

## A comparison of oral clonidine versus oral midazolam as premedication in adults

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### Abstract

**Introduction:** Premedication is an important aspect in anaesthesia. We conducted a double blind randomised controlled study to compare the clinical efficacy of oral premedication using clonidine 200 µg versus midazolam 15mg with respect to anxiolytic, sedative, antisialogogue effect and attenuation of haemodynamic response to intubation in adult patients undergoing general anaesthesia for various surgeries.

**Material and Methods:** One hundred patients belonging to ASA 1-2 physical status in the age group of 18-60 years, both males and females, weighing between 50-70 kg were randomly allocated into two groups of 50 each. Group 1 received oral clonidine 200µg and group 2 received midazolam 15mg, both 90 minutes prior to surgery. All patients were given general anaesthesia with thiopentone sodium, vecuronium, fentanyl, oxygen, nitrous oxide and sevoflurane. Patient's level of sedation was assessed using a five point sedation score. The antisialogogue effect was also studied. Pulse rate, systolic, diastolic, mean arterial blood pressure and rate pressure product were the haemodynamic parameters evaluated. Baseline values were obtained and recorded again 90 minutes after premedication. Thereafter, haemodynamic parameters were recorded after induction of anaesthesia with thiopentone sodium and vecuronium; one, five and ten minutes after intubation.

**Results and Conclusion:** Midazolam premedicated patients were sedated to a significantly greater extent than clonidine pretreated patients. Antisialogogue effect was seen in clonidine group. Haemodynamic parameters in the clonidine group were well maintained throughout the study period. There was significant attenuation of pressor response to laryngoscopy and intubation in the clonidine group as compared to midazolam therefore drug of choice for premedication.

**Keywords:** Premedication, Clonidine, Midazolam, Sedation, Antisialogogue, Haemodynamic response.

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### Introduction

“No one, however phlegmatic, can contemplate the prospect of an operation without some nervousness or apprehension” - Rendell Baker.<sup>(1)</sup> Premedication is an important step before giving anaesthesia to patient. Midazolam, a benzodiazepine, has short duration of action, causes anxiolysis, muscular relaxation, amnesia in lower doses and sedation, hypnosis in higher ones. Clonidine, an alpha-2 agonist, causes reduction of anaesthetic and analgesic requirements, haemodynamic stability, sedation, antisialogogue effect.<sup>(2)</sup>

This study was conducted to compare the clinical efficacy of oral premedication using clonidine 200 µg versus midazolam 15mg with respect to anxiolytic, sedation, antisialogogue effect, attenuation of haemodynamic response to intubation and adverse effects in adults undergoing general anaesthesia for a variety of surgeries.

### Materials and Methods

After approval from the hospital ethical committee, a randomised controlled double blind study was undertaken in adult patients and informed consent was obtained for the same. A total of 100 patients were enrolled for the study who were posted for elective surgeries under general anaesthesia like general, ENT, orthopaedic and gynaecological surgery. The total duration of surgery was about one to three hours.

Patients were randomly divided into two groups of 50 patients each.

Group 1: to receive oral clonidine 200µg (two tablets of 100 µg each) with sips of water 90 minutes prior to surgery.

Group 2: to receive oral midazolam 15mg (two tablets of 7.5 mg each) with sips of water 90 minutes prior to surgery.

**Inclusion criteria:** ASA physical status 1-2, age group of 18-60 years, both males and females, weight between 50-70 kg.

**Exclusion criteria:** Hypertension, renal dysfunction, hepatic dysfunction, obesity, anticipated difficult airway, baseline pulse rate <50 beats/minute, cardiovascular, pulmonary and psychiatric disorders, known hypersensitivity to the drugs used.

A thorough preoperative assessment was made which included detailed history, physical examination and airway evaluation. Pulse rate (beats/minute), systolic and diastolic blood pressure, mean arterial pressure and oxygen saturation were recorded as baseline resting parameters prior to premedication in the operation theatre and also 90 minutes after premedication in both the groups; during this period patient was monitored. Once patient was taken on operation table, the following monitors were attached: pulse oximeter, ECG, non invasive BP monitoring.

Anxiolytic Effect was assessed using Visual Analog Scale.

Sedative effect was assessed using a five point sedation score:<sup>(3)</sup> grade 1-awake; grade 2-drowsy but easily arousable to alert state by oral commands; grade 3- asleep, no reaction to speech but immediate reaction to tactile stimuli; grade 4- reaction only to stronger tactile stimuli; grade 5- difficulty in arousing patient immediately falling asleep again. Antisialagogue effect was assessed by asking patients about oral secretions and graded as normal secretions or dry mouth.

Intravenous access was secured using an 18gauge IV cannula and lactated Ringers solution was started. All patients were given IV ondansetron 4mg. Patients were adequately preoxygenated with 100% oxygen for five minutes. Induction was carried out using IV thiopentone sodium 2.5% 4-5mg/kg. Once the patient lost consciousness as assessed by loss of eyelash reflex, mask ventilation was confirmed and IV vecuronium was given in the dose of 0.1mg/kg. Patients were mask ventilated with 60% nitrous oxide and 40% oxygen for three minutes. Quick and smooth laryngoscopy was performed and tracheal intubation done with appropriate sized cuffed tube. Anaesthesia was maintained using 60% nitrous oxide, 40% oxygen and sevoflurane 1-2%. Muscle relaxation was maintained with IV vecuronium 1mg bolus as needed. For analgesia, IV fentanyl 2µg/kg initial dose (ten minutes post intubation) and top up of 1µg/kg was given as required. End tidal carbon dioxide was maintained around 35-40mmHg. One gram IV paracetamol infusion was given towards the end of surgery. At the end of surgery, neuromuscular blockade was reversed using IV neostigmine 0.05mg/kg and IV glycopyrrolate 0.01mg/kg.

Haemodynamic response to intubation was assessed by recording pulse rate (P) beats/ minute, systolic and diastolic blood pressure (SBP and DBP), and mean arterial pressure (MAP) at the following time intervals: P0- baseline prior to premedication, P1- pre induction (90 minutes after premedication), P2- post induction, P3- one minute post intubation, P4- five minutes post intubation, P5- ten minutes post intubation. Rate pressure product (RPP) was calculated using the following formula: systolic blood pressure in mm of Hg x pulse rate (beats/minute).

Patients were monitored for adverse effects such as bradycardia (pulse rate less than 50 beats/minute),<sup>(4)</sup> hypotension(decrease in systolic BP of more than 30% compared with the baseline level),<sup>(5)</sup> dysrhythmias (ventricular or supraventricular premature beat or any rhythm other than sinus),<sup>(6)</sup> respiratory depression(oxygen saturation less than 95%),<sup>(7)</sup> and grade 5 sedation.

**Statistical analysis:** SPSS statistical package was used to calculate mean, standard deviation and P value. Unpaired t test was applied for intergroup comparison of following variables – Pulse rate, Systolic blood

pressure, Diastolic blood pressure, Mean arterial pressure, Rate pressure product, visual analogue scale Sedation score. Chi-square test was used for comparison of antisialagogue effect between the two groups. ANOVA (Analysis of Variance) method was used for intragroup comparison of: Pulse rate, Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure, Rate pressure product. P value of >0.05 was considered not significant and <0.05 significant.

## Results

There were no significant differences between the two groups regarding age, sex and weight.

VAS Score showed similar antianxiety effect in both groups.

**Sedation score:** Patients in group 2 (midazolam) were found to be significantly more sedated than patients in group 1 (clonidine), P value less than 0.05. Table 1 shows group wise comparison of sedation score.

Antisialagogue effect: 36 out of 50 patients (72%) in clonidine group experienced antisialagogue effect. None of the patients in midazolam group had antisialagogue effect.

### Haemodynamic Response to Intubation

A. **Pulse rate:** The baseline mean pulse rate (P0) in group 1 was 82.44 beats per minute and in group 2 was 82.92 beats per minute and was comparable in two study groups. In group 1, the pulse rate remained significantly low compared with baseline (P0), following the induction of anaesthesia (P2) and 1 minute (P3), following intubation i.e. P2 of 74.60 beats per minute (p<0.05) and P3 of 77.88 beats per minute (P<0.05). But in the group 2, there was significant rise in P2 (80.04 beats per minute) and P3 (88.48 beats per minute) compared to baseline (P<0.05). Fig. 1 depicts intergroup comparison of pulse rate.

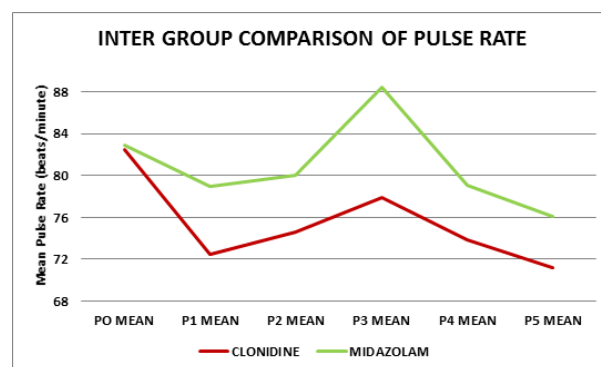
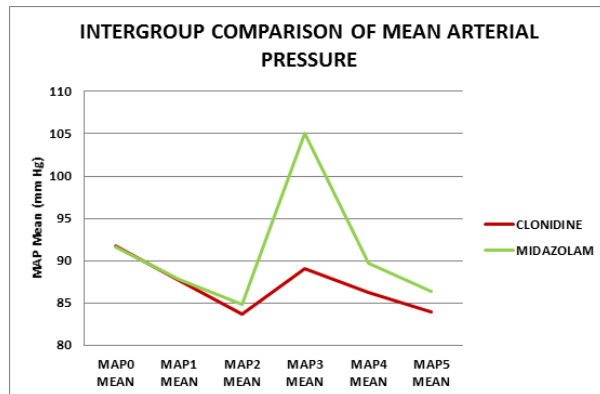


Fig. 1: Intergroup Comparison of Pulse Rate

B. **Blood pressure:** Baseline systolic, diastolic and mean arterial blood pressure difference in both the groups were not statistically significant. In group 1, mean SBP, DBP, MAP one minute post intubation remained low compared to baseline values. But in group 2 there was a statistically significant increase

in SBP, DBP, and MAP from baseline. Thus increase in blood pressure in group 2 was statistically significant ( $P < 0.05$ ) in the intergroup comparison (Table 2, Fig. 2).



**Fig. 2: Intergroup Comparison of Mean Arterial Pressure**

**C. Rate pressure product:** Baseline mean rate pressure product is 9869.68 units in group 1 and 9859.76 units in group 2. There was no significant difference between the two groups ( $p = 0.969$ ). RPP one minute after intubation remained significantly low at 9017.76 units in Clonidine group compared to baseline ( $p < 0.05$ ) whereas in group 2, it increased significantly to 12,462.40 units compared to baseline in this group ( $p < 0.05$ ).

Regarding adverse effects, in midazolam group, two patients developed transient dysrhythmias (ventricular premature complexes) during intubation which subsided without any pharmacological intervention (Table 3).

## Discussion

The aims of premedication are sedation, to allay preoperative fear and anxiety, to produce amnesia and analgesia, to reduce secretions from salivary glands and respiratory tract, to depress reflex vagal activities, to reduce pH and volume of gastric contents and risks associated with regurgitation and aspiration, to attenuate reflex sympathetic activities and stress associated with anaesthesia and surgery, to facilitate decrease in anaesthetic requirements. This study was conducted to compare the clinical efficacy of oral premedication using clonidine versus midazolam with respect to anxiolytic, sedative, antisialogogue effect and attenuation of haemodynamic response to intubation. The mean weight in both the groups was approximately 60kg which implied that the mean dose of oral clonidine used (200µg) was approximately 3.3µg/kg and the mean dose of oral midazolam used (15mg) was about 0.25mg/kg.

In our study we assessed anxiolytic effect by VAS and both clonidine and midazolam showed anxiolytic effect which was found to be comparable. In previous

studies by Frank T, et al.<sup>(8)</sup> and Paris A et al.<sup>(16)</sup> also reported that anxiolytic effect of clonidine and midazolam were similar.

Sedation was assessed using a five point sedation score 90 minutes after premedication. It was seen in present study that midazolam causes significantly more sedation than clonidine. All patients in the midazolam group were sedated whereas 26% patients in the clonidine group did not experience any level of sedation. In clonidine group, 72% of patients experienced dryness of mouth. Clonidine decreases salivary flow, hence dry mouth was associated with clonidine use. However, none of the patients in the midazolam group experienced dryness of mouth as it has no antisialogogue effect. Similar results were reported in a study by Chaurasia SK et al.<sup>(9)</sup>

The sympathetic responses to laryngoscopy and tracheal intubation include hypertension, tachycardia, and dysrhythmias; elevation in arterial pressure typically starts within five seconds of laryngoscopy, peaks in one to two minutes and returns to control levels within five minutes.<sup>(10)</sup> Haemodynamic response to laryngoscopy and intubation is poorly tolerated in patients with limited coronary or myocardial reserve, elevated intracranial pressure, open eye injuries and glaucoma.<sup>(11,12,13)</sup> Clonidine being a centrally acting  $\alpha_2$  agonist, decreases the central sympathetic outflow and also stimulates parasympathetic outflow, which may contribute to the slowing of heart rate as a consequence of increased vagal tone and diminished sympathetic drive.<sup>(14)</sup> As observed in our study, premedication with Clonidine thus effectively blunts reflex tachycardia associated with laryngoscopy and intubation. Stresses of endotracheal intubation and surgery are not blocked by midazolam.<sup>(15)</sup> Similarly, Paris A et al.<sup>(16)</sup> found that oral clonidine (150µg), but not midazolam (7.5mg) prevented an increase in heart rate during the perioperative period.

There was a decrease in systolic, diastolic and mean arterial pressure in both the study groups 90 minutes after premedication. The decrease in systolic blood pressure in Midazolam group may be attributed to its sedative and anxiolytic properties. Immediately after induction of anaesthesia with thiopentone, there was decrease in systolic, diastolic and mean arterial blood pressure in both the groups, the decrease being comparable. One minute after intubation, there was a significant increase in systolic, diastolic and mean arterial pressure in midazolam premedicated group. Whereas in the clonidine premedicated group, these parameters did not rise above baseline values post intubation which was significant.

These results were comparable with the results of Paris A et al.<sup>(16)</sup> who found that clonidine (150µg orally), but not midazolam (7.5 mg orally) augmented haemodynamic stability and partially blunted stress responses as determined by adrenocorticotrophic hormone plasma levels. Attenuation of haemodynamic

response to intubation and intraoperative haemodynamic stability with clonidine was also demonstrated in studies conducted by Talebi H et al.<sup>(17)</sup> Laurite CE et al.,<sup>(18)</sup> Traill R, Gillies R,<sup>(19)</sup> Wawrzyniak K et al.<sup>(20)</sup> and Singhal SK et al.<sup>(21)</sup>

Rate pressure product is defined as the product of pulse rate and peak systolic blood pressure. There is a correlation between rate pressure product and myocardial blood flow, myocardial oxygen consumption as a result of which it correlates with signs of ischaemia.<sup>(6)</sup> This study shows that Clonidine effectively attenuates increase in rate pressure product following laryngoscopy and intubation; in accordance with studies conducted by Thomas MG et al.<sup>(22)</sup> and Montazeri K et al.<sup>(6)</sup>

### Conclusion

Clonidine, when used as premedication showed a comparable anxiolytic effect, with no sedation, better antisialogogue effect and well maintained haemodynamic parameters following laryngoscopy and intubation as compared with midazolam therefore constitutes optimal choice of two drugs.

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