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Effect of Oral Moxonidine in the Attenuation of the Hemodynamic Responses Seen during Laparoscopic Cholecystectomy: A Clinical Study

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Abstract

Background and Aims: Moxonidine is a selective Imidazoline type 1 receptor agonist. It has a central sympatholytic action and it is used orally as an antihypertensive agent. Selective stimulation of I 1 receptors in the cardiovascular regulatory centers of the medulla oblongata, causes inhibition of central sympathetic activity, leading to a reduction in blood pressure. Laparoscopic procedures are becoming increasingly common in the current era of minimal- access surgeries and anesthesiologists need to be prepared for the perioperative challenges. Creation of pneumoperitoneum causes hemodynamic changes due to increased intra- abdominal pressures and hypercarbia. Several agents have been studied for attenuating the hemodynamic responses to pneumoperitoneum, including antihypertensives, opioids, alpha-2 agonists, ventilatory strategies and positional alterations. This study aims to analyze the effect of oral Moxonidine premedication in the attenuation of hemodynamic responses during laparoscopic cholecystectomies. *Methods:* Sixty ASA grade 1 and 2 patients were randomly selected after ethical approval. Patients were blinded by sealed envelope technique and randomly allocated into one of the two groups to receive either tablet Moxonidine 0.2mg at 8pm the day before surgery and at 8am on the day of surgery (group M, n=30) or placebo, control group (group C, n=30). The anesthesiologist was also blinded about the groups or medications received by the patients.Standard general anesthesia with endotracheal intubation and muscle relaxation was administered. All vital parameters were recorded at different time intervals as before induction (B), after intubation (AI), before pneumoperitoneum (BPN), after pneumoperitoneum (APN), and later at every 10 minutes (APN 10, APN 20, APN 30, APN 40, APN 50, APN 60, APN 90), at release of pneumoperitoneum (RPN), after reversal (AR) and at 15 and 30 minutes after reversal (AR 15 , AR 30). Any change in hemodynamic variables more than 20% from the baseline was considered significant. The observations were recorded and subjected to statistical analysis using SPSS statistical software. Student's 't' test was used for inter-group comparison, with P value < 0.05 considered significant. *Results:* The preoperative baseline mean HR was lower in group M (85.90±17.60) as compared to group C (100.90±9.40). The preoperative basal values of mean (±SD) SBP were significantly lower in group M (121.70±10.10) as compared to group C (129.40±6.10). The preoperative basal values of mean (±SD) DBP were significantly lower in study group (78.80±8.30) when compared to control group (86.00±7.30). *Conclusion:* Moxonidine is a new generation centrally acting anti-hypertensive, licensed for the treatment of mild to moderate essential hypertension. The use of oral Moxonidine in minimal-access procedures can be recommended as a routine premedication in view of its safety profile.

Keywords: Moxonidine; Hemodynamic Responses; Laparoscopic Cholecystectomy; Imidazoline Receptor; Pneumoperitoneum; Central Sympatholytics.

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Introduction

The laparoscopic approach for both diagnostic and operative surgeries is considered to be a safe and reliable technique with several advantages over the standard open procedure [1,2].

Laparoscopic abdominal surgery is one of the most commonly undertaken procedures in general surgery with the overall complication rate and mortality being less than 1.5% and 0.1% respectively [3]. Because of its better cosmesis, less postoperative pain, decreased hospital stay and lesser complication rate in expert hands, it has become the gold standard for treatment of gall stone diseases [4].

The primary anesthetic goal during laparoscopic abdominal surgery is to maintain hemodynamic stability especially during the duration of pneumoperitoneum (PNP) namely carbon dioxide (CO_2) insufflations and patient positioning [5,6].

The cardiopulmonary changes occurring during laproscopy are complex and depend on the interaction of patients pre-existing cardiopulmonary status, the anaesthetic technique (ventilator technique and anaesthetic agent used), intra-abdominal pressure (IAP) [7], CO_2 absorption, patient's position and duration of the surgical procedure.

Insufflation of CO_2 and increased IAP (>10 mmHg) produces significant alterations in hemodynamic parameters characterized by decreased cardiac output, increased arterial pressure, increased systemic and pulmonary vascular resistance [8,9] due to release of vasopressin and catecholamine [10].

Pneumoperitoneum decreases thoracopulmonary compliance by 30-50% [11]. There is also reduction in (Functional Residual Capacity) FRC [12] and atelectasis due to elevation of the diaphragm. Changes in ventilation and perfusion also result from increased airway pressure [13].

Various anaesthetic interventions like preoperative epidural catheter insertion [14], combined epidural and general anaesthesia [15] and pharmacological agents like adrenoreceptor blockers [16], beta blockers [17], calcium channel blockers, lignocaine [18], opioids [19], magnesium sulfate [20], nitroglycerine [21], remifentanyl [19], α-2 agonists such as clonidine [22-25] and dexmedetomidine [26-30] have been used to attenuate these adverse hemodynamic changes associated with pneumoperitoneum with varying success.

Moxonidine (chemical formula: C9H12ClN5O) is a selective imidazoline type 1 (I_1) receptor agonist. Selective stimulation of I_1 receptors in the cardiovascular regulatory centers of the medulla oblongata, causes inhibition of central sympathetic activity, leading to a reduction in blood pressure [31].

With this background, the present study was designed to evaluate the effect of orally administered Moxonidine as premedication in the attenuation of the hemodynamic responses seen during laparoscopic cholecystectomy.

Material and Method

After obtaining ethical and patient consent, the present study was carried out on 60 randomly selected patients with the following inclusion and exclusion criteria:

Inclusion Criteria Included the following

- Patients of ASA grade 1 and 2.
- Patients between age group of 20 to 50 years of either sex.
- Patients undergoing laproscopic cholecystectomy under general anaesthesia.

Exclusion Criteria

- ASA grade 3 and above.
- BMI ≥ 30.
- Patients undergoing conversion from laparoscopic to open surgery intraoperatively.
- Pneumoperitoneum duration >90 minutes.
- Known history of allergy or sensitivity to study drug (Moxonidine).
- Patients with cardiovascular or respiratory disorders.
- Patients with hypertension on treatment with beta blockers, methyldopa, MAO inhibitors, tricyclic antidepressants.
- Patients with psychiatric illness.
- Patients with hepatic or renal dysfunction.
- Pregnant or lactating females.

Pre-anaesthetic assessment of all the selected patients were done with complete history, general physical and systemic examination, airway assessment along with routine investigations, as for

any standard laparoscopic cholecystectomy procedure.

Patients were blinded by sealed envelope technique and randomly allocated into one of the two groups to receive either tablet Moxonidine 0.2mg at 8pm the day before surgery and at 8am on the day of surgery (group M, n=30) or placebo, control group (group C, n=30). The observer (Anesthesiologist) was totally blinded about the groups or medications received by the patients.

All the patients were kept nil orally for 8 hours prior to procedure and were uniformly premedicated with inj. Ranitidine 50mg and inj. Ondansetron 4mg, 30 minutes before shifting to operation theatre. All the baseline vital parameters (HR, SBP, DBP, MAP and SpO_2) were recorded, pre-induction. All the patients were preoxygenated with 100% O_2 for 3 minutes. Induction of anaesthesia was carried out with inj. Propofol 2.5mg/kg BW along with inj. Pentazocine 0.5mg/kg BW. Endotracheal intubation was facilitated with intravenous Vecuronium bromide (0.1 – 0.2mg/Kg). End tidal CO_2 was monitored intraoperatively and kept between 30 to 35 mmHg.

General anaesthesia was maintained with N_2O:O_2 (66%:33%), intermittent doses of inj. Vecuronium and Isoflurane (0.5-1.0%) using circle absorber system connected to anaesthetic workstation. Pneumoperitoneum was created and maintained by insufflation of CO_2. Intra-abdominal pressure was maintained between 12-15mmHg during the surgery.

Throughout the study period, all the parameters were recorded at different time intervals as before induction (B), after intubation (AI), before pneumoperitoneum (BPN), after pneumoperitoneum (APN), and later at every 10 minutes (APN_{10}, APN_{20}, APN_{30}, APN_{40}, APN_{50}, APN_{60}, APN_{90}), at release of pneumoperitoneum (RPN), after reversal (AR) and at 15 and 30 minutes after reversal (AR_{15}, AR_{30}).

Any change in hemodynamic variables more than 20% from the baseline was considered significant. Any increase in MAP up to 20% from baseline was treated by increasing the concentration of Isoflurane to a maximum of 2%. Heart rate less than 50bpm was treated with inj. Atropine 0.6mg IV.

After surgery, patients were reversed with inj. Neostigmine 0.08mg/kg BW IV and inj. Glycopyrrolate 0.005mg/kg BW IV. After extubation patients were observed with full monitoring in the PACU (post-anesthesia care unit). The observations were recorded and subjected to statistical analysis using SPSS statistical software. Student's 't' test was used for inter-group comparison. P-value >0.05 and <0.05 were considered statistically insignificant and significant, respectively.

Results

In the present study, there were no statistically significant differences between both the groups regarding demographic data such as age, sex, weight and duration of anaesthesia or pneumoperitoneum. The results were expressed as mean(±SD).

1. The preoperative baseline mean HR was lower in group M (85.90±17.60) as compared to group C (100.90±9.40) ($p<0.05$).

   Compared to baseline values, rise in mean HR were statistically significant ($p<0.05$) at all intervals in group C.

   While in group M, significantly lower ($p<0.05$) HR were observed at all times except at APN, APN_{90}, RPN and AR compared to baseline (B) values.

   While comparing group C with group M, significantly lower ($p<0.05$) HR were observed in group M at all the intervals.

2. The preoperative basal values of mean(±SD)SBP were significantly lower in group M (121.70±10.10) as compared to group C (129.40±6.10).

   On comparing groups C and M, significant changes in systolic blood pressure were present in all values except after intubation (AI), 90 minutes after pneumoperitoneum (APN_{90}) and 30 minutes after reversal (AR_{30}) ($p<0.05$)

3. The preoperative basal values of mean (±SD) DBP were significantly lower in study group (78.80±8.30) when compared to control group (86.00±7.30).($p<0.05$)

   DBP did not show any significant fluctuation from the baseline throughout the study period and remained stable even in postoperative period except after intubation (AI) and 90 minutes after pneumoperitoneum (APN_{90})as compared to control group. ($p<0.05$)

4. The MAP in the control group was fluctuating and maintaining on a higher side compared to Moxonidine group throughout the study period. The results were statistically significant ($p<0.05$).

Table 1: Demographic profile

S. No.	Parameters	Control Group	Moxonidine Group
1.	Age (years)	40±12.8	40±13.1
2.	Gender ratio (M:F)	12:18	14:16

Table 2: Duration (min) of anaesthesia (mean ±SD) between study groups

Duration of Anaesthesia	Group C	Group M
Minutes	89.16±19.47	91.16±18.36

Table 3: Duration (min) of pneumoperitoneum (mean ±SD) between study groups

Mean duration of pneumoperitoneum	Group C	Group M
Minutes	62.96±18.14	62.73±17.80

Table 4: Statistical analysis of mean (± SD) pulse rate (BPM) in study groups

S. No	Time in Min.	Group C (Mean±SD)	Group M (Mean±SD)	P-value
1	Before induction (B)	100.90±9.4	85.90±17.60	0.001 (HS)
2	After intubation (AI)	102.10±10.87	94.10±12.41	0.010 (S)
3	Before PNP (BPN)	93.26±11.83	75.26±10.71	0.00 (HS)
4	After PNP (APN)	98.43±10.09	80.60±10.95	0.00 (HS)
5	10min after PNP (APN_{10})	91.80±11.31	75.86±11.57	0.00 (HS)
6	20min after PNP (APN_{20})	90.93±11.03	74.23±11.74	0.00 (HS)
7	30min after PNP (APN_{30})	90.63±10.50	74.63±11.20	0.00 (HS)
8	40min after PNP (APN_{40})	91.00±11.83	73.64±10.58	0.00 (HS)
9	50min after PNP (APN_{50})	94.30±13.93	72.12±8.72	0.00 (HS)
10	60min after PNP (APN_{60})	92.55±10.71	70.25±6.15	0.00 (HS)
11	90min after PNP (APN_{90})	93.80±6.87	71.77±6.41	0.00 (HS)
12	Release of PNP (RPN)	99.13±13.67	79.00±9.73	0.00 (HS)
13	After reversal (AR)	102.26±11.99	82.16±9.15	0.00 (HS)
14	15min after reversal (AR_{15})	91.18±11.82	76.16±9.02	0.00 (HS)
15	30min after reversal (AR_{30})	89.40±10.73	75.26±8.61	0.00 (HS)

Table 5: Statistical analysis of mean (± SD) systolic blood pressure (MMHG) in study groups

S. No	Time in min.	Group C (Mean±SD)	Group M (Mean±SD)	P-value
1	Before induction (B)	129.40±6.10	121.70±10.10	0.001 (HS)
2	After intubation (AI)	137.40±14.63	138.00±14.48	0.834 (NS)
3	Before PNP (BPN)	124.93±14.40	117.73±12.23	0.041 (S)
4	After PNP (APN)	131.40±15.70	123.66±11.93	0.036 (S)
5	10min after PNP (APN_{10})	134.20±5.80	126.50±11.10	0.004 (HS)
6	20min after PNP (APN_{20})	133.5±6.10	125.30±10.80	0.001 (HS)
7	30min after PNP (APN_{30})	124.06±10.49	115.46±10.21	0.002 (HS)
8	40min after PNP (APN_{40})	124.57±12.19	114.07±7.97	0.00 (HS)
9	50min after PNP (APN_{50})	122.81±8.87	112.50±7.48	0.00 (HS)
10	60min after PNP (APN_{60})	123.23±9.36	112.90±6.13	0.00 (HS)
11	90min after PNP (APN_{90})	115.53±6.22	111.55±3.12	0.104 (NS)
12	Release of PNP (RPN)	130.33±13.43	119.20±10.88	0.001 (HS)
13	After reversal (AR)	136.86±12.21	125.20±9.33	0.00 (HS)
14	15min after reversal (AR_{15})	123.20±8.62	118.13±8.43	0.025 (S)
15	30min after reversal (AR_{30})	119.46±8.91	116.86±7.83	0.051 (NS)

Table 4 is showing inter-group statistical analysis of pulse rate (bpm) at different time intervals. On comparing groups C and M significant changes in pulse rate were present in all values. $p > 0.05$ – Not significant (NS), $p \leq 0.05$ – Significant (S), $p < 0.01$ – Highly significant (HS).

Table 5 is showing inter-group statistical analysis of systolic blood pressure (mmHg) at different time intervals. On comparing groups C and M, significant changes in systolic blood pressure were present in all values except after intubation (AI), 90 minutes after pneumoperitoneum (APN_{90}) and 30 minutes after reversal (AR_{30}). $p > 0.05$ – Not significant (NS), $p \leq 0.05$ – Significant (S), $p < 0.01$ – Highly significant (HS).

Table 6: Statistical analysis of mean (± SD) diasystolic blood pressure (MMHG) in study groups

S. No	Time in min.	Group C (mean±SD)	Group M (mean±SD)	P-value
1	Before induction (B)	86.0±7.30	78.80±8.30	0.001 (HS)
2	After intubation (AI)	92.53±11.02	93.36±9.86	0.359 (NS)
3	Before PNP (BPN)	82.73±8.78	74.40±10.71	0.002 (HS)
4	After PNP (APN)	87.46±10.66	80.86±9.39	0.014 (S)
5	10min after PNP (APN_{10})	79.73±6.29	74.60±8.75	0.012 (S)
6	20min after PNP (APN_{20})	89.20±9.80	82.90±10.50	0.036 (S)
7	30min after PNP (APN_{30})	83.20±8.49	73.40±8.74	0.000 (HS)
8	40min after PNP (APN_{40})	84.57±10.25	72.42±6.42	0.000 (HS)
9	50min after PNP (APN_{50})	83.11±8.43	73.91±9.04	0.000 (HS)
10	60min after PNP (APN_{60})	84.66±8.67	73.90±8.69	0.000 (HS)
11	90min after PNP (APN_{90})	79.00±9.58	71.77±6.11	0.070 (NS)
12	Release of PNP (RPN)	88.96±9.37	81.53±7.56	0.001 (HS)
13	After reversal (AR)	91.66±8.93	85.80±7.59	0.008 (HS)
14	15min after reversal (AR_{15})	85.40±7.70	77.46±7.12	0.000 (HS)
15	30min after reversal (AR_{30})	82.80±7.40	76.13±7.82	0.001 (HS)

Table 7: Statistical analysis of mean (± SD) mean arterial pressure (MMHG) in study groups

S. No	Time in min.	Group C (Mean±SD)	Group M (Mean±SD)	P-value
1	Before induction (B)	100.50±5.6	93.10±8.50	0.001 (HS)
2	After intubation (AI)	107.56±11.93	107.53±14.45	0.992 (NS)
3	Before PNP (BPN)	95.70±10.74	89.63±10.42	0.030 (S)
4	After PNP (APN)	101.90±11.86	94.56±10.80	0.015 (S)
5	10min after PNP (APN_{10})	104.80±4.30	97.90±9.20	0.002 (HS)
6	20min after PNP (APN_{20})	91.33±9.38	88.63±8.62	0.025 (S)
7	30min after PNP (APN_{30})	97.63±10.02	88.53±8.41	0.000 (HS)
8	40min after PNP (APN_{40})	97.50±11.06	86.78±6.53	0.000 (HS)
9	50min after PNP (APN_{50})	96.59±8.47	87.33±8.54	0.000 (HS)
10	60min after PNP (APN_{60})	97.76±8.56	87.00±8.48	0.000 (HS)
11	90min after PNP (APN_{90})	91.30±9.01	85.88±4.75	0.126 (NS)
12	Release of PNP (RPN)	102.56±10.45	93.56±8.26	0.000 (HS)
13	After reversal (AR)	106.10±9.50	98.66±7.79	0.002 (HS)
14	15min after reversal (AR_{15})	98.43±8.62	90.53±7.41	0.000 (HS)
15	30min after reversal (AR_{30})	96.30±6.44	90.26±7.95	0.002 (HS)

Table 6 is showing inter-group statistical analysis of diastolic blood pressure (mmHg) at different time intervals. On comparing groups C and M, significant changes in diastolic blood pressure were present in all values except after intubation (AI) and 90 minutes after pneumoperitoneum (APN_{90}). $p > 0.05$ – Not significant (NS), $p \leq 0.05$ – Significant (S), $p < 0.01$ – Highly significant (HS).

Table 7 is showing inter-group statistical analysis of mean arterial pressure (mmHg) at different time intervals. On comparing groups C and M, significant ($p<0.05$) difference in mean arterial pressure was seen in all values exceptafter intubation (AI) and 90 minutes after pneumoperitoneum (APN_{90}). $p > 0.05$ – Not significant (NS), $p \leq 0.05$ – Significant (S), $p < 0.01$ – Highly significant (HS).

Discussion

Pneumoperitoneum (PNP) used for laparoscopic procedures is associated with significant hemodynamic variation, produced by administration of CO_2 [32,33]. Both PNP and CO_2 cause adverse cardiovascular effects due to increase in plasma level of epinephrine, nor-epinephrine, vasopressin, neurophysin and plasma renin activity [34,35]. All these changes contribute to increase in HR, BP, SVR and PVR and reduced cardiac output. In addition, trendelenburg position causes diminished venous return and reduction in cardiac output [5].

Various studies have been done over the years for attenuating these unwanted detrimental effects which occur during pneumoperitoneum and intraoperative period.

Moxonidine is a new generation centrally acting antihypertensive drug, a selective agonist at the imidazoline receptor subtype (I_1). This receptor subtype is found in both rostral ventrolateral pressor and ventromedial depressor areas of medulla oblongata. Moxonidine therefore causes a decrease in sympathetic nervous system activity and therefore, a decrease in blood pressure [31,37].

Compared to older centrally acting antihypertensives, Moxonidine binds with much greater affinity to the imidazoline I_1 receptors than to the α-2 receptors [31,37]. This mechanism is claimed to lead to fewer adverse effects such as sedation and dry mouth than older centrally acting agents like Clonidine [36,37].

In addition, Moxonidine may also promote sodium excretion, improve insulin resistance and glucose tolerance and protect against hypertensive target organ damage [37].

In our study, the overall hemodynamic profile was stable in the Moxonidine group when compared to control group. The mean HR, SBP, DBP, MAP were stable throughout the procedure in the Moxonidine group without any significant fluctuations intra and postoperatively. The results obtained in our study were consistent with the previous studies which used Clonidine [24, 38-42] and Dexmedetomidine [30, 43-45] in attenuation of hemodynamic responses to laparoscopic cholecystectomy.

Our findings were also supported by Raghuram CG et al. [46] who compared the effectiveness of oral Moxonidine premedication 0.3mg (group M, n=25) with placebo (n=25) for attenuation of hemodynamic responses seen during laparoscopic cholecystectomy. They concluded that Moxonidine premedication provides perioperative hemodynamic stability and it can be considered in all ASA grade patients (ASA 1, 2 and 3).

Conclusion

Moxonidine is a new generation centrally acting antihypertensive, licensed for the treatment of mild to moderate essential hypertension. It has been found to demonstrate favourable effects on parameters of the insulin resistance syndrome, independent of blood pressure reduction. The use of oral Moxonidine in minimal-access procedures can be recommended as a routine premedication in view of its safety profile. It may be considered in hypertensive and diabetic patients undergoing laparoscopic surgeries.

The limitation of the study is that, we did not compare Moxonidine with other centrally acting antihypertensives like Clonidine and Dexmedetomidine. Its major advantage is its hemodynamic stability and no gross sedation. The common adverse effects of Clonidine and Dexmedetomidine such as dryness of mouth, rebound hypertension and bradycardia are not observed with Moxonidine, which makes it a more preferable choice.

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