Original Research Article

# Comparison of midazolam and clonidine in attenuation of vasopressor response to pneumoperitoneum

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## Abstract

**Background:** Benzodiazepines are used as premedicants during anaesthesia for sedation, anxiolysis and sympatholysis. Alpha 2 agonists are also widely used now a days **Aim**: To differentiate the efficacy of intravenously administrated clonidine and midazolam as premedication during laparoscopic surgery. **Methods:** This study was a prospective and randomized clinical trial in which Group M included the patients who received Midazolam 0.02mg/kg diluted in 5ml normal saline given slowly before induction of general anaesthesia. Group C included the patients who received Clonidine 2mcg/kg diluted in 5 ml normal saline given slowly over 10 minutes before induction of general anaesthesia. **Results:** The data was presented as Mean SD. Groups were compared by students t test. Patients were demographically similar in both the groups .Significant variation was observed in heart rate, SBP, DBP and MAP especially after pneumoperitoneum with higher scores in Group M as compared to Group C patients. **Conclusion:** It can be concluded from the present study that Alpha 2 agonists were effective in attenuating the hemodynamic response to pneumoperitonem during laparoscopic surgery.

**Key Words:** Clonidine, Midazolam, Vasopressor response, Pneumoperitoneum, Hemodynamics.

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## INTRODUCTION

Laparoscopy surgery has become the standard of care for cholecystectomy. It has multiple advantages like shorter hospital stay, more rapid return to normal activities, less pain, small incisions and less postoperative ileus compared with the traditional open cholecystectomy.[1,2] It involves use of a gas preferably CO2 to create pneumoperitoneum. A pneumoperitoneum is required in order to visualize the intrabdominal contents. Creation of pneumoperitoneum involves insufflation of gases into the abdominal cavity. This leads to alteration in cardiovascular, pulmonary physiology and stress response.[3,4] The extent of cardiovascular changes associated with pneumoperitoneum includes an increase in mean arterial pressure, decrease in cardiac output and increase in systemic vascular resistance which in turn compromise tissue perfusion [5,6]. Various pharmacological agents were chosen to prevent hemodynamic change associated with pneumoperitoneum. Aho *et al*[7] used α 2 adrenergic receptor agonist for prevention of hemodynamic responses associated with laparoscopic surgery. They found that dexmedetomidine effectively reduces the maximum heart rate response after intubation and pneumoperitoneum. Clonidine inhibits the release of catecholamine and vasopressin and thus modulates the hemodynamic changes induced by pneumoperitoneum[7].

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We can choose our pharmaceutical premedication for anxiolysis and sedation from different substance classes as benzodiazepines, barbiturates, α-2-agonists, being aware of specific effects and side effects. Considering all these observations, the present study is designed to evaluate the type and extent of hemodynamic changes associated with laparoscopic surgery and also to find out the efficacy of Clonidine and Midazolam in the prevention of such hemodynamic changes. The preoperative period for the majority of patients is distressing situation which is characterized by anxiety and fear. This is not only uncomfortable, but the activation of the sympathetic nervous system also is potentially dangerous for a predisposed patient. Therefore, the primary goal for the patients preoperatively is to reduce anxiety and to induce sedation.

## MATERIALS AND METHODS

The study was conducted in a tertiary care hospital and was approved by the Hospital Ethics Committee and conducted as a prospective randomized clinical trial on 60 adult patients. Sample size is selected based on the calculation according to EPI Info 6 version of guidelines issued by Centre for Disease Control (CDC) Atlanta, Georgia, United States with population size of 1000 and with high expectation of 10 % and low expectation of 0.05 The study was conducted in the patients in the age group of 16 to 60 years for both the genders. Patients undergoing elective laparoscopic surgery and having ASA physical status I and II were taken. Patients with known allergy to alpha agonist and benzodiazepine group of drugs and patients with hypertension, ischemic heart disease, left ventricular failure, aortic stenosis and atrioventricular conduction block were excluded. These 60 patients were randomly divided into following two groups. Group M had 30 patients, each receiving premedication with Midazolam in dosage of 0.02 mg/kg prepared as 5 ml solution containing Midazolam 1 mg (0.2mg/ml), Group C had 30 patients, each receiving premedication with Clonidine in dosage of 2mcg/kg prepared as 5 ml solution containing 100mcg (20mcg/ml) Both the drugs were prepared as clear, colourless 5 ml solutions containing either midazolam 1mg (0.2mg/ml) or clonidine 100mcg(20mcg/ml) Airway management and tracheal intubation to be carried out by anaesthesiologist who is unaware of the group allocation. A detailed pre – anaesthetic evaluation including history of previous medical illness, previous surgeries, general examination and appropriate baseline investigations were carried out. An informed written consent was obtained. Nil by mouth status for 6 hours preceding the surgery was confirmed. Patients were re-examined on table, baseline values of pulse, systolic blood pressure, diastolic blood pressure and mean arterial pressure were recorded with the help of Non Invasive Blood Pressure (NIBP) monitoring system, Pulse Oximeter and Electrocardiograph examination of the cardiovascular and respiratory system was done. Intravenous access was obtained with 18G venous cannula. Premedication was given with Inj. Glycopyrrolate 0.04 mg/kg body weight, Inj. Pentazocine 0.3 mg/kg body weight and the third drug as per the randomly allocated group (Group M Midazolam 0.02mg/kg and Group C Clonidine 2 mcg/kg body weight) given 15 minutes prior to induction. All patients were pre –oxygenated with 100 % oxygen by face mask for 3 minutes. Patients in both the groups received 2.5 % Thiopentone sodium in a dose of 5-7 mg / kg body weight intravenously as induction agent, titrated to loss of eyelash reflex and depolarizing muscle relaxant succinylcholine 1-1.5mg/kg body weight .Patient was control ventilated with oxygen with bag and mask. Thirty seconds after administration of the muscle relaxant, using appropriate blade, direct laryngoscopy was performed every 15 seconds in sniffing position by the same experienced anaesthesiologist who performed tracheal intubation thereafter. Once vocal cords abducted and jaw completely relaxed patient was intubated with appropriate size cuffed Portex endotracheal tube. The hemodynamic parameters, namely heart rate, systolic and diastolic blood pressure and mean arterial pressure were recorded initially in the pre-operative period and noted as the baseline value, subsequent records were maintained prior to induction, 3 minutes after intubation, prior to pneumoperitoneum (pnp), 15 minutes after pneumoperitoneum, 30 minutes after pneumoperitoneum, 10 minutes after release of pneumoperitoneum and 10 minutes after extubation. Anaesthesia was maintained with $O_2$:$N_20$ as 40:60 ratio with halothane 0.5% -1% with intermittent positive pressure ventilation. Additional top-ups of muscle relaxant were given as required with Vecuronium Bromide 0.02mg/kg intermittently. At the end of surgery, reversal with adequate doses of Neostigmine (0.05mg/kg body weight) and Glycopyrrolate (0.1mg/kg body weight) was given and patient was extubated. The patient was assessed post operatively after shifting to recovery room and for one day after surgery.

## OBSERVATIONS AND RESULTS

The data obtained was subjected to statistical analysis using Students unpaired ‘t’ test to find out significant difference between the groups and Chi square test was used for qualitative data. For statistical comparisons, difference was considered significant when p value found less than 0.05.

**Table 1:** Demographical data between two groups

| Parameters | Group M | Group C | p Value |
|---|---|---|---|
| No Patients | 30 | 30 | |
| @Age (yrs)<br>Mean<br>SD<br>Range | <br>46.43<br>13.82<br>16 – 65 yrs | <br>46.63<br>11.67<br>22 – 70 yrs | <br><br><br>0.9519 |
| Weight (kgs)<br>Mean<br>SD<br>Range | <br>59.67<br>8.93<br>40 – 75 kgs | <br>61.07<br>7.94<br>48 – 78 kgs | <br><br><br>0.5236 |
| #Sex (%)<br>Male<br>Female | <br>20 (66.7)<br>10 (33.3) | <br>22 (73.3)<br>08 (26.7) | <br><br>0.5731 |
| #ASA Grade (%)<br>I<br>II | <br>23 (76.7)<br>07 (23.3) | <br>25 (83.3)<br>05 (16.7) | <br><br>0.5186 |

@ By Student 't' Test # By Chi – Square

The patients were demographically similar in both groups (Table 1). The above table shows that age of the patients was ranging from 16 – 70 years with mean age of 46.43 years in Midazolam group and 46.63 years among Clonidine group which was same and difference was not statistically significant (Table1)The mean weight of the patient was comparable in both the groups (Table1). In the study 66.7% of patients in Midazolam group and 73.3% of patients in Clonidine group of the total patients were male (Table1). While 76.7% of patient in Midazolam group and 83.3% of patient in Clonidine group belong to ASA physical status I and 23.3% of patient in Midazolam group and 16.7% of patient in Clonidine group belong to ASA physical status II (Table 1).

**Table 2:** comparison of heart rate between two groups

| HEART RATE | Group M (Mean±SD) | Group C (Mean±SD) | p value |
|---|---|---|---|
| Base line | 78±7 | 78±8 | 0.974 |
| Prior to induction | 84±9 | 84±9 | 1.000 |
| 3 minutes after intubation | 91±9 | 93±10 | 0.420 |
| Prior to Pneumoperitoneum | 85±10 | 81±7 | 0.115 |
| 15 minutes after Pneumoperitoneum | *95±8 | *79±7 | 0.000 |
| 30 minutes after Pneumoperitoneum | *97±8 | *78±6 | 0.000 |
| 10 minutes after release of pneumoperitoneum | *92±7 | *75±5 | 0.000 |
| 10 minutes after extubation | *97±9 | *87±7 | 0.000 |

By Student 't'

Mean pulse rate varied from 78±7 to 97±8 in group M. In group C, it varied from 75±5 to 93±10. Upon statistical comparison in two group of patients, significant variation was observed in the heart rate after 15 minutes of pneumoperitoneum, 30 minutes after pneumoperitoneum, 10 minutes after release of pneumoperitoneum and 10 minutes after extubation.(Table 2)

**Table 3:** comparisons of changes in systolic blood pressure between two groups

| Systolic blood pressure | Group M (Mean±SD) | Group C (Mean±SD) | p value |
|---|---|---|---|
| Base line | 116±11 | 113±13 | 0.402 |
| Prior to induction | 122±13 | 120±12 | 0.575 |
| 3 minutes after Intubation | 129±13 | 128±11 | 0.925 |
| Prior to Pneumoperitoneum | *125±10 | *120±9 | 0.037 |
| 15 minutes after Pneumoperitoneum | *135±9 | *118±8 | 0.000 |

| | | | |
|---|---|---|---|
| 30 minutes after Pneumoperitoneum | *138±8 | *115±7 | 0.000 |
| 10 minutes after release of pneumoperitoneum | *131±7 | *114±6 | 0.000 |
| 10 minutes after Extubation | *137±8 | *124±7 | 0.000 |

By Student 't' test

Mean systolic pressure varied from 116±11 mm of Hg to 138±8 mm of Hg in group I and in group II, it varied from 113±13 mm of Hg to 128±11 mm of Hg. Upon statistical comparison between two groups, there was significant difference prior to pneumoperitoneum, 15 minutes after pneumoperitoneum, 30 minutes after pneumoperitoneum, 10 minutes after release of pneumoperitoneum and 10 minutes after extubation. (Table 3)

**Table 4:** comparison of changes in diastolic blood pressure between two groups

| Diastolic blood pressure | Group M (Mean±SD) | Group C (Mean ±SD) | p value |
|---|---|---|---|
| Base line | 75±6 | 73±12 | 0 .616 |
| Prior to induction | 77±8 | 75±8 | 0.433 |
| 3 minutes after intubation | 82±8 | 81±6 | 0.457 |
| Prior to Pneumoperitoneum | 80±5 | 77±5 | 0.071 |
| 15 minutes after Pneumoperitoneum | *87±5 | *76±5 | 0.000 |
| 30 minutes after Pneumoperitoneum | *89±4 | *75±5 | 0.000 |
| 10 minutes after release of pneumoperitoneum | *86±4 | *74±5 | 0.000 |
| 10 minutes after Extubation | *88±5 | *80±4 | 0.000 |

By Student 't' test

Mean Diastolic Blood Pressure varied from 75±6 mm of Hg to 89±4 mm of Hg in group I and in group II, it varied from 73±12 mm of Hg to 81±6 mm of Hg. Upon statistical comparison, there is significant difference in mean diastolic blood pressure after 15 minutes of pneumoperitoneum, 30 minutes after pneumoperitoneum, 10 minutes after release of pneumoperitoneum and 10 minutes after extubation. (Table 4)

**Table 5:** comparison of changes in mean arterial pressure between two groups

| Mean arterial pressure | Group M (Mean±SD) | Group C (Mean ±SD) | p value |
|---|---|---|---|
| Base line | 89±7 | 85±8 | 0.072 |
| Prior to induction | 92±10 | 90±9 | 0.470 |
| 3 minutes after intubation | 98±9 | 97±7 | 0.564 |
| Prior to pneumoperitoneum | *95±6 | *91±6 | 0.034 |
| 15 minutes after pneumoperitoneum | *103±6 | *90±5 | 0.000 |
| 30 minutes after pneumoperitoneum | *105±5 | *88±5 | 0.000 |
| 10 minutes after release of pneumoperitoneum | *100±4 | *87±5 | 0.000 |
| 10 minutes after Extubation | *104±5 | *94±5 | 0.000 |

Student't' test

Mean arterial pressure varied from 89±7 mm of Hg to 105±5 mm of Hg in group I, and in group II, it varied from 85±8 mm of Hg to 97±7mm of Hg. There is significant difference in mean arterial pressure prior to pneumoperitoneum, 15 minutes after pneumoperitoneum, 30 minutes after pneumoperitoneum, 10 minutes after release of pneumoperitoneum and 10 minutes after extubation. (Table 5)

## DISCUSSION

Pneumoperitoneum during laparoscopy produces significant hemodynamic changes [4], which can be detrimental especially in elderly and hemodynamically compromised patients. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitoneum Clonidine, an imidazoline derivative is a selective α 2 adrenergic agonist. It is a potent antihypertensive drug. It produces a fall in the heart rate and blood pressure associated with decreased systemic vascular resistance and cardiac output [8]. Carabine *et al* [9] found that their was partial attenuation of pressor response to intubation on using intravenous clonidine. Muzi *et al* [10] reported baroreceptor reflex was maintained when clonidine was used. Midazolam, an imidazobenzodiazepine derivative is utilized as a premedicant, sedative, and an anesthetic induction agent. Midazolam is a good anxiolytic agent. Midazolam exerts its anxiolytic effect like other benzodiazepines by increasing the glycine inhibitory neurotransmitter. In our study, patients were divided in two groups with 30 patients each. All patients were scheduled for elective laparoscopic surgery under general anaesthesia with tracheal intubation. The demographic data of both the groups was comparable (Table 1). The mean age of the patient was 46.43 years in Midazolam group and 46.63 years among Clonidine group which was same and difference was not statistically significant. Cardiovascular stability was monitored by assessing the changes in pulse rate, systolic, diastolic and mean blood pressure during baseline recording, prior to induction, 3 minutes after intubation, prior to pneumoperitoneum, 15 minutes after pneumoperitoneum, 30 minutes after pneumoperitoneum, 10 minutes after release of pneumoperitoneum and 10 minutes after extubation. In our study in the Midazolam and Clonidine groups the mean baseline pulse rate, mean systolic pressure, mean diastolic pressure and mean arterial were comparable. There was a significant rise in the pulse rate at the time of intubation as compared to baseline in both the groups. A similar trend was followed by the systolic blood pressure, diastolic blood pressure and mean arterial pressure and there was no statistical significance on comparing the change in both the groups. Insignificant fall in systolic blood pressure, diastolic blood pressure and mean arterial pressure was noticed following premedication with clonidine. Following intubation, increase in arterial pressure was noticed but it never crossed the base line value. After the pneumoperitoneum was created, it was found that there was no significant rise in the Pulse Rate, Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial pressure as compared to the baseline in the Clonidine group, while there was a significant increase in the hemodynamic parameters in the Midazolam Group. This was similar to a study to Aho *et al* [7], though in our study a lower dosage was used in order to suppress the hemodynamic response to creation of a pneumoperitoneum. This had the advantage of not causing a significant fall in blood pressure prior to induction as reported in their study.

Aho *et al*[7] used 3mcg/kg and 4mcg/kg clonidine per oral for suppression of hemodynamic response to pneumoperitoneum. Rise in blood pressure and heart rate was less in both the groups but 4.5µg/kg clonidine produced greater fall in mean arterial pressure before induction. Similar findings were reported by Joris *et al*[5], Sung *et al*[11], Yu *et al*[12] , Malek *et al*[13] and Laisalmi *et al*[14].Joris *et al*[5] used high dose of clonidine 8 µg/kg for reducing the level of catecholamine and vasopressin following pneumoperitoneum. Malek *et al*[13] used 150 µg of clonidine as intravenous infusion and intramuscularly while Sung *et al*[11] and Yu *et al*[12] used 150 µg of oral clonidine as premedication for maintenance of hemodynamic stability during pneumoperitoneum. Aho *et al*[7] observed that 4.5mcg/kg of clonidine significantly decreased the mean arterial pressure before induction of anaesthesia. So they recommended 3mcg/kg of clonidine for perioperative hemodynamic stability. Joris *et al*[5] used higher dose of clonidine for reduction of catecholamine and vasopressin associated with pneumoperitoneum. Clonidine significantly reduced the concentration of catecholamine but not vasopressin and cotisol concentration. Similarly Sung *et al*[11] observed hemodynamic stability during pneumoperitoneum with 150 mcg of clonidine. Requirement of inhalational agent was also less by 30% in the clonidine group. Yu *et al*[12] recommended the routine use of clonidine premedication in laparoscopic patient. Significant rise in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was noticed in Group Midazolam. Rise in systolic, diastolic and mean arterial pressure was more than 20% from the baseline after creation of the pneumoperitoneum. Based on our study we propose that Clonidine in a dose of 2 mcg/kg is an appropriate premedication in order to prevent the hemodynamic response to intubation as well as creation of a pneumoperitoneum.

## CONCLUSION

The present study was performed as a randomized, prospective, clinical trial in 60 adult patients in age group of 16-70 years with ASA grade I or II patients to compare the two pre-medicant intravenous drugs Midazolam (0.02 mg/kg body weight) and Clonidine (2 mcg/kg body weight) in elective laparoscopic surgery under general anaesthesia with respect to hemodynamic parameters. It can be observed that use of Clonidine as premedication causes a significant fall in pulse rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure following pneumoperitoneum, during pneumoperitoneum, after release of pneumoperitoneum and after extubation. The advantage of Clonidine in providing cardiovascular stability makes this a drug of choice for premedication in laparoscopic procedures requiring general anaesthesia with endotracheal intubation for controlled ventilation.

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