e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 13(1); 230-237

Original Research Article

# Effect of Oral Moxonidine in the Attenuation of the Haemodynamic Responses Seen During Laparoscopic Cholecystectomy

**Anija Pattnaik[1], D.V. Ravi Kumar[2], Suryasnata Sahoo[3], Amiya Kumar Nayak[4]**

[1]Assistant Professor, Department of Anaesthesiology, S.C.B. Medical College, Cuttack. Odisha, India.
[2]Assistant Professor, Department of Anaesthesiology, S.C.B. Medical College, Cuttack. Odisha, India.
[3]Assistant Professor, Department of Anaesthesiology, S.C.B. Medical College, Cuttack. Odisha, India.
[4]Assistant Professor, Department of Anaesthesiology, P.R.M. Medical College, Baripada, Odisha, India

**Received: 25-11-2022 / Revised: 25-12-2022 / Accepted: 15-01-2023**
**Corresponding author: Dr. Amiya Kumar Nayak**
**Conflict of interest: Nil**

**Abstract**

**Background:** In this study, we wanted to evaluate the effect of orally administered moxonidine in attenuating the hemodynamic responses that occur during laparoscopic cholecystectomy.

**Materials and Methods:** This was a hospital based prospective double blinded randomized study conducted among 50 patients underwent elective laparoscopic cholecystectomy in the Department of General Surgery and Department of Surgical Gastroenterology, in S.C.B. Medical College and Hospital, Cuttack, Odisha, over for a period of one and a half years, from January 2021 to October 2022 after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

**Results:** 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 was lower in moxonidine group than placebo group. The results were statically significant ($P < 0.05$). The mean systolic blood pressure between moxonidine and placebo at various intervals during the surgery was recorded and the result was statistically significant ($P < 0.05$). Whereas in comparison of mean diastolic blood pressure between moxonidine and placebo, most of the results were statistically significant ($P < 0.05$).

**Conclusion:** The use of moxonidine in laparoscopic cholecystectomy is a promising approach in attenuating the hemodynamic response (PR, SBP, DBP and MAP) not only during the operative procedure but also at induction of anaesthesia, endotracheal intubation, recovery from anaesthesia and post-operative period. There were no side effects or deleterious influences on the hepatic, renal and gastro-intestinal function in any of the patients of the moxonidine group 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 too because of the stable haemodynamic it ensures when used. As it seems placebo group resulted in a stable hemodynamic (within 10 % of base line) in ASA grade I and II patients. So, 5 – 10 % increase in hemodynamic parameter can be detrimental in ASA III and IV patients.

**Keywords:** Moxonidine, Haemodynamic, Laparoscopic, Cholecystectomy

## Introduction

No other surgery has been as profoundly affected by the advent of laparoscopy as cholecystectomy has. In fact, laparoscopic cholecystectomy has been instrumental in ushering in 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 surgery is one of the most important diagnostic and therapeutic tools in the present surgical era. Since 1987, when the first laparoscopic cholecystectomy was successfully performed by Phillipe Mouret, this has become the gold standard. Laparoscopic cholecystectomy is one of the most commonly undertaken procedures in general surgery, with overall complication rate being less than 1.5 %, and the mortality 3.3 times greater in open cholecystectomy group than laparoscopic cholecystectomy group.[1] The initial driving force behind rapid development of laparoscopic cholecystectomy was patient's demand. Prospective randomized trials were late and largely irrelevant and gained acceptance not through organized and carefully conceived clinical trials but by acclamation.

Laparoscopic cholecystectomy requires pneumoperitoneum and thus routinely requires general anaesthesia with endotracheal intubation and intermittent positive pressure ventilation.[2] The pneumoperitoneum created for laparoscopy produces complex physiologic events and changes that make anaesthetic management difficult.[3] The pathophysiologic processes resulting from a pneumoperitoneum are directly related to and have a cause-and-effect relationship to clinical outcomes. 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. Preventing or beneficially modifying these pathophysiologic processes directly affects clinical outcomes. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum. These changes though better tolerated in ASA I and II patients can be detrimental in elderly and ASA III patients particularly with compromised cardiovascular system physiology. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum. These included gasless laparoscopy,[4,5] uses of β adrenergic blockers,[6] Nitroglycerine,[7] calcium channel blockers and α-2 agonists such as clonidine[8] and dexmedetomidine.[9] The central antihypertensive drug moxonidine, which has a weak affinity for the α2-adrenoceptor (α2AR), is generally described as a selective I1-imidazoline receptor (I1R) agonist that lowers blood pressure (BP) by decreasing sympathetic activity within the central nervous system.[10]

It is well known that the rostral ventrolateral medulla (RVLM) plays a critical role in tonic and reflex control of sympathetic outflow and BP.[11] The pre-sympathetic neurons in the RVLM project directly to sympathetic preganglionic neurons in the spinal cord and are recognized as a major target responsible for the action of centrally acting antihypertensive agents such as clonidine and moxonidine.[12,13] Moxonidine causes a decrease in sympathetic nervous

system activity as measured by norepinephrine, and plasma renin activity[14] and, therefore, a decrease in blood pressure. Hemodynamic studies show that moxonidine reduces arterial pressure by lowering systemic vascular resistance while sparing heart rate, cardiac output and stroke volume. In this study, orally administered moxonidine was evaluated in reducing the hemodynamic response that occur during laparoscopic cholecystectomy.

**Aims and Objectives**

The aim of the study was to evaluate effect of orally administered moxonidine in attenuating the hemodynamic responses that occur during laparoscopic cholecystectomy.

**Materials and Methods**

This was a hospital based prospective double blinded randomized study conducted among 50 patients underwent elective laparoscopic cholecystectomy in the Department of General Surgery and Department of Surgical Gastroenterology, in S.C.B. Medical College and Hospital, Cuttack, Odisha, over for a period of one and a half years, from January 2021 to October 2022 after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

**Inclusion Criteria**

- Healthy adult patients of ASA physical status I and II of Either sex aged 20 to 60 years,
- Weighing 50 to 90 Kg

**Exclusion Criteria**

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

**Statistical Methods**

Data was entered in MS Excel and analysed using Statistical Package for Social Sciences (SPSS) software. Results were presented as tables.

**Results**

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 1: Comparison of Mean Pulse Rate between Moxonidine and Placebo**

| Mean Pulse Rate | | | |
|---|---|---|---|
| | **Moxonidine Mean ± SD** | **Placebo 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 2: Comparison of Mean Systolic Blood Pressure between Moxonidine and Placebo**

| Mean Systolic Blood Pressure | | | |
|---|---|---|---|
| | **Moxonidine Mean ± SD** | **Placebo 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 |

The results of comparing the mean systolic blood pressure between moxonidine and placebo recorded at various intervals during the surgery were statistically significant ($P < 0.05$).

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

| Mean Diastolic Blood Pressure | | | |
|---|---|---|---|
| | **Moxonidine Mean ± SD** | **Placebo 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 |

The results of comparing the mean diastolic blood pressure between moxonidine and placebo group recorded at various intervals during the surgery were statistically significant ($P < 0.05$).

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

| Mean Arterial Blood Pressure |
|---|

| | Moxonidine Mean ± SD | Placebo 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 |
| **Comparison of Mean Arterial Blood Pressure between Moxonidine and Placebo** | | | |

The above table compares the mean arterial blood pressure recorded at various intervals during the surgery. Most of the results are statistically significant ($P < 0.05$).

## Discussion

Jean L Joris et al. in 1998 investigated endocrine correlates of the hemodynamic changes induced by carbon dioxide pneumoperitoneum and concluded that vasopressin and catecholamines probably mediate the increase in systemic vascular resistance.

Moxonidine [4-chloro-N-(imidazoline-2-yliden)-6-2-methyl-5-pyrimidineamin] is a centrally active antihypertensive agent that is effective in mild to moderate hypertension and have a favourable adverse effect. Moxonidine stimulates the imidazoline-1 receptors in the ventrolateral area of the medulla oblongata, leads to a decreased sympathetic tone in resistance vessels, the heart, and the kidney. When applied in dosages equipotent to clonidine, its side effects, ie, dry mouth and dizziness, are less pronounced than with the α2-receptor agonist clonidine.[15]

A study by Joris J L concluded that vasopressin and catecholamines probably mediate the increase in systemic vascular resistance observed during PNP. Moxonidine when given before PNP reduces catecholamine release and attenuates hemodynamic changes during Laparoscopy.

In our study the following results are observed.

- There were no significant differences found with respect to age, weight, gender, time between premedication to anaesthetic induction, duration of laryngoscopy and surgical procedure. The anaesthetic technique did not differ among the study groups.
- The preoperative mean pulse rate was lower in the Moxonidine group (85.76 ± 9.76) per min when compared to the placebo group (98.08 ± 0.08) per min; (p value 0.0001). 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 (119.20 ± 8.63) mm Hg was

comparable to that of the placebo group (126.92 ± 7.60) mm Hg; (p value 0.0016). 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 whereas it was maintained at a stable in the moxonidine group. The results were statistically significant. ($P < 0.05$).

- The pre-operative DBP values were lower in the Moxonidine group (77.44 ± 6.48) mmHg than that of the placebo group (84.76 ± 7.13) mmHg; (p value 0.001). Moxonidine group did not show significant rise in DBP post intubation and after creation of pneumoperitoneum. The DBP in the placebo group was fluctuating throughout the procedure, maintaining on the higher side. The intubation and extubation response of DBP were attenuated in the moxonidine group but not in the placebo group. The results were statistically significant ($P < 0.05$).
- Moxonidine group did not show significant rise in MAP in post intubation and after creation of pneumoperitoneum. 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) and the post op MAP (108.04 + 4.15 vs. 95.16 ± 4.24 mm of Hg). The results were statistically significant. ($P < 0.05$).

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 intra-operatively. The results obtained in our study are consistent with previous study [16,17,18,19] in attenuating hemodynamic responses to laparoscopic cholecystectomy.

Málek J.et al.[19] 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 µgi.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 favourable effect on the metabolic profile in the body, its 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 edge over other centrally acting antihypertensive 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.

In our study, hemodynamic profiles were pretty stable throughout the operative procedure requiring very minimal or negligible pharmacological interventions intra-operatively.

## Conclusion

The use of moxonidine in laparoscopic cholecystectomy is a promising approach in attenuating the hemodynamic response (PR, SBP, DBP and MAP) not only during the operative procedure but also at induction of anaesthesia, endotracheal intubation, recovery from anaesthesia and post-operative period. There were no side effects or deleterious influences on the

hepatic, renal and gastro-intestinal function in any of the patients of the moxonidine group 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 too because of the stable haemodynamic it ensures when used. As it seems placebo group resulted in a stable hemodynamic (within 10 % of base line) in ASA grade I and II patients. So 5 – 10 % increase in hemodynamic parameter can be detrimental in ASA III and IV patients.

## References


1. Zacks SL, Sandler RS, Rutledge R, Brown RS. A population-based cohort study comparing laparoscopic cholecystectomy and open cholecystectomy. Am J Gastroenterol 2002;97(2):334-40.
2. Marco AP, Yeo CJ, Rock P. Anesthesia for a patient undergoing laparoscopic cholecystectomy. Anesthesiology 1990;73(6):1268-70.
3. Jean IJ. Anaesthesia for Laparoscopic surgery. In: Miller RD, anaesthesia. 7thedn. New York: Chruchill Livingstone and 2009: 2010; 2185-202.
4. Lindgren L, Koivusalo AM, Kellokumpu I. Conventional pneumoperitoneum compared with abdominal wall lift for laparoscopic cholecystectomy. Br J Anaesth 1995; 75(5):567-72.
5. Gurusamy KS, Samraj K, Davidson BR. Abdominal lift for laparoscopic cholecystectomy. Cochrane Database Syst Rev 2008;16(2):CD006574.
6. Koivusalo AM, Scheinin M, Tikkanen I, Yli-Suomu T, Ristkari S, Laakso J, et al. Effects of esmolol on haemodynamic response to CO2 pneumoperitoneum for laparoscopic surgery. Acta Anaesthesiol Scand 1998; 42(5):510-7.
7. Feig BW, Berger DH, Dougherty TB, Dupuis JF, Hsi B, Hickey RC, Ota DM. Pharmacologic intervention can reestablish baseline hemodynamic parameters during laparoscopy. Surgery 1994;116(4):733-9.
8. Joris J, Chiche JD, Lamy M. Clonidine reduced hemodynamic changes induced by pneurnoperitonetim during laparoscopic cholecystectomy. Br J Anaesth1995;74: A124.
9. Aho M, Lehtinen AM, Erkola O, Vuorinen J, Korttila K. Intramuscularly administered dexmedetomidine attenuates hemodynamic and stress hormone responses to gynecologic laparoscopy. AnesthAnalg 1992;75(6):932-9.
10. Ernsberger PA, Damon TH, Graff LM, SchäferSG, Christen MO. Moxonidine, a centrally acting antihypertensive agent, is a selective ligand for I1-imidazoline sites. J PharmacolExpTherap 1993;264(1):17 2-82.
11. Dampney RA. Functional organization of central pathways regulating the cardiovascular system. Physiol Rev 1994; 74:323-64.
12. Haxhiu MA, DreshajI, Schafer SG, Ernsberger P. Selective antihypertensive action of moxonidine is mediated mainly by 11-imidazoline receptors in the rostral ventrolateral medulla. J Cardiovasc Pharmacol 1994 ;24Suppl1: S1-8.
13. Reis DJ. Neurons and receptors in the rostroventrolateral medulla mediating the antihypertensive actions of drugs acting at imidazoline receptors. J Cardiovasc Pharmacol 1996;27Supp l3: S11-8.
14. Sanjuliani AF, Francischetti EA, Genelhu de Abreu V. Effects of moxonidine on the sympathetic nervous system, blood pressure, plasma renin activity, plasma aldosterone, leptin, and metabolic

profile in obese hypertensive patients. J Clin Basic Cardiol 2005;7(1):19-25.
15. Van Zwieten PA, Peters LM. Central I1-imidazonline receptors as a target of centrally acting antihypertensive drugs. Clinical pharmacology of moxonidine and rilmenidine. Ann N Y AcadSci 1999; 881:420-9.
16. Sarac B, Korkmaz O, Altun A, Bagcivan I, Göksel S, Yildirim S, Berkan O. Investigation of the vasorelaxant effects of moxonidine and its relaxation mechanism on the human radial artery when used as a coronary bypass graft. Interactive Cardiovascular and Thoracic Surgery 2015;21(3):342-5.
17. Raghuram CG, Adithya G. Effect of oral moxonidine in the attenuation of the hemodynamic responses seen during laparoscopic cholecystectomy: a clinical study. Journal of Evolution of Medical and Dental Sciences 2014; 3(17):4428-37.
18. Mrinmoy D, Manjushree R, Gauri M. Hemodynamic Changes during laparoscopic cholecystectomy: effect of oral clonidine premedication. Indian J Anaesth 2007;51(3):205-10.
19. Malek J, Know J, Kurzova A, Lopourova M. Adverse hemodynamic changes during laparoscopic cholecystectomy and their possible suppression with clonidine premedication. Comparison with intravenous and intramuscular premedication. Rozhl Chir 1999; 78(6): 286-91.