact, laparoscopic cholecystectomy has been instrumental in ushering the laparoscopic era. Laparoscopic cholecystectomy has rapidly become the procedure of choice for routine gallbladder removal and has become the most common major abdominal procedure performed. Laparoscopic cholecystectomy requires pneumoperitoneum and thus routinely requires general anesthesia with endotracheal intubation and intermittent positive pressure ventilation.[1] The pneumoperitoneum created for the procedure induce various pathophysiologic changes that makes anesthetic management difficult.[2]

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. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum. These included gasless laparoscopy,[3, 4] use of β adrenergic

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blockers,[5] Nitroglycerine,[6] calcium channel blockers and α-2 agonists such as Clonidine[7] and Dexmedetomidine.[8]

Moxonidine is a selective imidazoline receptor agonist. Moxonidine stimulates imidazoline type 1(I_1) receptors in the cardiovascular regulatory centers of the medulla oblongata, the Rostral Ventrolateral Medulla (RVLM). Selective stimulation of I_1 receptors inhibits central sympathetic activity, leading to a reduction in blood pressure. With this background, the study was designed to evaluate the effect of orally administered moxonidine in the attenuation of the hemodynamic responses seen during laparoscopic cholecystectomy.

MATERIALS AND METHODS: The present study was conducted in Osmania General Hospital, Afzalgunj, Hyderabad in the Dept. of General Surgery and Dept. of Surgical Gastroenterology. The study spanned over a period of one and a half year; from January 2012 to May 2013. After approval of Institutional Ethics Committee and written informed consent, 50 healthy adult patients of ASA physical status I and II of either sex aged 20 to 60 years, scheduled for elective laparoscopic cholecystectomy under general anesthesia were enrolled for this double blind prospective randomized study.

Patients with Hypertension, History of cardiac, pulmonary, hepatic or renal disease, psychiatric disorder, any drug therapy of beta blockers, methyldopa, and monoamine oxidase (MAO) inhibitors were excluded from the study. Other exclusion criterion were Body mass index >30, Patients with the base line heart rate<60 beats per minute, Base line systolic blood pressure <100mmhg, ECG abnormalities, patients in whom intubation was thought to be difficult.

Preanaesthetic checkup and routine investigations like complete blood count, serum creatinine and ECG were done. Patients were kept nil by mouth for 8 hours preoperatively.

They were randomly assigned to one of the two groups to receive either Moxinidine 0.3 mg at 8 pm the day before surgery and at 8 am on the day of surgery (Moxonidine group) or Placebo. The observer was totally blind about the groups or medications received by the patients.

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 15^0 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,

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SpO_2 and $ETCO_2$) 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 10 µg/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. The results were expressed as Mean+ S.D. Mean and standard deviation were calculated for all the quantitative variables using SPSS statistical software version 20.

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, gender [Table 1], time between premedication to anesthetic induction, duration of laryngoscopy and surgical procedure. The anesthetic technique did not differ among the study groups.

The overall hemodynamic profile was stable in the Moxonidine group when compared to the placebo group.

- The preoperative mean pulse rate was lower in the Moxonidine group (85.9 + 17.6) per min when compared to the placebo group (100.9 + 9.4) per min; (p value 0.001) [Table 2]. There was no difference in the intubation response with regard to mean pulse rate in both the groups but the rise in the pulse rate after creating pneumoperitoneum was higher in the placebo group whereas the pulse rate was maintained at a stable level in the moxonidine group. The results were statistically significant. ($P < 0.05$)
- 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 (121.7+10.1) mm Hg was comparable to that of the placebo group 129.4+6.1 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. ($P < 0.05$)
- There was no gross variation in the DBP in both the groups. The pre op DBP values were lower in the Moxonidine group (78.8+8.3) mm Hg than that of the placebo group (86.0+7.3) mm Hg; (p value 0.001) [Table 4]. But there were no fluctuation in the diastolic blood pressures

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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).

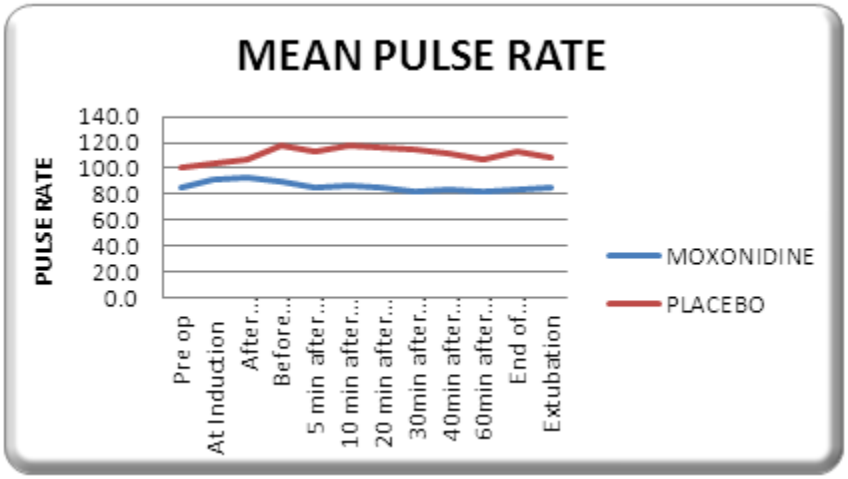
- The mean arterial pressure in the Moxonidine group did not show gross variations. The preop (93.1+8.5) mm Hg, intraop (96.0+7.8 mmHg) and post op (96.2+7.9) mm Hg MAP values were around the same range in the Moxonidine group. The MAP in the placebo group was on a higher side compared to the moxonidine group; pre op 100.5+ 5.6 mm Hg vs. 93.1+8.5 mm Hg, p value: 0.001 and the post op MAP 109.4+6.8 vs. 96.2+ 7.9, p value: 0.001[Table 5]. The results were statistically significant. (P < 0.05).

PARAMETERS	MOXONIDINE	PLACEBO
AGE (YRS)	41+13.2	40+12.9
GENDER RATIO (M:F)	11:14	12:13

TABLE 1: DEMOGRAPHIC PROFILE

MEAN PULSE RATE (per min)			
EVENT	MOXONIDINE (MEAN+S.D)	PLACEBO (MEAN+S.D)	P value
Pre op	85.9+ 17.6	100.9+ 9.4	.001
At Induction	90.8+ 15.6	103.1+ 9.6	.002
After Intubation	92.8+16.5	106.2+7.7	.004
Before PNP	90.6+ 13.5	117.3+ 5.6	.001
5 min after PNP	85.4+ 22	113.4+ 5.5	.001
10 min after PNP	86.9+ 16.2	117.9+ 9.6	.001
20 min after PNP	85.8+ 14.1	116.8+ 10.4	.001
30min after PNP	82.6+ 14.7	114.2+ 8.8	.001
40min after PNP	83.3+ 13.9	111.4+ 6	.001
60min after PNP	81.9+ 13	106.6+ 10	.001
End of PNP	83.4+ 12.2	112.4+6.6	.001
Extubation	85.5+ 14	109.2+ 8.8	.001

TABLE 2: COMPARISION OF MEAN PULSE RATES BETWEEN MOXONIDINE AND PLACEBO



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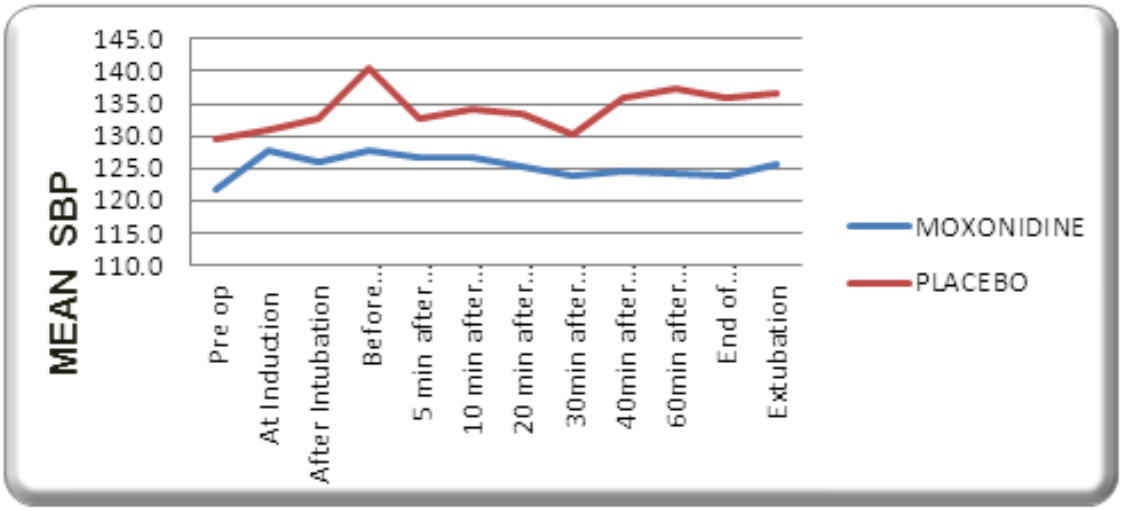
MEAN SYSTOLIC BLOOD PRESSURE (mm Hg)			
EVENT	**MOXONIDINE (MEAN+S.D)**	**PLACEBO (MEAN+S.D)**	**P value**
Pre op	121.7 + 10.1	129.4 + 6.1	.001
At Induction	127.7 + 12.1	130.8 +12.3	.573
After Intubation	126.1 + 25.7	132.8 + 5.9	.874
Before PNP	127.9 + 13.9	140.6 + 5.2	.001
5 min after PNP	126.8 + 12.3	132.8 + 5.3	.03
10 min after PNP	126.5 + 11.1	134.2 + 5.8	.004
20 min after PNP	125.3 + 10.8	133.5 +6.1	.001
30min after PNP	123.7 + 10.1	130.2 + 14.8	.152
40min after PNP	124.7 + 13.6	135.9 + 10	.01
60min after PNP	124.1 + 10.2	137.3 + 11.3	.001
End of PNP	123.7 + 11.3	136.0 + 8.9	.002
Extubation	125.4 + 10.5	136.4 + 9.1	.001

TABLE 3: COMPARISION OF MEAN SYSTOLIC BLOOD PRESSURES BETWEEN MOXONIDINE AND PLACEBO



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MEAN DIASTOLIC BLOOD PRESSURE (mm Hg)			
EVENT	**MOXONIDINE (MEAN+S.D)**	**PLACEBO (MEAN+S.D)**	**P value**
Pre op	78.8 + 8.3	86.0 + 7.3	.001
At Induction	84.0 + 12.3	88.2 + 7	.383
After Intubation	82.1 + 16.4	92.0 + 11.1	.137
Before PNP	85.7 + 12.5	90.6 + 5.7	.08
5 min after PNP	83.1 + 11.5	92.6 + 10.4	.004
10 min after PNP	83.5 + 10	90.0 + 6.3	.009
20 min after PNP	82.9 + 10.5	89.2 + 9.8	.036
30min after PNP	83.3 + 12.2	92.5 + 8.9	.015
40min after PNP	81.7 + 11.4	91.8 + 7.3	.011
60min after PNP	81.4 + 9.9	90.4 + 6.8	.012
End of PNP	80.9 + 9.3	92.2 + 8.8	.001
Extubation	81.6 + 7.5	95.8 + 8.2	.001

TABLE 4: COMPARISION OF MEAN DIASTOLIC BLOOD PRESSURES BETWEEN MOXONIDINE AND CONTROL

MEAN ARTERIAL PRESSURE (mm Hg)			
EVENT	**MOXONIDINE (MEAN+S.D)**	**PLACEBO (MEAN+S.D)**	**P value**
Pre op	93.1 + 8.5	100.5 + 5.6	.001
At Induction	98.6 + 11.6	102.4 + 6.3	.383
After Intubation	96.8 + 19.1	105.6 + 7.9	.306
Before PNP	99.8 + 12.1	107.3 + 5.1	.008
5 min after PNP	97.7 + 10.9	106.0 + 7.1	.003
10 min after PNP	97.9 + 9.2	104.8 + 4.3	.002
20 min after PNP	96.0 + 7.8	103.9 + 6.9	.001
30min after PNP	96.2 + 10.1	105.0 + 6	.006
40min after PNP	96.0 + 11.1	106.5 + 5.8	.004
60min after PNP	95.6 + 9.6	106.0 + 6.3	.001
End of PNP	95.2 + 9.6	106.8 + 7	.001
Extubation	96.2 + 7.9	109.4 + 6.8	.001

TABLE 5: COMPARISION OF MEAN ARTERIAL PRESSURES BETWEEN MOXONIDINE AND PLACEBO

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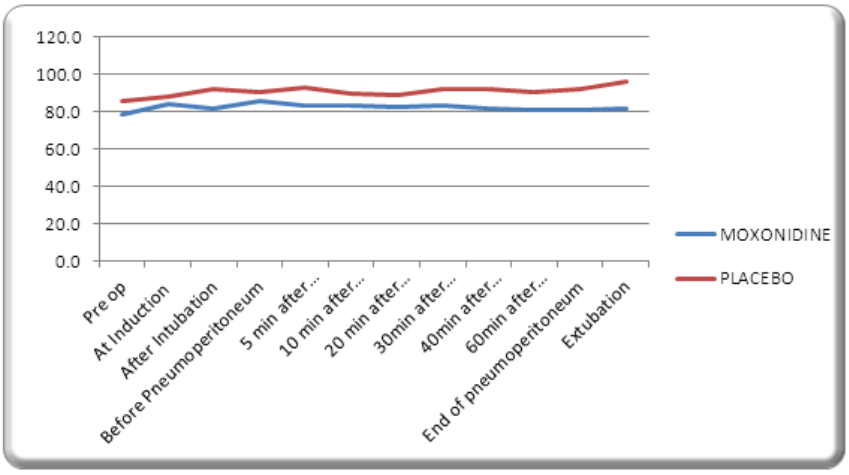

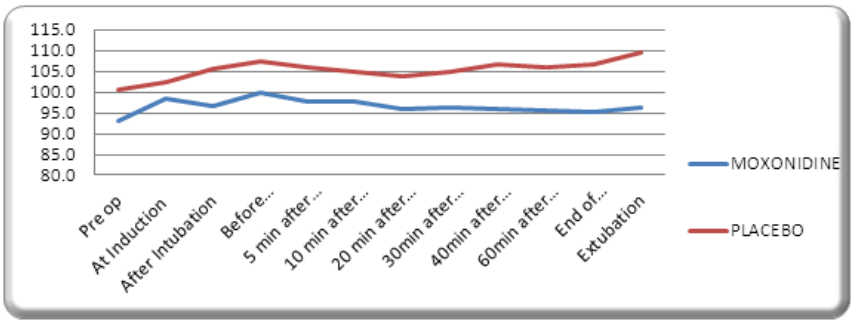

DISCUSSION: Pneumoperitoneum during laparoscopic surgery leads to significant hemodynamic changes such as an increase in MAP and systemic vascular resistance (SVR) and a decrease in cardiac output. These hemodynamic responses can be detrimental due to associated risk of myocardial ischemia or cerebral hemorrhage; therefore these should be attenuated.[9, 10]

A Study by Joris JL et al[11] concluded that Vasopressin and catecholamines probably mediate the increase in systemic vascular resistance observed during PNP.

Moxonidine is a centrally acting anti-hypertensive drug that reduces arterial blood pressure by inhibiting sympathetic activity. Its chemical formula is 4-chloro-N-(imidazolidin-2-ylidine)-6-methoxy-2-methyl-5-pyrimidinamine.Its empirical formula is $C_9H_{12}CIN_5O$, and its molecular weight is 241.68. Moxonidine is an imidazoline compound which acts on I_1 imidazoline receptors in the central nervous system to reduce blood pressure.[12]

The site of action of Moxonidine in the CNS is thought to be the rostral ventrolateral medulla (RVLM), an area of the medullary reticular formation that contains neurones which control the preganglionic sympathetic neurons in the spinal cord. Maintenance of arteriolar smooth muscle tone and thus of peripheral resistance is dependent on the tonic discharge of neurons in this area. The RVLM is also the site of termination of afferent baroreceptor neurons, and this area orchestrates the reflex control of BP. This novel mechanism is claimed to lead to fewer adverse effects (sedation and dry mouth) than older centrally-acting agents such as Clonidine.[13]

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In our study, the overall hemodynamic profile was stable in the Moxonidine group when compared to the placebo group. The mean pulse rate, SBP, DBP, MAP were stable throughout the procedure in the moxonidine group without any significant fluctuations intraoperatively. The results obtained in our study are consistent with previous studies which used Clonidine,[7,14-16] Dexmedetomidine[8] in attenuating hemodynamic responses to laparoscopic cholecystectomy.

Málek J.et al[17] evaluated the effect of Moxonidine 0.3 mg (n = 22) and 0.4 mg (n = 25) p.o. on the attenuation of haemodynamic response during laparoscopic cholecystectomy in comparison with clonidine 150 μg i.v. (n = 23) and control group (n = 22). Though Málek J. et al had concluded that administration of Clonidine in premedication before laparoscopic cholecystectomy provides better results; compared to moxonidine we have not done any comparison with Clonidine. Only a control group was used for comparison.

As Moxonidine has a favorable effect on the metabolic profile in the body, it's use in patients undergoing laparoscopic cholecystectomy is advantageous as most of these patients have some derangement in the metabolic profile with regard to blood sugar levels, lipid profile etc. Moxonidine has an edge over other centrally acting anti-hypertensive like Clonidine and Dexmedetomidine in avoiding gross sedation. Other adverse effects of Clonidine such as dryness of mouth, rebound hypertension are not observed with Moxonidine which makes it a more preferable choice.

CONCLUSION: The use of Moxonidine in laparoscopic cholecystectomy is a promising approach in attenuating the hemodynamic response (PR, SBP, DBP, MAP) not only during the operative procedure but also at induction of anaesthesia, endotracheal intubation, recovery from anesthesia and post-operative period. In view of its safety profile, Moxonidine is worth considering not only in ASA grade I and II patients but also in ASA grade III patients also because of the stable hemodynamics it ensures when used.

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