Archives of Anesthesiology and Critical Care (Autumn 2022); 8(4): 288-294.

Available online at http://aacc.tums.ac.ir

Research Article

Comparison of Premedication with Midazolam and Dexmedetomidine on Sedation and Anxiety in Controlled Hypertensive Patients Undergoing Elective Surgery under General Anaesthesia

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ARTICLE INFO

Article history:
Received 28 January 2022
Revised 19 February 2022
Accepted 04 March 2022

Keywords:
Midazolam;
Dexmedetomidine;
Ramsay sedation score;
Visual analog scale

ABSTRACT

Background: The study is a double-blind randomized trial aiming to compare intravenous midazolam and dexmedetomidine as premedication for sedation and anxiety control in controlled hypertensive patients undergoing elective surgery under general anaesthesia.

Methods: The patients who met the inclusion criteria were randomly divided into two groups of 50 patients each. Thirty minutes prior to induction, Group 1 patients received midazolam 0.02mg/kg i.v and Group 2 patients received dexmedetomidine 1mcg/kg i.v in 100 ml normal saline over 10 minutes. Preoperative sedation and anxiety levels and vital parameters (heart rate, blood pressure, respiratory rate, arterial oxygen saturation) were assessed for 30 min at every 5 minutes interval.

Results: Preoperative sedation was found to be better with dexmedetomidine as compared to midazolam. Decrease in anxiety was comparable in both the groups. Significant fall in heart rate was observed in dexmedetomidine group but it was within the acceptable limits for age. Mean arterial pressure was comparable in both the groups. There was no statistical difference between the groups with respect to respiratory rate and arterial oxygen saturation.

Conclusion: Dexmedetomidine provides better sedation and good anxiety control with better maintainence of hemodynamic parameters as compared to midazolam. Thus it is a safe and effective drug to be used for premedication in controlled hypertensive patients.

Preoperative anxiety is a challenging problem especially in patients who are on antihypertensive medications. Anxiety and fear arising just before surgery may lead to psychosomatic effects like increase in level of stress hormones and gastric secretions, resulting in undesirable metabolic consequences [1]. It also interferes with the initial anaesthetic requirements and might lead to preoperative procedure difficulties as well [2]. High catecholamine levels cause an increase in heart rate, arterial blood pressure and oxygen consumption [3-4]. Excessive increase in blood pressure has been noticed in controlled hypertensive patients who are highly anxious. Preventing these metabolic responses is a necessity for modern anaesthesia especially in hypertensive patients who are on antihypertensive treatment [5].

Midazolam is a short-acting imidazobenzodiazepine and it helps in allevating anxiety, aids in sedation, provides anterograde amnesia and has anticonvulsant effects, by acting on GABA-A receptors [6-7]. It quickly passes through the blood–brain barrier and thus has a fast onset of action [7]. Rapid redistribution leads to a rapid recovery as it has lipid solubility at physiological pH [7-

The authors declare no conflicts of interest.
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8]. For these reasons, midazolam is one of the preferred premedication drugs being used before surgery.

Dexmedetomidine is a highly selective alpha-2 adrenergic receptor agonist [9]. Its specificity for α-2 receptors is 1600:1, which is 8 times higher than its predecessor, clonidine. [9-11]. Properties such as sedation, analgesia, perioperative sympatholysis, anaesthetic sparing effect, hemodynamic stability and lack of respiratory depression make dexmedetomidine a good choice for use as a premedicant [12-14]. Central nervous system sympathetic outflow is decreased in a dose dependant manner [14].

The purpose of this study was to compare intravenous dexmedetomidine and midazolam for premedication in controlled hypertensive patients undergoing elective surgery under general anesthesia.

Methods

After obtaining approval from the Institutional Review Board and Institutional Ethics Committee this double-blind randomized comparative study was conducted in the Department of Anaesthesiology in our hospital from 1st November 2019 to 31st March 2021.

Hundred patients scheduled for elective surgery under general anaesthesia aged between 20 to 75 years belonging to ASA class I or II were included in the study. The patients were randomly allocated into two groups of fifty patients each, using a computer-generated number sequence. Group 1 (midazolam group) received i.v midazolam and Group 2 (dexmedetomidine group) received i.v dexmedetomidine. Patients with renal and hepatic dysfunction, cardiovascular disease, uncontrolled hypertension, pregnancy, history of drug sensitivity, seizures, psychiatric disorders and those on beta-blockers were excluded from the study.

All the patients underwent a thorough pre-anaesthetic evaluation. On arriving in the operating room, all standard monitoring devices were attached and baseline heart rate, non-invasive blood pressure, respiratory rate, arterial oxygen saturation and electrocardiography were noted. Peripheral venous access was secured and supplemental oxygen was given via simple facemask. Thirty minutes prior to induction of anaesthesia patients received either intravenous midazolam or intravenous dexmedetomidine as per the group allocated. Group 1 patients received 0.02 mg/kg i.v midazolam in 100 ml normal saline over 10 minutes. Group 2 patients received 1mcg/kg i.v dexmedetomidine in 100 ml normal saline over 10 minutes. Following parameters were measured and recorded before and after administration of midazolam or dexmedetomidine at every 5 minutes interval till general anesthesia was induced: level of sedation (using Ramsay Sedation Score (RSS): 1=agitated,restless; 2=cooperative, tranquil; 3=responds to verbal commands while sleeping; 4=brisk response to flagellation tap or loud voice while sleeping; 5=sluggish response to flagellation tap or loud voice; 6= no response to flagellation tap or loud voice), level of anxiety (using Visual Analogue Score-Anxiety (VAS-A): scale of 1 to 10 ranging from calm and not anxious to extremely anxious), heart rate, blood pressure (systolic, diastolic and mean), respiratory rate and arterial oxygen saturation [15-16].

Anaesthesia was induced using fentanyl (2mcg/kg) and propofol (till loss of verbal response). Orotracheal intubation was facilitated using vecuronium 0.1mg/kg. Patients were mechanically ventilated with anaesthesia being maintained using oxygen-nitrous oxide mixture (50:50) with sevoflurane and intermittent vecuronium and fentanyl. Routine monitoring (HR, NIBP, ECG, SpO2, EtCo2, temperature) was done throughout the case. After completion of the surgery, residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg intravenously. After extubation, patients were transferred to post anaesthesia care unit for observation.

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected, then Non-parametric test was used. Quantitative variables were compared using Unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed) between the two groups. Qualitative variables were compared using Chi-Square test /Fisher's exact test. A 'p' value of less than 0.05 was considered statistically significant. Data was entered and coded in MS Excel spreadsheet and all statistical analysis was performed using SPSS software (Version 22, SPSS Inc, Chicago, IL, USA).

Results

The study was a double-blind randomized trial of 100 controlled hypertensive adult patients undergoing elective surgery under general anaesthesia. Study subjects were randomly divided into two groups of 50 patients each and given preoperative intravenous midazolam or dexmedetomidine accordingly. Both the groups were found to be comparable with respect to the baseline characteristics like age, gender, body mass index (BMI) and presence of co-morbidities (Table 1).

In terms of Ramsay Sedation Score (RSS), the two groups differed significantly at 10, 15, 20, 25 and 30 minutes. In Group 1, the mean RSS increased progressively from a minimum of 1.36 at 0 minutes to a maximum of 3.82 at 30 minutes. This change was found to be statistically significant (Friedman Test: $\chi 2 = 232.1$, $p = <0.001$). Similarly, in Group 2, the mean RSS increased from a minimum of 1.44 at 0 minutes to a maximum of 5.50 at 30 minutes. This change was statistically significant as well (Friedman Test: $\chi 2 = 275.5$, $p = <0.001$). The overall change in RSS over time was compared between the two groups using the Generalized Estimating Equations method. There was a significant difference in the trend of RSS over time

between the two groups (p = <0.001). 10 minutes onwards the mean RSS was significantly higher in Group 2 as compared to Group 1 (Figure 1).

Visual Analogue Score - Anxiety (VAS-A) varied significantly from 0 to 30 minutes in both the groups. The mean VAS-A was comparable between the groups at 0, 25 and 30 minutes. However, at 5, 10, 15 and 20 minutes the mean VAS-A was significantly higher in Group 1 as compared to Group 2 (Figure 2).

Non-Parametric tests were used to make statistical inference as data was not normally distributed. Wilcoxon-Mann-Whitney Test test was used to compare the two groups in terms of heart rate at each of the timepoints. Friedman test was used to explore the change in heart rate over time within each group. Generalized Estimating Equations method was used to explore the difference in change in heart rate between the two groups. In Group 1, the mean heart rate (bpm) decreased from a maximum of 93.44 at 0 minutes to a minimum of 88.06 at 5 minutes, and then increased to 89.06 at 30 minutes. This change was statistically significant (Friedman Test: $\chi2 = 107.9$, p = <0.001). In Group 2, the mean heart rate decreased from a maximum of 94.74 at 0 minutes to a minimum of 62.46 at 25 minutes, and then increased to 63.38 at 30 minutes. This change was also statistically significant (Friedman Test: $\chi2 = 238.9$, p = <0.001). Between the two groups, 10 minutes onwards the mean heart rate was significantly lower in group 2 as compared to group 1 [p = <0.001] (Figure 3).

In terms of blood pressure, mean systolic blood pressure was significantly lower in group 2 as compared to group 1 at 10, 15, 25 and 30 minutes. Mean diastolic blood pressure was lower in group 2 at 0, 10 and 30 minutes. However, it was lower in group 1 at 15, 20 and 25 minutes. Mean blood pressure was significantly lower in group 2 at 10 minutes but lower in group 1 at 20 and 25 minutes (Figure 4).

The two groups did not differ in terms of respiratory rate at any of the timepoints. In Group 1, the mean respiratory rate decreased from 14.56 at 0 minutes to a minimum of 14.42 at 25 minutes, and then increased to 14.58 at 30 minutes. This change was not statistically significant (Friedman Test: $\chi2 = 3.7$, p = 0.723). In Group 2, the mean respiratory rate decreased from a maximum of 14.58 at 0 minutes to a minimum of 14.44 at 30 minutes. This change was also not statistically significant (Friedman Test: $\chi2 = 4.7$, p = 0.583). The overall change in respiratory rate over time was compared between the two groups using Generalized Estimating Equations method and no significant difference was found [p = 0.805] (Figure 5).

Similar to the respiratory rate, the mean arterial oxygen saturation (SpO2) did not change significantly either within or between the two groups [p = 0.091] (Figure 6).

Table 1- Comparison of baseline characteristics between the groups

Parameters	Midazolam (group 1)	Dexmedetomidine (group 2)	P value
Age (Years)	55.50 ± 9.58	54.48 ± 9.41	0.612
Gender			0.548
Male	28 (56.0%)	25 (50.0%)	
Female	22 (44.0%)	25 (50.0%)	
Weight (Kg)	63.40 ± 6.84	64.48 ± 7.51	0.454
Height (cm)	164.38 ± 6.73	166.06 ± 8.73	0.171
BMI (Kg/m²)	23.00 ± 1.92	22.94 ± 1.87	0.792
Comorbidities			0.720
HTN	43 (86.0%)	45 (90.0%)	
HTN + COPD	3 (6.0%)	1 (2.0%)	
HTN + DM	4 (8.0%)	4 (8.0%)	

Figure 1- Change in Ramsay Sedation Score over time in the two groups

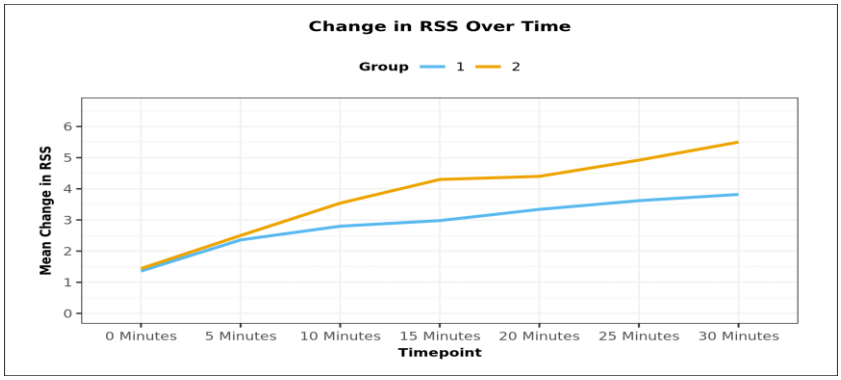


Figure 2- Change in Visual Analog Score - Anxiety over time in the two groups

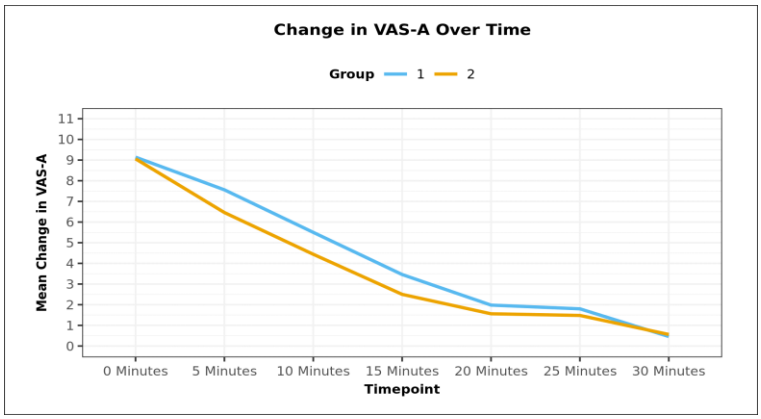


Figure 3- Change in heart rate over time in the two groups

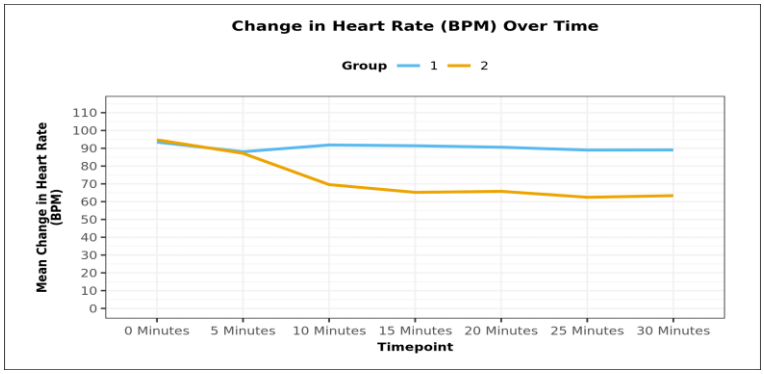


Figure 4- Comparison of Systolic, Diastolic and Mean Blood Pressure between the two groups

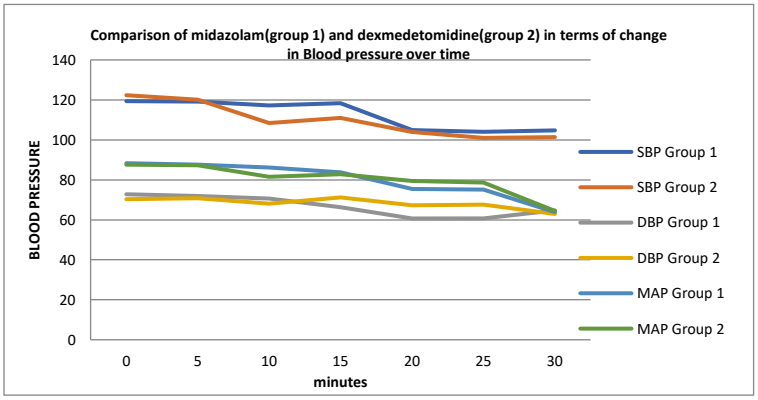


Figure 5- Comparison of respiratory rate between the two groups

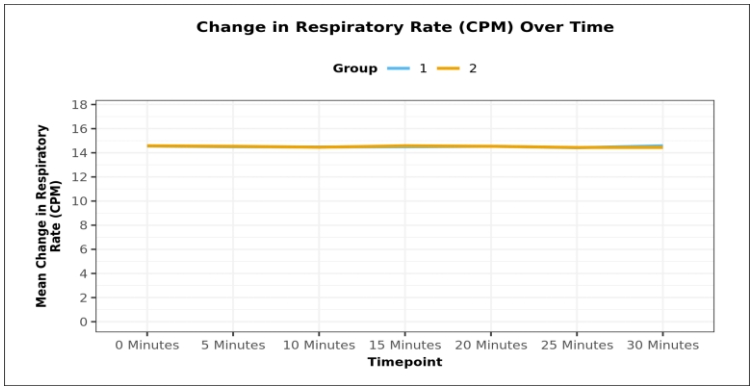
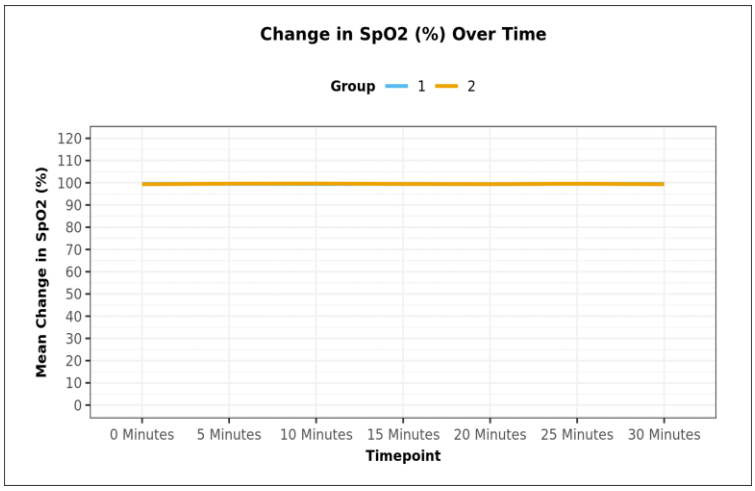


Figure 6- Comparison of arterial oxygen saturation between the two groups



Discussion

The premedicant when properly selected and administered in an appropriate way can produce the desired effects without any significant side effects and helps in better outcomes especially in patients with comorbidities. This current double-blind randomized comparative trial was undertaken in our hospital to study the effect of intravenous midazolam and dexmedetomidine for premedication in controlled hypertensive patients undergoing elective surgery under general anaesthesia. The patients were assessed for level of sedation and anxiety at baseline and at every 5 min interval for 30 minutes till induction. Vital parameters like heart rate, blood pressure, respiratory rate and arterial oxygen saturation were also assessed and recorded to look out for any potential adverse effects of the drugs used.

Both midazolam group and dexmedetomidine group were comparable with respect to age, gender, body mass index and presence of comorbidities and no statistically significant difference was found between the groups. Hence, the confounding effects of these variables were taken care of. In a randomized controlled study as ours, the similarity of baseline characteristics of patients ensures that any difference in outcome is purely due to intervention and not due to chance bias.

Quality of sedation was assessed by Ramsay Sedation Score and was compared between both the groups [15]. All the patients were awake before giving the respective drugs. After slow administration of the drugs, the level of sedation was noted. The mean sedation score at baseline (1.36±0.48 vs 1.44±0.50) and at 5 minutes after administration of drug (2.36 ±0.56 vs 2.50±0.51) was comparable in both the groups. A statistically significant increase in the level of sedation was observed in patients in dexmedetomidine group at 10 min, 15 min ,20 min, 25min and 30 min ($p<0.05$). The patients who received dexmedetomidine were better sedated (5.50 ± 0.51) compared to those who received midazolam (3.38±0.87) and the difference in the level of sedation was found to be statistically significant. Thus it was concluded that between the two drugs, dexmedetomidine was a better sedative when used as a premedicant. These findings correlate well with a study by Eran et al where dexmedetomidine (1mcg/kg) and three different doses of midazolam (0.02/kg, 0.04/kg, 0.06/kg) were compared and it was found that dexmedetomidine at a dose of 1mcg/kg and midazolam at a dose of 0.06 mg/kg provided better sedation compared to lower doses of midazolam (0.02mg/kg, 0.04mg/kg) [1].

Anxiety was assessed by Visual Analogue Score for Anxiety [16]. The mean VAS-A at baseline (9.14+ 0.88 vs 9.06+ 0.74) was comparable between the groups. Decrease in anxiety was observed in dexmedetomidine group at 5, 10, 15 and 20 minutes which was found to be statistically significant ($p<0.05$). Dexmedetomidine provided faster and better anxiolysis in the first 20 min. Later at 25 and 30 minutes, as the patients started getting sedated, the difference between both the groups in terms of reduction in anxiety became insignificant. Therefore, it was found that dexmedetomidine and midazolam were equally effective in producing anxiolysis at 25 and 30 minutes. Similar to our findings, Sajid et al reported in their study that oral midazolam and oral dexmedetomidine were equally effective in producing anxiolysis in the pediatric age group [17]. Diwan et al had compared intranasal dexmedetomidine and intranasal midazolam and found that dexmedetomidine provided better anxiolysis than midazolam which is in contrast to the findings in our study [18].

The heart rate at baseline (93 ±7.76 vs 94.74 ± 8.30) and at 5 min (88.06 ±4.75 vs 87.16 ± 4.32) was comparable between both the groups. Significant decrease in heart rate was seen with dexmedetomidine as compared to midazolam at 10 min, 15 min, 20 min, 25

min and 30 min ($p<0.05$). It was observed that dexmedetomidine causes a greater decrease in heart rate as compared to midazolam. However the fall in heart rate was within the acceptable limits for age and did not require the use of chronotropic agents. Similar to our findings, Alhashemi et al had found that heart rate reduction was more significant with dexmedetomidine as compared to midazolam in a study where they both were used for monitored anaesthesia care during cataract surgery [19].

In the present study there was a significant decrease in systolic blood pressure with dexmedetomidine as compared to midazolam. In midazolam group, the mean SBP decreased from a maximum of 119.38 at baseline to 104.68 at 30 minutes. In dexmedetomidine group, SBP decreased from 122.34 at baseline to 101.34 at 30 minutes. Even though SBP was decreased with midazolam, a greater decrease in SBP was seen with dexmedetomidine. However, the fall in blood pressure was within the acceptable limit for the age and did not require the use of ionotropic agents in midazolam group, the mean DBP decreased from a maximum of 72.80 mmHg at baseline to 64.74 at 30 minutes. In dexmedetomidine group, the mean DBP decreased from maximum of 70.26 at baseline to 62.96 at 30 minutes. Though there was an overall decrease in DBP with both midazolam and dexmedetomidine, the reduction in DBP was more marked with dexmedetomidine at 15 min, 20 min, 25 min. There was a significant decrease in MAP with dexmedetomidine at 20 min and 25 min, but at 30 min fall in MAP was comparable in both the groups. In midazolam group, the mean MAP reduced from 88.32 at baseline to 63.88 at 30 minutes. In dexmedetomidine group, the mean MAP reduced from 87.60 at baseline to 64.46 at 30 minutes. The fall in MAP was comparable in both the groups at 30 minutes. In a study by Eren et al, MAP had reduced significantly in dexmedetomidine group as compared to midazolam group and the difference was found to be statistically significant [1].

The respiratory rate and mean arterial oxygen saturation were comparable in both the groups and no statistically significant change was observed for both the parameters ($p>0.05$).

Conclusion

In our study, we compared the effectiveness of intravenous midazolam and dexmedetomidine for premedication in controlled hypertensive patients undergoing elective surgery under general anaesthesia. Pre-operative anxiety and sedation level were assessed using separate scoring systems along with variations in vital parameters. It was observed that intravenous dexmedetomidine in a dose of 1 mcg/kg was associated with an increased level of sedation than intravenous midazolam in a dose of 0.02 mg/kg. Both midazolam and dexmedetomidine were however equally effective in attenuating pre-operative anxiety. Hemodynamic parameters like heart rate and blood pressure showed greater reduction with dexmedetomidine but were well within the acceptable range and did not require any rescue intervention. Respiratory rate and arterial oxygen saturation did not show any significant change in any of the groups. Thus, it can be concluded that dexmedetomidine is a safe and effective drug for preoperative sedation and anxiety control in controlled hypetensive patients with better control of hemodynamic parameters.

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