Original Article

# Comparison of dexmedetomidine and three different doses of midazolam in preoperative sedation

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## Abstract

**Background:** This study was conducted to compare the efficacy and effects of dexmedetomidine and midazolam in preoperative sedation.

**Materials and Methods:** A total of 125 patients in American Society of Anaesthesiologists (ASA) I-II were divided into three groups: Group I ($n$ = 40) for controls, Group II ($n$ = 40) for Dexmedetomidine (1 $\mu$g/kg), and group III was the midazolam group ($n$ = 45). Group III was further divided into three subgroups according to the doses of midazolam: Group IIIA ($n$ = 15) received 0.02 mg/kg, group IIIB ($n$ = 15) received 0.04 mg/kg, and group IIIC ($n$ = 15) received 0.06 mg/kg of midazolam. Drugs were infused over a 10-minute period with appropriate monitoring. Ramsay and visual analog scores, for sedation and anxiety, respectively, and mean arterial pressure, heart rate, and $SpO_2$ measurement, including respiratory rates were recorded, every 5 minutes for 30 minutes following infusion.

**Results:** There was marked sedation and a decrease in anxiety in groups II and IIIC ($P < 0.01$). Mean arterial pressure (MAP) and heart rate (HR) decreased significantly in group II ($P < 0.01$ and $P < 0.05$, respectively), but there was no associated hypotension (MAP <60 mm Hg) or bradycardia (HR <50 bpm) ($P < 0.05$). Respiratory rates and $SpO_2$ values decreased in groups II, IIIA, IIIB, and IIIC. The differences in respiratory rates were not significant ($P > 0.05$); however, decrease in $SpO_2$ was significant in group IIIC ($P < 0.01$).

**Conclusions:** Dexmedetomidine was as effective as higher doses of midazolam in sedation. The hemodynamic and respiratory effects were minimal. Although dexmedetomidine caused significant decrease in the blood pressure and heart rate, it probably just normalized increased levels caused by preoperative stress.

**Key words**: Dexmedetomidine, general anesthesia, midazolam, premedication, sedation

## Introduction

Preoperative anxiety is a frequent condition. Generally, it starts two days before the operation and reaches its peak just prior to induction of anesthesia.[1] Anxiety is more common among younger patients, women, and people with negative experience of anesthesia or fear of death.[2] Anxiety, stress, and fear that arise just before the operation and anesthesia may lead to psychological trauma and increase the levels of stress hormones, resulting in undesirable metabolic responses before anesthesia. High catecholamine levels increase arterial blood pressure, heart rate, and oxygen consumption.[3,4] Controlling these metabolic reactions is a necessity for modern anesthesia.[5] Comfortable anesthesia induction and maintenance can be achieved by controlling anxiety.

Various agents such as phenothiazines, benzodiazepines, barbiturates, opioids, and antihistamines are used to relieve anxiety and provide sedation. Today, the most frequently used drugs are benzodiazepines.[6] Midazolam is a medication from this group with rapid onset and short lasting effect. Its sedative effect has been shown in many studies.[7-12]

Dexmedetomidine is a selective, specific, and highly potent alpha-2 adrenoceptor agonist.[13-15] The affinity of alpha-2/alpha-1 is 1620/1. While both alpha-1 and alpha-2 effects are present in higher doses and rapid administrations, only alpha-2 effects are observed in low-moderate doses and slow administrations. It has anxiolytic, hypnotic, sedative, and analgesic effects. It affects alpha-2 receptors in the central

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nervous system, peripheral nerves, and autonomic ganglions. It is widely used in intensive care units due to these characteristics.

In this study, our primary objective was to compare the effectiveness of dexmedetomidine vis-a-vis midazolam in preoperative sedation prior to minor surgical procedures. And our secondary goal was to find out the equivalent dose of midazolam to a dose of 1 $\mu$g/kg dexmedetomidine infusion used.

## Materials and Methods

Appropriate approval of the ethics committee of the hospital was obtained prior to the study. A total of 125 patients, aged 20-60 years, in American Society of Anaesthesiologists (ASA) groups I-II, and to undergo a minor or moderate in-hospital surgical procedure under general anesthesia were included in the study. During a preanesthetic visit, the patients were informed about the procedure and written informed consents of all participants were obtained, a day before surgery. Patients using alpha- and beta-blockers as antihypertensive agents or hypertensive patients without any treatment, patients on concurrent sedative medications, patients with psychiatric disease and those with body weight not within 20% of the ideal weight were excluded from the study.

The participants were randomized into three groups. Group I was control, Group II was dexmedetomidine, and Group III was the midazolam group. Group III was further divided into three subgroups: IIIA, IIIB, and IIIC. Group I received 100 ml of physiological saline. Group II received 1 $\mu$g/kg dexmedetomidine (Precedex 200 $\mu$g/ml, Hospira Inc., Rocky Mount, USA) in 100 ml physiological saline. Group IIIA received 0.02 mg/kg, Group IIIB received 0.04 mg/kg, and Group IIIC received 0.06 mg/kg midazolam (Dormicum 15 mg/ml, F. Hoffman-La Roche Ltd., Basel, Switzerland) in 100 ml physiological saline. The agents used in sedation were administered by an intravenous slow infusion in the preparation room in order to provide better control and stop them in case of any complication.

The patients were transferred to preparation room 40 minutes prior to anesthesia induction. They were reminded about the procedure and on how to use the visual analog score (VAS). Non-invasive blood pressure measurement, electrocardiography, and peripheral oxygen saturation monitoring was performed (Nihon-Kohden BSM 4113 K, Nihon-Kohden Corporation, Tokyo, Japan). Peripheral venous routes were accessed via 20-G catheters. The infusions of the medications were started 30 minutes before anesthesia induction and infusions were completed in 10 minutes. Balanced electrolyte solution with an infusion rate of 100 ml/h was started simultaneously using another IV route. The onset time of sedative agent infusion was taken as minute zero and the following parameters were measured and recorded with intervals of 5 minutes: Ramsay sedation scores (1 = agitated, restless; 2 = cooperative, tranquil; 3 = responds to verbal commands while sleeping; 4 = brisk response to glabellar tap or loud voice while sleeping; 5 = sluggish response to glabellar tap or loud voice; 6 = no response to glabellar tap or loud voice), VAS (patients were asked to self-evaluate their feelings of anxiety with scores of 0-10, with 0 = absent and 10 = very much), mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation ($SpO_2$), and respiratory rate (RR).

It was planned to intervene the patients with atropine sulfate 0.5 mg in case of bradycardia (HR <50 bpm) and with ephedrine HCl 5 mg incremental doses in case of hypotension (MAP <60 mm Hg). If respiratory rates <8 and hypoxemia ($SpO_2$ <90%) were observed, the depth and rate of respiration were planned to be increased with verbal or painful stimuli and oxygen support with mask.

Power analysis done before the study showed that: Taken as $\Delta$:2,5 SD:2, for power of 0.80, $\beta$:0.20 and $\alpha$:0.05; the subject number of groups was to be 11. Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) for Windows 15.0 software. In addition to descriptive statistical methods (mean, Standard Deviation), One-way analysis of variance (ANOVA) test was used to compare parameters with normal distribution between groups. Tukey's Honest Significant Difference (HSD) test was used to determine the group that caused the difference. Kruskal–Wallis and Mann–Whitney *U* tests were used to compare the parameters without normal distribution. Intra-group comparisons were performed with repeated-measures ANOVA and paired *t* test for parameters having normal distribution; and with Friedman test and Wilcoxon index test for parameters without normal distribution. Comparison of qualitative data was performed with Chi-square test. Confidence interval was defined as 95% and the level of significance was set at $P < 0.05$.

## Results

Demographic characteristics of the groups are presented in Table 1. Comparison of the groups in respect of MAP, HR, RR, and $SpO_2$ are demonstrated on Figures 1-3, and 4, respectively. There were no significant differences between groups by means of MAP and HR. On the other hand, the differences in $SpO_2$ from the baseline in group II, group IIIB, and, especially Group IIIC, were prominent [Figure 4].

Ramsay scores of Group I were significantly lower than those

**Table 1: Demographic characteristics of patients**

| | Group I ($n$ = 40) | Group II ($n$ = 40) | Group IIIA ($n$ = 15) | Group IIIB ($n$ = 15) | Group IIIC ($n$ = 15) |
|---|---|---|---|---|---|
| Gender (F/M) | 21/19 | 23/17 | 13/2 | 9/6 | 7/8 |
| Age (yr) (Mean ± SD) | 34.72 ± 10.61 | 34.25 ± 10.98 | 37.13 ± 9.36 | 39.87 ± 12.88 | 36.80 ± 13.38 |
| Weight (kg) (Mean ± SD) | 66.80 ± 11.75 | 71.47 ± 12.21 | 65.93 ± 11.02 | 73.47 ± 14.20 | 67.27 ± 7.64 |
| Height (cm) (Mean ± SD) | 165.22 ± 9.54 | 167.60 ± 9.34 | 162.00 ± 7.54 | 167.27 ± 7.64 | 169.27 ± 8.54 |

*Group I = Control group, Group II = Dexmedetomidine, Group IIIA = Midazolam 0.02 mg/kg, Group IIIB = Midazolam 0.04 mg/kg, Group IIIC = Midazolam 0.06 mg/kg, F/M = female:male ratio, SD = standart deviation, yr = age in years, kg = weight in kilos, and cm = height in centimeters*

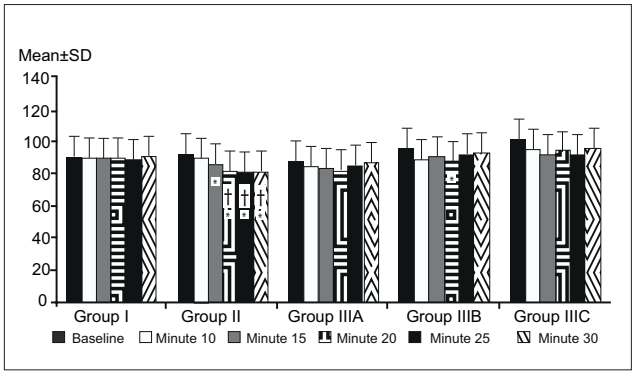


**Figure 1:** Mean arterial pressures in the groups. group 1: Control, group II: Dexmedetomidine 0.1 $\mu$g/kg, groups IIIA-C: Midazolam, 0.02, 0.04, and 0.06 mg/kg, respectively. Columns = mean values, antennae = standard deviation. † = Significant difference versus group I, one-way analysis of variance (ANOVA) test, $P < 0.05$ * = Significant difference versus baseline, Repeated-measures ANOVA, $P < 0.05$

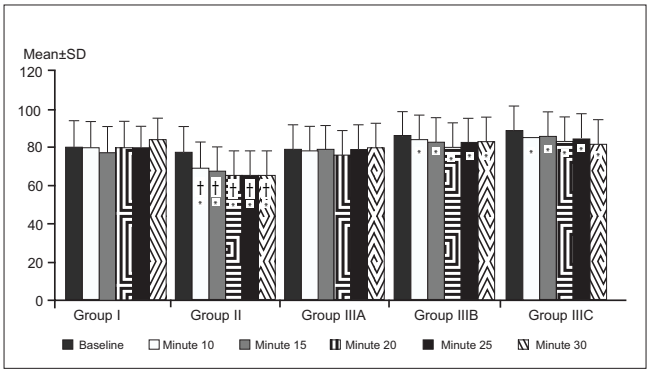


**Figure 2:** Heart rate values of the study groups before (baseline) as well as 10, 15, 20, 25, and 30 min after infusion of the study drugs. group 1: Control, group II: Dexmedetomidine 0.1 $\mu$g/kg, groups IIIA-C: Midazolam, 0.02, 0.04, and 0.06 mg/kg, respectively. Columns = mean values, antennae = standard deviation. † = Significant difference versus group I, one-way analysis of variance (ANOVA) test, $P < 0.05$ * = Significant difference versus baseline, repeated-measures ANOVA, $P < 0.05$

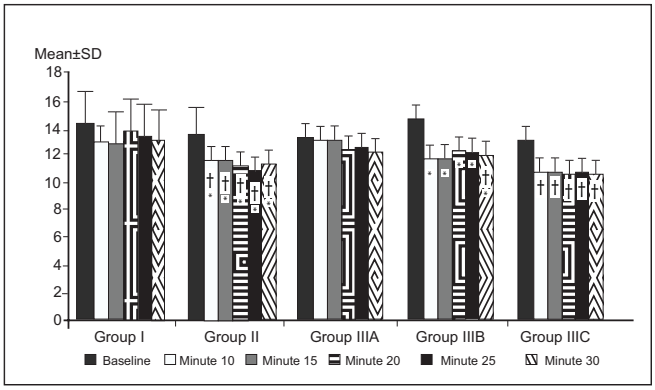


**Figure 3:** Respiratory rates measurements of the study groups before (baseline) as well as 10, 15, 20, 25, and 30 min after infusion of the study drugs. group 1: Control, group II: Dexmedetomidine 0.1 $\mu$g/kg, groups IIIA-C: Midazolam, 0.02, 0.04, and 0.06 mg/kg, respectively Columns = mean values, antennae = standard deviation. † = Significant difference versus group I, one-way analysis of variance (ANOVA) test, $P < 0.05$ * = Significant difference versus baseline, repeated-measures ANOVA, $P < 0.05$

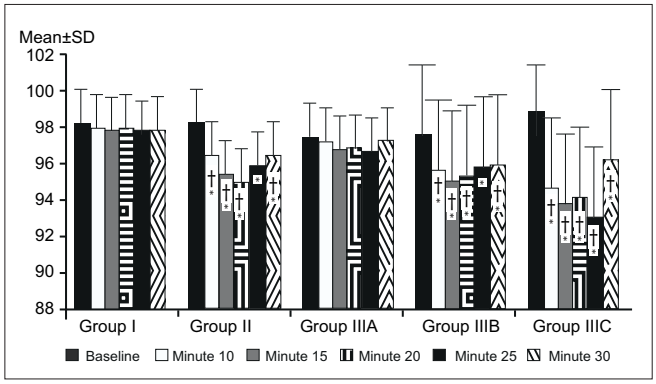


**Figure 4:** $SpO_2$ values of the study groups. Group 1: Control, group II: Dexmedetomidine 0.1 $\mu$g/kg, groups IIIA-C: Midazolam, 0.02, 0.04, and 0.06 mg/kg, respectively. Begining from the 10th mimute until the end of 30 minutes $SpO_2$ values of groups II, IIIB, and IIIC were found to be lower compared to both baseline and group I ($P < 0.01$). Columns = mean values, antennae = standard deviation. † = Significant difference versus group I, one-way analysis of variance (ANOVA) test, $P < 0.05$ *= Significant difference versus baseline, repeated-measuresANOVA, $P < 0.05$

of groups II, IIIB, and IIIC at the 10th, 15th, and 30th minutes and as compared to those of groups II, IIIA, IIIB, and IIIC at the 20th and 25th minutes ($P < 0.05$). Ramsay scores of group II were significantly higher than those of groups IIIA and IIIB at the 10th, 15th, 20th, and 25th minutes ($P < 0.05$). Ramsay score of group II was significantly higher than those of groups IIIA, IIIB, and IIIC at the 30th minute ($P < 0.05$) [Figure 5]. In-group comparisons: Compared to the baseline values, Ramsay scores of groups II, IIIB, and IIIC started increasing at 10 minutes; this increase persisted thereafter ($P < 0.01$). Ramsay scores of group IIIA at the 20th and 25th minutes were significantly higher than the baseline values

($P < 0.05$); however, but this increase did not sustain until the 30th minute [Figure 5].

VAS of group I were significantly higher than those of groups II, IIIB, and IIIC at the 10th, 15th, 20th, and 25th minutes and as compared to those of groups II, IIIA, IIIB, and IIIC at the 30th minute ($P < 0.05$). VAS of group II were significantly lower than those of group IIIA and IIIB at the 10th and 15th minutes and as compared to groups IIIA, IIIB, and IIIC at the 20th, 25th, and 30th minutes ($P < 0.05$) [Figure 6].

Intra-group comparisons: VAS of groups II, IIIB, and IIIC, beginning from 10 minutes, declined significantly and persisted until the end ($P < 0.01$). Whereas, in group IIIA, the VAS decreased significantly at 20 minutes ($P < 0.01$), but increased back to the prior levels at 25th minute [Figure 6].

Prevalence of side effects such as bradycardia (HR <50 bpm), nausea, and dry mouth were not different between the groups ($P > 0.05$). However, the prevalence of hypoxemia (SpO2 <90%) was significantly different among the groups ($P < 0.05$). The prevalence of hypoxemia was significantly higher in group IIIC than other groups. Three patients developed bradycardia, but only one of them needed 0.5 mg of atropine (HR <40 bpm). Hypoxemia was present in 11 patients, and in two of them (who received 0.06 mg midazolam), the depth and RR could not be increased and $O_2$ support with mask was needed [Table 2].

## Discussion

Potential side effects of dexmedetomidine, an alpha-2 receptor agonist, such as hypotension, bradycardia, hypertension, and tachycardia were considered at the planning stage. Hypotension and bradycardia have been observed in studies done earlier.[4,15,16] These effects are known to be related to the dose, route of administration, and infusion rate (in intravenous administrations).[17-21] Reports of its use state that alpha-2 agonist effect is observed, but not alpha-1 effect, on administration of low and moderate doses and slow rates of infusion. Consequently, peripheral vasoconstriction and hypertension would not be expected in these instances.[22-24] Taking these data into account, we elected to use it in a dosage of 1 $\mu$g/kg, so as to avoid side effects associated with high infusion rates.

Dexmedetomidine significantly decreased MAP and HR levels following its sedative effect compared to other groups

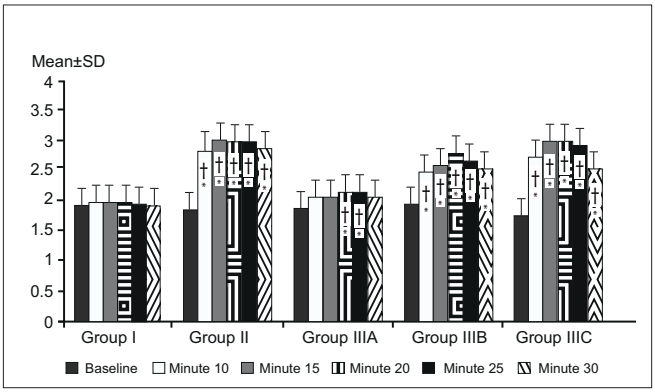


**Figure 5:** Ramsay scores of the study groups. Group 1: Control, group II: Dexmedetomidine 0.1 $\mu$g/kg, groups IIIA-C: Midazolam, 0.02, 0.04, and 0.06 mg/kg, respectively Ramsay scores of the groups II, IIIB, and IIIC evaluated at all times showed significance compared to baseline levels ($P < 0.01$), whereas those of Group IIIA were only significant at 20 and 25th minutes ($P < 0.05$). Likewise, the significance was present again at all measured times for groups II, IIIB, and IIIC compared to group I ($P < 0.01$); and only at 20 and 25th minutes for group IIIA ($P < 0.05$)

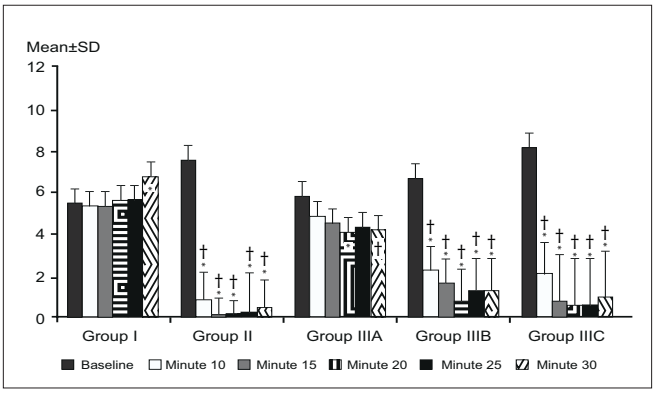


**Figure 6:** VAS scores for anxiety evaluation of the study groups. VAS scores at all periods in groups II, IIIB, and IIIC were lower compared to baseline values ($P < 0.01$); significance was present at the 30th and 20th minutes in groups I and IIIA, respectively, compared to baseline ($P < 0.01$, $P < 0.01$). Columns = mean values, antennae = standard deviation, †= Significant difference versus group I, Kruskall-Wallis test, $P < 0.05$, *= Significant difference versus baseline, Friedman test, $P < 0.05$

**Table 2: Distribution of side effects**

| | Group I *n* (%) | Group II *n* (%) | Group IIIA *n* (%) | Group IIIB *n* (%) | Group IIIC *n* (%) | *P*+ |
|---|---|---|---|---|---|---|
| Bradycardia | 1 (2.5) | 2 (5.0) | - | - | - | 0.688 |
| Nausea | - | 1 (2.5) | - | - | - | 0.710 |
| Dry mouth | - | 1 (2.5) | - | - | - | 0.710 |
| Hypoxemia | - | 5 (12.5) | - | 2 (13.3) | 4 (26.7) | 0.015* |

*Group I = Control group, Group II = Dexmedetomidine, Group IIIA = Midazolam 0.02 mg/kg, Group IIIB = Midazolam 0.04 mg/kg, Group IIIC = Midazolam 0.06 mg/kg. *Significant at P <0.05 level when compared to other groups. + = Chi-square test*

or pre-sedation levels. This sedative effect was observed in group IIIC (0.06 mg/kg midazolam group). The sedative effect of midazolam decreased at the 25th minute according to Ramsay and VAS, and MAP levels slightly increased at the 25th and 30th minutes. However, the sedative effect of dexmedetomidine continued at the 25th and 30th minutes, but MAP and HR measurements did not increase. The decrease in MAP measurements was not to a level that could compromise hemodynamics of the patients in both groups. These effects were present in both groups with similar sedative characteristics but were more evident in the dexmedetomidine group. In two patients who received dexmedetomidine, HR decreased below 50 bpm, and 0.5 mg of atropine was administered since HR decreased to below 40 bpm (during laryngoscopy in one). No medication was administered, as HR increased spontaneously in the other patient and in one patient from the control group. When compared with controls, dexmedetomidine-induced bradycardia was not statistically significant and was not found to be clinically challenging. Similar observations were reported by Dyck and colleagues who compared intravenous and intramuscular administration of dexmedetomidine and by Erkola and colleagues who compared the effects of dexmedetomidine and midazolam in elective abdominal hysterectomy.[15,20]

When RR and $SpO_2$ values were evaluated, dexmedetomidine and all doses of midazolam caused significant decreases in RR compared to the controls and the levels at the onset of administration. This decrease was less evident in 0.02 mg/kg midazolam group and lasted shorter in this group as compared to the other groups. There was no difference between dexmedetomidine and 0.06 mg/kg midazolam groups that were equally sedative. The decrease in $SpO_2$ levels was more evident and resultant hypoxemia was more frequent in 0.06 mg/kg midazolam group. The effects of dexmedetomidine on respiratory parameters were reported to be minimal in a number of studies performed with similar doses. Hall and colleagues studied the effects of low-dose dexmedetomidine on amnesia, analgesia, and sedation, while Venn and colleagues investigated respiratory effects of dexmedetomidine in postoperative intensive care unit patients and found similar results.[25,26] On the other hand, Bhana *et al.*, Belleville *et al.*, and Venn *et al.* reported that higher doses and rapid infusion rates might suppress respiration.[27-29]

We enrolled ASA I-II patients for the study, as they are not much compromised. The average age of the patients in the study groups was approximately 37 years. This can be considered as a limitation of the study, as geriatric and more compromised patients may possibly develop respiratory depression and altered hemodynamics.

When sedative effects were compared, dexmedetomidine and midazolam at the dosage of 0.04 mg/kg and 0.06 mg/kg caused an evident sedative effect beginning at the 10th minute according to Ramsay and VAS. The sedative effect of midazolam at the dose of 0.02 mg/kg was not adequate, started later, and lasted shorter. Sedative effects of dexmedetomidine and 0.06 mg/kg midazolam were similar until the 30th minute and significantly more evident than other groups according to Ramsay and VAS. While the efficacy of dexmedetomidine persisted in the 30th minute, the sedative effect of 0.06 mg/kg midazolam decreased. This decrease was suggested to be due to shorter half-life of midazolam. Rosen and colleagues had previously reported similar results.[30] Dexmedetomidine and midazolam at the doses of 0.04 mg/kg and 0.06 mg/kg caused statistically significant differences in Ramsay scores and VAS when compared with baseline values, but the effect was more pronounced in the dexmedetomidine group as compared to midazolam groups ($P < 0.01$).

The limitation of the study is that the number of patients is too small for broad generalizations. Sample size limits the power for subgroup analyses.

## Conclusions

Our results indicate that dexmedetomidine is an effective agent for preoperative sedation and its administration results with equal or even longer sedation compared to high doses (0.06 mg/kg) of midazolam. It leads to depressive effects on hemodynamic parameters at the dose of 1 $\mu$g/kg, but this effect does not reach the level of severe impairment. It may be suggested that its use normalizes increased blood pressure and HR due to preoperative anxiety. Its effects on respiratory parameters are definitely less than midazolam. We suggest that dexmedetomidine is a safe agent for premedication of non-compromised patients and may also be used outside of the intensive care units. However, more studies focusing on its effects on more debilitated older patients are needed.

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