

THE EFFECTS OF MIDAZOLAM AND DEXMEDETOMIDINE INFUSION ON PERI-OPERATIVE ANXIETY IN REGIONAL ANESTHESIA

ELIF ŞENSES^{*}, ALPARSLAN APAN^{**},
EMINE ARZU KÖSE^{***}, GÖKŞEN ÖZ^{***} AND HATICE REZAKI^{****}

Abstract

Background: This study aimed to compare the influences of midazolam and dexmedetomidine infusion on anxiety scores in patients undergoing surgery with regional anesthesia.

Methods: Eighty ASA I or II class patient undergoing elective surgery with regional anesthesia were included in the study. Permanent anxiety scores were determined using the State-Trait Anxiety Inventory (STAI)-1 and 2 one day before the surgery. In Group I patients, dexmedetomidine 0.5 µg/kg basal infusion for 10 min and 0.5 µg/kg/h for maintenance was administered. In Group II patients, midazolam infusion at a rate of 0.05 mg/kg for 10 min and 0.05 mg/kg/h for maintenance was administered. The sedation scores were determined every 5 min. The steady state anxiety scores of the patients were determined one day before, 30 min after operation, at the end of the operation, and at 30 min and day 7 postoperatively using STAI-1 score. Side effects were determined and recorded.

Results: Sedation scores were comparable in both of two treatment groups. Anxiety scores were maintained with drug infusions. The incidences of side effects were significantly decreased in midazolam group compared to the dexmedetomidine group.

Conclusion: Midazolam infusion was found to be more appropriate and efficient than dexmedetomidine during regional anesthesia practice. Dexmedetomidine infusion should be cautiously used in regional anesthetic techniques performing symphathetic blockade.

Key words: Anxiety, dexmedetomidine, midazolam, regional anesthesia, sedation.

Conflict of interest: Authors declare that there is no conflict of interest.

Disclose source: The study was performed without requiring external source.

* MD, Resident, Department of Anesthesiology.

** MD, Professor, Department of Anesthesiology.

*** MD, Assistant Professor, Department of Anesthesiology.

**** MD, Assistant Professor, Department of Psychiatry, Kırıkkale University, Faculty of Medicine.

Corresponding author: Alpaslan Apan, MD, Urankent THK Blokları E-2 Blok No: 15 Yenimahalle, Ankara Turkey. Tel: +90-318-2252820, Fax: +90-318-2244683. E-mail: alpaslanapan@gmail.com

Introduction

Surgical operation is one of the most serious stresses experienced by humans and fear and anxiety may influence the mortality by increasing neuroendocrine stress response¹.

Regional anesthesia used commonly in day-case surgery offers advantages such as, being vigilant during surgery, continuing spontaneous breathing, and preservation of protective reflexes such as swallowing and coughing. In addition, early mobilization in the postoperative period, minimizing pulmonary complications, persisting analgesia, and shortening of the duration of hospitalization are other benefits. On the other hand, vigilance during surgery may increase concerns including being aware of surgical intervention and pain. Pain at the puncture site, needle fear, and recalling the procedures are the other undesired concerns regarding regional anesthesia. Patients may hence experience intense stress and anxiety, which is unfavorable for patient, anesthesia and surgical team. These points may be alleviated by sedating the patient during surgery.

Dexmedetomidine activates central nervous system and decreases plasma catecholamine level with stimulation of α -2 adrenoreceptors in postsynaptic site, resulting in decrease of heart rate and blood pressure and is used for sedation and anxiolysis. It was demonstrated to decrease pain and catecholamine response to cold pressure in healthy volunteers². In a study comparing dexmedetomidine with propofol infusion, only propofol was found to be efficient on anxiety in healthy volunteers³.

Midazolam which is a short acting, water soluble form of benzodiazepine is commonly used for premedication in order to perform amnesia, sedation and to reduce peri-operative anxiety. This effect depends on to binding to the gamma amino butyrate receptors at benzodiazepine site⁴. It is also shown in a placebo controlled study that, premedication with midazolam was decreased nausea and vomiting in patients undergoing day-case surgery⁵. Although it was shown a decrease in psychomotor performance with midazolam, there was no change on attention span⁶.

The aim of the present study was to compare dexmedetomidine and midazolam for the quality

of sedation, hemodynamic changes, influence on perioperative anxiety and side effect profiles.

Methods

The uni-centric study was conducted at Departments of Anesthesiology and Psychiatry in Kırıkkale University Süleyman Demirel Training and Investigation Hospital after obtaining approval from Local Ethics Committee (2009/038). Eighty American Society of Anesthesiology (ASA) class I-II patients scheduled for elective extremity surgery under regional anesthesia, aged between 18-70 years were randomly recruited. Randomization was performed using sealed opaque envelopes chosen from the patients before the operation. Drug dilutions were prepared and labeled in a separate room from an investigator (AA) who was not participated to the further evaluation.

Patients including ASA class III or more, aged under 18 years or more than 70 years, with morbid obesity (patients exceeds 50% of their ideal body weight), with asthma and other pulmonary disorders, with uncontrolled systemic pathology (such as diabetes mellitus), with unknown central nervous system disease, with debility or disorders influencing cooperation, with known psychiatric disorders, with history of sleep apnea, patients with obvious arrhythmia or conduction defects, with analgesic use within 3 days, receiving monoamineoxydase type of antihypertensive drug, alcohol, drugs including carbamazepine, agonist antagonist type of opioids, allergy to the any type of anesthetics used including midazolam and dexmedetomidine were excluded from the study. All patients were informed about the procedure and written consents were obtained a day before surgery. Steady state (State Trait Anxiety Inventory: STAI-2) and anxiety levels (STAI-1) were determined using anxiety scores⁷ and values before sedative infusions was accepted as baseline. Patients were randomly allocated into two equal groups (40 in each) namely dexmedetomidine (Group D) and midazolam (Group M). Venous access was found at non dominant site of dorsum of hand in the holding area using 20 G cannula, lactate ringer infusion was started initially at a rate of 7-8 mL.kg⁻¹.h⁻¹ within 15-20 min as pre-hydration and decreased to 5 mL.kg⁻¹

$^1.h^{-1}$. Premedication was not performed. A nasal cannula was applied and oxygen was supplemented at a rate of $2 L.min^{-1}$. As a standard anesthetic care, vital parameters including ECG at V5 derivation and oxygen saturation were monitored continuously; arterial blood pressure was determined and recorded every 5 min (Datex-Ohmeda Cardiocap 5, Helsinki, Finland). Regional anesthesia was performed after obtaining appropriate position and cleansing. Anesthetic distribution was determined using pin pricks.

Sedative drugs (Midazolam 20 mg or dexmedetomidine 200 μg) were diluted in 50 mL saline and started via stopcock. Midazolam initial bolus dose $0.05 mg.kg^{-1}$ infused within 10 min and followed at a dose of $0.05 mg.kg^{-1}.h^{-1}$ in Group M, or dexmedetomidine $0.5 \mu g.kg^{-1}$ was given within 10 min and infusion was made with $0.5 \mu g.kg^{-1}.h^{-1}$ in Group D according to calculated volumes (Body weight / 8 = mL for initial bolus and maintenance infusion). Sedation was monitored by determining Observer's Assessment of Alertness Scale (OAAS) determined before and every 5 min during infusion⁸. Infusion was adjusted according to the target OAAS around 4. Infusion was stopped in lower and increased in higher values. OAA/S was rated as follows 5: response to the question asked with the normal voice, 4: lethargic response to the normal voice (sleepy), 3: response to only repeated or loud voice, 2: response to the gentle shaking or pushing, 1: no response to the gentle shaking or pushing. Patient's anxiety was also assessed using STAI-1 at 30 min after starting the operation, at the end of the operation, 30 min after operation and 1 week after operation with a telephone interview. Sedative infusion was followed until skin closure. Recovery time was accepted as time to reach OAA/S 5.

Perioperative side effects including hypotension (MAP < 70 mmHg or decrease more than 20% from initial value), bradycardia (HR < 45 beats.min), desaturation (SpO₂ < 90 for more than 5 sec), headache, nausea and vomiting were noted. Infusion of crystalloid fluid was increased for hypotension and ephedrine at a dose of 5 mg iv was given and repeated when indicated, and atropine sulphate 0.5 mg iv was administered for bradycardia. Metoclopramide 10 mg

iv was performed slowly in the case of moderate and severe nausea and/or vomiting. Patients were evaluated for an hour at recovery area. Supplemental O₂ $2 L.min^{-1}$ was given through nasal cannula, vital signs were also determined during this period.

Statistical analysis

Statistical analysis was performed using package program (SPSS15.0, Chicago, USA). Our preliminary data indicates that 28 patients in each group was required to find any difference between side effect profiles with a power of 80%. We therefore included 40 patients in each group in order to increase power and to account for possible dropouts. Demographic variables were compared using chi-square, continuous variables were evaluated with t test, and non parametric data with using Kruskal-Wallis analysis. A p value under 0.05 was considered for statistical significance.

Results

All patients in either group completed the study. Demographic variable, duration of surgery and anesthesia are shown in Table 1. There were no differences between study groups with respect to these parameters. Table 2 indicates the distribution of regional techniques performed in study groups.

Table 1

Patient characteristics, duration of surgery and anesthesia, ASA: American society of Anesthesiology

	Group D	Group M
	n= 40	n= 40
Age (year)	39.7 ± 14.9	39.2 ± 12.6
Height (cm)	167.9 ± 10.3	169.5 ± 9.8
Weight (kg)	74.6 ± 13.9	80.2 ± 9.9
Gender (F/M)	18/22	13/27
ASA physical status (I/II)	28/12	26/14
Duration of operation (min)	73.6 ± 17.9	82.8 ± 24.0
Duration of anesthesia (min)	85.1 ± 18.2	93.7 ± 24.2

Table 2

Distribution of regional anesthetic techniques, BPB: brachial plexus block, SNB: sciatic nerve block, N (%)

	Group D	Group M
	n= 40	n= 40
Spinal	21 (52.5%)	17 (42.5%)
Spinal and epidural	1 (2.5%)	3 (7.5%)
Axillary BPB	11 (27.5%)	17 (42.5%)
Supraclavicular BPB	6 (15%)	3 (7.5%)
Popliteal SNB	1 (2.5%)	0 (0%)

Hemodynamic variables including HR and MAP pressure in the perioperative and early postoperative period are shown in Figure 1 and 2. There was no significant difference between groups during the observation period.

Fig. 1

Heart rate (HR) variables

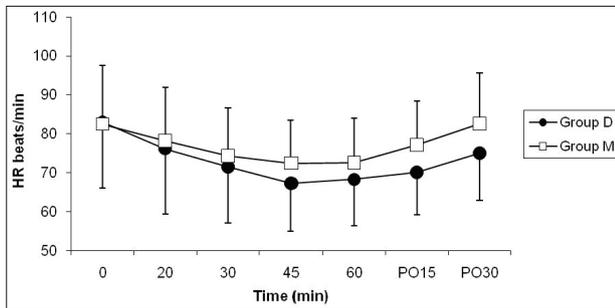
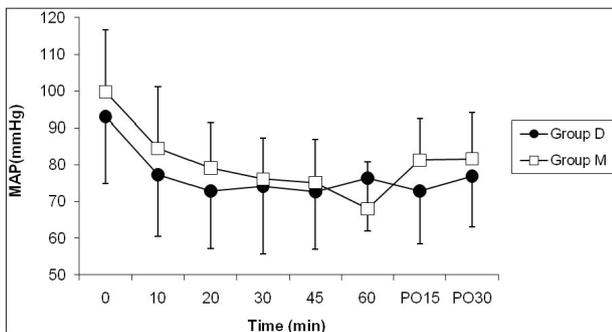


Fig. 2

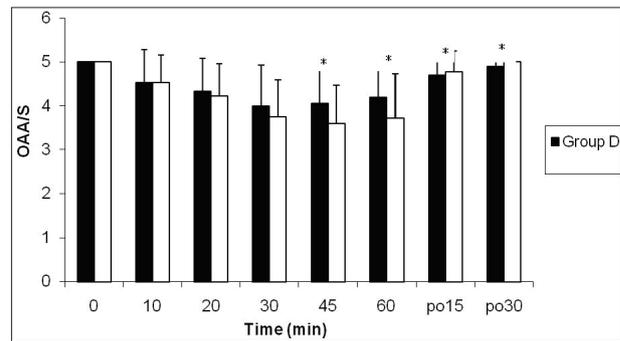
Mean arterial blood pressure (MAP) changes



Sedation scores are shown in Figure 3. While, patients in the Group D were significantly more sedated at 45 and 60 min during perioperative period, sedation was more pronounced in Group M at postoperative 15 and 30 min periods ($p < 0.05$).

Fig. 3

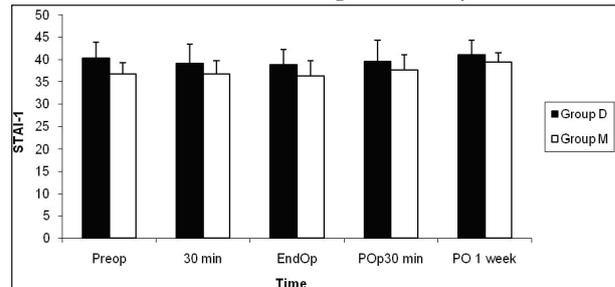
Sedation determined with observer's assessment of alertness (OAA/S) scale, *: $p < 0.05$



Anxiety scores of study groups (STAI-1) are shown in Figure 4. Although there were significant differences between groups in each time period, no significant change was found compared to the baseline value. Steady state anxiety levels (STAI-2) were similar between treatments (Group D; 42.0 ± 4.6 , Group M: 42.9 ± 5.1 , $p = 0.411$).

Fig. 4

Time-related changes on anxiety



Side effect profiles of the study groups in perioperative and early postoperative periods are summarized in Table 3. Bradycardia was significantly increased in Group D (25% versus 2.5%, $p = 0.004$). Nausea was increased in Group M (10% versus 2.5%, $p = 0.041$).

Table 3

Side effects during perioperative and early postoperative period, N(%)

	Group D	Group M
	n= 40	n= 40
Hypotension	4 (10%)	1 (2.5%)
Bradycardia	10 (25%)	1 (2.5%)
Nausea	1 (2.5%)	4 (10%)
Vomiting	-	1 (2.5%)
Dizziness	-	-
Headache	2 (5%)	-

Discussion

The results of the present study showed that, in equal sedative doses dexmedetomidine and midazolam demonstrated the same level of anxiolysis, but side effect profiles were increased with dexmedetomidine infusion during regional anesthetic practice.

When compared with the preoperative values, heart rates decreased in both study groups. While there was only one patient in midazolam group that required treatment for bradycardia, there were eight patients with bradycardia and two patients with hypotension along with bradycardia in dexmedetomidine infusion group that necessitated treatment. Spinal anesthesia was performed in 10 patients in whom bradycardia and hypotension developed. It was concluded that decrease in HR and MAP occurred at the same period due to sympathetic block established during spinal anesthesia and pharmacologic effects of dexmedetomidine, and therefore side effects were increased.

Dexmedetomidine dose dependently decreases heart rate and arterial blood pressure by decreasing plasma catecholamine levels⁹. Mean arterial blood pressure and heart rate was significantly decreased by 22% and 27% respectively in ten healthy volunteers after infusion in a rate of $2\mu\text{.kg}^{-1}/\text{h}^{-1}$ ⁽¹⁰⁾. A transient increase in blood pressure may occur due to peripheral α -2 adrenoceptor activation induced vasoconstriction¹¹. In our study, compared to the intraoperative measurements, the baseline MAP values were higher in both of two groups, with more significant increase in dexmedetomidine. In contrast, the changes in HR were more pronounced and the decrease in dexmedetomidine was greater than in midazolam. However, changes were not able to reach significance level at any observation period.

There are few studies performing intraoperative sedation during regional anesthesia with dexmedetomidine. Kuzucuoglu et al.¹² compared dexmedetomidine and midazolam infusion when epidural anesthesia reached the predetermined level and similar decrease in HR with dexmedetomidine and relatively stable MAP changes were observed in our study. They concluded that both drugs may be used for sedation but choosing midazolam should be more appropriate. Comparing propofol with dexmedetomidine sedation during postoperative period of cervical spine surgery in adult patients, Terao et al.¹³ indicated that hemodynamic variations were more prominent with dexmedetomidine.

Alhashemi¹⁴ compared midazolam and dexmedetomidine during cataract surgery according to the Ramsay sedation scale (RSS) and they concluded although dexmedetomidine caused more prominent decreasing on MAP and HR, it had no significant superiority to midazolam. In a similar study with omitting initial bolus dose, we revealed no significant difference between two drugs¹⁵.

Anxiety scores determined with visual analogue scale were similarly decreased with dexmedetomidine or midazolam infusion during gastroscopy in adult patients¹⁶. We used STAI-2 for determining anxiety scores and there was no significant difference between study groups with respect to the anxiety. Both drugs were found to be effective in decreasing perioperative anxiety during regional anesthesia.

In conclusion, dexmedetomidine and midazolam infusion preserved anxiety levels and caused no obvious variations in vital signs but midazolam might be preferred due to the side effect profile. Anesthetists should beware of dexmedetomidine infusion especially in patients performing central neuroaxial blockade.

References

1. BUCKINGHAM JC: Hypothalamo-pituitary responses to trauma. *Br Med Bull*; 1985, 41:203-211.
2. SALENGROSS JC, PANDIN P, VANDESTEEZE A, BAURAIN M: Propofol patient - controlled sedation versus midazolam sedation for orthopedic surgery. *B J Anaesth*; 1998, 64:143-14.
3. ANGST MS, RAMASWAMY B, DAVIES F, MAZE M: Comparative analgesic and mental effects of increasing plasma concentrations of dexmedetomidine and alfentanil in humans. *Anesthesiology*; 2004, 01:744-52.
4. SHAFER A, WHITE PF, URQUHART ML, DOZE VA: Outpatient premedication: use of midazolam and opioid analgesics. *Anesthesiology*; 1989, 71:495-501.
5. BAUER KP, DOM PM, RAMIREZ AM, O'FLAHERTY JE: Preoperative intravenous midazolam: benefits beyond axiolysis. *J Clin Anesth*; 2004, 16:177-183.
6. NAGUIP M, SAMARKANDI AH: Premedication with melatonin: a double-blind, placebo-controlled comparison with midazolam. *Br J Anaesth*; 1999; 82:875-80.
7. SPIELBERGER CD, O'NEIL HF JR, HANSEN DN: Anxiety drive theory and computer-assisted learning. *Prog Exp Pers Res*; 1972, 6:109-48.
8. JOHNSON CE, CHERNIK DA: Sedative-hypnotics and human performance. *Psychopharmacology*; 1982, 76:101-13.
9. BLOOR BC, WARD DS, BELLEVILLE JP: Effects of intravenous dexmedetomidine in humans. II hemodynamic changes *Anesthesiology*; 1992, 67:402-9.
10. DYCK JB, MAZE M, HAACK C, VUORILEHTO L, SHAFER SL: The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology*; 1993, 78:813-20.
11. COURSIN DB, COURSIN DB, MACCIOLI GA: Dexmedetomidine. *Curr Opin Crit Care*; 2001, 7:221-6.
12. KUZUCUOĞLU T, BÖLÜKBAŞIOĞLU I, ARSLAN G, YÜCEL E, AYAZ B: Comparison of the activity and reliability of intravenous administration of midazolam and dexmedetomidine on sedation levels under epidural anesthesia. *Agri*; 2010, 22:121-30.
13. TERAU Y, ICHINOMIYA T, HIGASHIJIMA U, TANISE T, MIURA K, FUKUSAKI M, ET AL: Comparison between propofol and dexmedetomidine in postoperative sedation after cervical spine surgery. *J Anesth*; 2011, dec. 16:DOI 10, 1007/s00450-011-1300-7.
14. ALHASHEMI JA: Dexmedetomidine vs midazolam for monitored anaesthesia care during cataract surgery. *Br J Anaesth*; 2006, 96:722-6.
15. APAN A, DOGANCI N, ERGAN A, BUYUKKOÇAK U: Bispectral index-guided intra-operative sedation with dexmedetomidine and midazolam in outpatient cataract surgery. *Minerva Anestesiologica*; 2009, 75:239-44.
16. DEMIRARAN Y, KORKUT E, TANER A, YORULMAZ I, KOCAMAN B, SEZEN G, ARKAN Y: The comparison of dexmedetomidine and midazolam used for sedation of patients during upper endoscopy: a prospective, randomized study. *Can J Gastroenterol*; 2007, 21:25-9.