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Original Article

Effects of low dose midazolam on bradycardia and sedation during dexmedetomidine infusion

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Abstract: Dexmedetomidine is a sedative which does not cause respiratory depression. But the initial loading dose of dexmedetomidine can lead to bradycardia which requires intervention. We tried to evaluate the effect of low dose midazolam on bradycardia and sedation during dexmedetomidine infusion. 72 patients were randomly assigned to the Dex 1.0 group or Dex 0.5 group. After intrathecal anesthesia, the Dex 1.0 group received an initial loading dose of 1.0 μg/kg of dexmedetomidine. The Dex 0.5 group was given midazolam 0.025 mg/kg and 0.5 μg/kg of dexmedetomidine. Heart rate (HR), blood pressure, respiratory rate, bispectral index (BIS), and the Observer's Assessment of Alertness/Sedation Scale (OAA/S) were recorded at ten time points (baseline, after anesthesia, before dexmedetomidine administration, 5, 10, 15, 20, 40, 60, 80 min after dexmedetomidine administration).The incidence of bradycardia requiring atropine was significantly higher in the Dex 1.0 group than in the Dex 0.5 group (15/33 vs. 5/32, P = 0.009). The Dex 0.5 group had a significantly lower BIS and OAA/S score than the Dex 1.0 group (P = 0.002 and P = 0.000, respectively) 5 min after dexmedetomidine administration. HR was significantly lower in the Dex 1.0 group (P = 0.003) 10 min after dexmedetomidine administration. But BIS and OAA/S score were lower in the Dex 0.5 group (P = 0.034 and P = 0.001, respectively). Other hemodynamic variables at other time points were similar between two groups. Low dose midazolam with halved loading dose of dexmedetomidine was superior in terms of bradycardia and sedation than dexmedetomidine alone.

Keywords: Dexmedetomidine, bradycardia, midazolam

Introduction

Dexmedetomidine being a highly selective adrenergic α-2 agonist, has sedative and analgesic properties resulting from reduced endogenous norepinephrine release in the brain and spinal cord [1]. The main advantage of dexmedetomidine over other sedatives is that it does not cause respiratory depression [1]. Therefore, dexmedetomidine has been used as a sedative for various purposes, including ICU sedation, awake fiberoptic intubation, and various surgical and medical procedures.

In general practice, dexmedetomidine is not given by a single shot bolus but needs to be given as an initial loading dose of up to 1 ug/kg followed by a continuous infusion. But during the initial loading period or too rapid administration can lead to bradycardia due to sympatholytic effects of dexmedetomidine [2-7].

We therefore performed a randomized, double-blind clinical study to investigate the effects of low dose midazolam on bradycardia and sedation during dexmedetomidine infusion.

Materials and methods

This randomized and double-blind study was registered with the Clinical Research Information Service, registration number KCT0000467. The study protocol was approved by the Institutional Review Board of Bundang CHA Hospital and all patients provided written informed consent. A total of 72 patients, aged 20-60 yrs, with an ASA status of I-II, undergoing elective surgery under spinal anesthesia, were randomized to the two groups. Patients with bradycardia (baseline heart rate < 60 beats/min), third degree heart block, or hypotension (baseline systolic arterial pressure < 100 mmHg), and those taking β-blockers, refused sedation dur-

ing surgery, and were unable or refused to give informed consent were excluded. Also, patients with a heart rate < 60 beats/min or who required ephedrine administration before the dexmedetomidine infusion were excluded from the study.

Patients were not premedicated. After standard monitoring of non-invasive arterial pressure, ECG, pulse oximetry, and bispectral index (BIS), intrathecal anesthesia was performed using bupivacaine. The level of sensory block was assessed with the patients in the supine position using a pin-prick test. The infusion of dexmedetomidine (4 μg/mL, Precedex®, Hospira, Lake Forest, IL) was prepared in a 50 mL syringe and it was connected as close as possible to the intravenous catheter.

Patients were randomly assigned to one of the two study groups: Dex 1.0 group (n = 37) or Dex 0.5 group (n = 35). After intrathecal anesthesia, the Dex 0.5 group was given midazolam 0.025 mg/kg intravenously, and the same volume of normal saline was given to the Dex 1.0 group. Then patients in the Dex 1.0 group received an initial loading dose of 1.0 μg/kg of dexmedetomidine over 10 min, followed by a continuous infusion of 0.4 μg/kg/h. Patients in the Dex 0.5 group received an initial loading dose of 0.5 μg/kg over 10 min, followed by a continuous infusion of 0.4 μg/kg/h. One anesthesiologist prepared the study drug before anesthesia and the study data were recorded by a blinded anesthetist.

All patients received supplemental oxygen via a facemask (5 L/min). Heart rate (HR), oxygen saturation (SpO_2), mean arterial blood pressure (MAP), respiratory rate (RR), BIS, and the Observer's Assessment of Alertness/Sedation Scale (OAA/S) [8] were recorded at ten time points (T0 = baseline; T1 = after intrathecal anesthesia; T2 = before dexmedetomidine administration; T5 = 5 min after T2; T10 = 10 min after T2; T15 = 15 min after T2; T20 = 20 min after T2; T40 = 40 min after T2; T60 = 60 min after T2; T80 = 80 min after T2).

Side effects such as hypotension, bradycardia, nausea, vomiting, and desaturation (SpO_2 < 90%) were monitored and treated appropriately. Hypotension was defined as a systolic blood pressure < 90 mmHg or a > 30% decrease from the baseline and bradycardia was defined as a HR < 50 beats/min. Hypotension was treated by administration of 4 mg of intravenous ephedrine, and bradycardia was treated with 0.5 mg of intravenous atropine. Patients were assessed for their level of sedation using the OAA/S (5 = completely alert; 4 = drowsy; 3 = with eyes close, but responsive to verbal stimulation promptly; 2 = with eyes close, only responsive to physical stimulation; and 1 = unresponsive to physical stimulation) [8], and any patients who had a score > 4 after fifteen minutes of dexmedetomidine administration was treated by rescue midazolam. This rescue midazolam could be administered as single intravenous boluses of 0.5 mg, and repeated as needed to achieve an OAA/S score ≤ 4. Also if a patient was not adequately sedated, the continuous infusion dose of dexmedetomidine was increased to ensure adequate sedation.

The study drug was discontinued when the patient left the operating room. In the post-anesthesia care unit (PACU), MAP, HR, SpO_2, OAA/S were checked on arrival and at the discharge. Also the time required to recover to the OAA/S score of 5 was measured and the time required to discharge the patient from PACU was measured. Post-operative nausea and vomiting (PONV) and any additional medications required were recorded.

The primary objective was the difference in incidences of bradycardia between the two groups. Bradycardia was defined as a HR < 50 beats/min and in the event of bradycardia, atropine 0.5 mg was given to the patient. The secondary objectives were the level of sedation, hemodynamic variables, BIS scores, and RR which were compared at the ten time points between the groups and differences were examined for. Also the time from the start of dexmedetomidine until a rescue dose of midazolam was administered was measured and any sign of PONV was recorded.

Hong et al. [4] reported a 40% incidence of bradycardia in a group given 1.0 μg/kg of dexmedetomidine, and this group was compared to a normal saline control group undergoing low dose intrathecal anesthesia. Therefore, the incidence of bradycardia in the Dex 1.0 group was set to be 40% and a reduction from 40% to 10% was considered to be of clinical importance ($\alpha = 0.05$, power = 0.8). The analysis showed that 32 patients per group would be

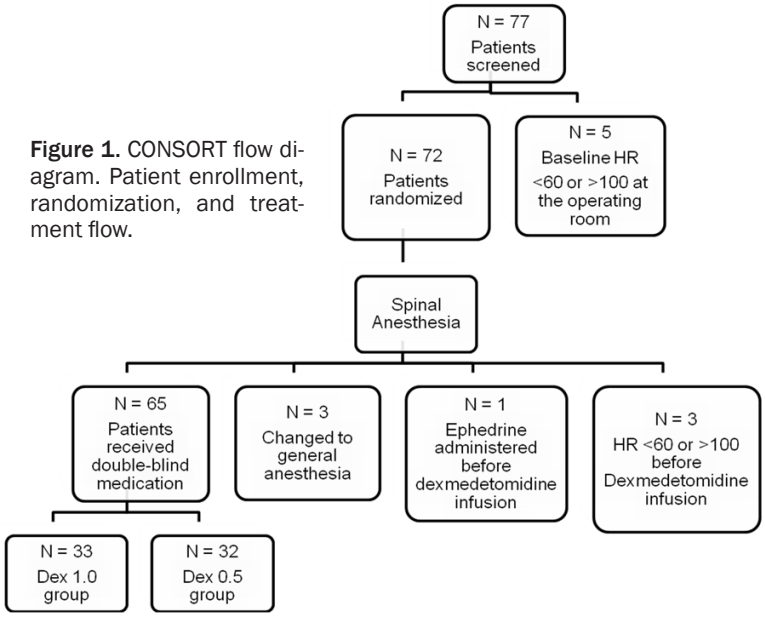

Figure 1. CONSORT flow diagram. Patient enrollment, randomization, and treatment flow.

Table 1. Patient demographics

	Dex 0.5 group	Dex 1.0 group	P
Age (year)	42.8 ± 12.4	40.2 ± 12.6	0.407
Height (cm)	164.6 ± 8.6	165.9 ± 10.5	0.588
Weight (kg)	62.0 ± 9.4	64.7 ± 12.1	0.334
Gender (M/F)	13/19	16/17	0.524
Block level	T10 (6-12)	T9 (4-12)	0.575

Data are mean ± SD or in numbers except block level. M = male; F = female.

sufficient to detect a difference between the two groups. The sample size was set at 36 patients per group, assuming a 10% dropout rate. In total, 72 patients were randomized. The analysis was performed using SPSS version 19.0 for Windows (SPSS, Chicago, IL, USA). Intergroup differences at the different time points were analyzed using the t-test for continuous variables. The χ^2 test was used to analyze categorical variables. Data are presented as the mean (SD) or as the count (%). *P*-values of < 0.05 were considered significant.

Results

Seventy-two eligible patients were randomized in this study. Of these, 65 patients were included in the analysis, with 33 in the Dex 1.0 and 32 in the Dex 0.5 group (**Figure 1**). The two groups were comparable with regard to the distributions of age, weight, height, and gender and exhibited non-significant differences upon statistical comparison (**Table 1**). Also, the maximum sensory block levels as assessed by pinprick between the two groups did not differ (**Table 1**).

The incidence of bradycardia requiring atropine was significantly higher in the Dex 1.0 group than in the Dex 0.5 group (15/33, 45.5% vs. 5/32, 15.6%, P = 0.009). The preoperative and pre-dexmedetomidine HR, MAP, SpO_2, RR, BIS, and OAA/S score were comparable between the two groups and were not statistically significantly different (**Table 2**). However, there was a statistically significant difference in BIS and OAA/S score between the Dex 1.0 and Dex 0.5 groups at T5, with the Dex 0.5 group of patients having a lower BIS and OAA/S score than the Dex 1.0 group (P = 0.002 and P = 0.000, respectively). At T10, HR was significantly lower in the Dex 1.0 group (P = 0.003). But BIS and OAA/S score were lower in the Dex 0.5 group (P = 0.034 and P = 0.001, respectively). The patients who required rescue midazolam within 20 min after dexmedetomidine infusion was 4/33 in the Dex 1.0 group and 4/32 in the Dex 0.5 group (P = 0.628). Other hemodynamic variables at othertime points were similar between the two groups (**Table 2**).

Table 3 shows the post-operative recovery data. The vital parameters were similar between the two groups. The time required to recover to the OAA/S score of 5 and the time required to discharge the patient from PACU did not differ between the two groups (P = 0.195 and P = 0.181, respectively). None of the patients experienced nausea and vomiting, and no other severe adverse effects were observed.

Discussion

Dexmedetomidine is widely used for sedation during surgery and many procedures. But bradycardia has been reported in up to 40% during dexmedetomidine administration [3, 4]. Therefore, we tried to find if a small dose of midazolam was effective in reducing bradycardia during dexmedetomidine infusion while pro-

Table 2. Intraoperative hemodynamic data

	Dex 0.5 group	Dex 1.0 group	P
T0			
MAP	93.1 ± 14.0	93.5 ± 13.0	0.914
HR	74.0 ± 9.6	75.5 ± 11.3	0.572
SpO_2	98.7 ± 1.6	99.0 ± 1.1	0.398
RR	16.6 ± 2.4	16.9 ± 2.2	0.661
BIS	95.0 ± 1.9	94.9 ± 3.5	0.826
OAA/S	5	5	
T1			
MAP	88.4 ± 15.3	85.8 ± 19.9	0.554
HR	76.8 ± 9.2	80.5 ± 11.5	0.162
SpO_2	99.4 ± 1.2	99.4 ± 0.8	0.842
RR	16.5 ± 3.1	17.0 ± 2.4	0.465
BIS	94.6 ± 1.9	95.0 ± 3.1	0.591
OAA/S	5	5	
T2			
MAP	86.3 ± 14.6	90.3 ± 19.8	0.351
HR	75.0 ± 9.2	76.7 ± 10.2	0.462
SpO_2	99.5 ± 1.1	99.7 ± 0.6	0.451
RR	16.1 ± 2.8	16.3 ± 3.3	0.753
BIS	94.8 ± 2.5	93.7 ± 4.5	0.263
OAA/S	5	5	
T5			
MAP	83.8 ± 14.5	88.2 ± 15.3	0.236
HR	62.9 ± 7.2	59.6 ± 9.9	0.127
SpO_2	99.8 ± 0.6	99.9 ± 0.5	0.802
RR	16.4 ± 2.7	15.9 ± 2.5	0.391
BIS	84.0 ± 6.9	89.3 ± 6.3	0.002
OAA/S	3.8 ± 1.1	4.7 ± 0.6	0.000
T10			
MAP	85.7 ± 15.1	90.6 ± 13.9	0.179
HR	61.1 ± 8.8	54.8 ± 7.6	0.003
SpO_2	99.8 ± 0.7	99.9 ± 0.5	0.677
RR	16.5 ± 2.5	15.9 ± 2.3	0.276
BIS	78.4 ± 9.5	83.6 ± 9.6	0.034
OAA/S	2.7 ± 0.9	3.6 ± 1.3	0.001
T15			
MAP	84.0 ± 13.4	88.5 ± 13.8	0.182
HR	62.4 ± 8.4	58.8 ± 8.2	0.083
SpO_2	100.0 ± 0.2	99.8 ± 0.5	0.130
RR	16.4 ± 2.6	15.6 ± 2.3	0.190
BIS	74.2 ± 10.8	74.5 ± 13.9	0.936
OAA/S	2.4 ± 0.8	2.8 ± 1.1	0.090
T20			
MAP	81.8 ± 13.9	88.0 ± 12.2	0.060
HR	62.2 ± 8.1	61.3 ± 8.8	0.674
SpO_2	100.0 ± 0.2	99.9 ± 0.4	0.157
RR	16.0 ± 2.5	15.7 ± 2.1	0.680
BIS	70.1 ± 13.2	71.8 ± 13.7	0.605
OAA/S	2.4 ± 0.9	2.3 ± 0.9	0.855
T40			
MAP	81.1 ± 13.2	85.3 ± 12.5	0.203
HR	60.7 ± 6.6	60.6 ± 7.5	0.976
SpO_2	99.9 ± 0.4	99.9 ± 0.4	0.969
RR	15.9 ± 3.2	15.5 ± 1.9	0.538
BIS	65.9 ± 14.8	63.7 ± 14.2	0.565
OAA/S	2.2 ± 0.8	2.2 ± 0.6	0.972
T60			
MAP	80.0 ± 16.0	84.1 ± 11.4	0.306
HR	59.3 ± 6.7	60.8 ± 6.7	0.434
SpO_2	99.9 ± 0.3	99.8 ± 0.5	0.768
RR	15.5 ± 2.8	15.2 ± 1.8	0.571
BIS	66.8 ± 12.3	67.5 ± 17.5	0.872
OAA/S	2.3 ± 0.5	2.3 ± 0.7	0.864
T80			
MAP	80.0 ± 15.7	84.3 ± 15.2	0.388
HR	59.2 ± 7.4	60.1 ± 6.9	0.709
SpO_2	99.8 ± 0.5	99.7 ± 0.6	0.825
RR	15.7 ± 3.3	14.5 ± 1.9	0.181
BIS	72.4 ± 12.9	73.2 ± 15.8	0.873
OAA/S	2.6 ± 0.7	2.7 ± 1.0	0.731

Data are mean ± SD. T0 = baseline; T1 = after intrathecal anesthesia; T2 = before dexmedetomidine administration; T5 = 5 min after T2; T10 = 10 min after T2; T15 = 15 min after T2; T20 = 20 min after T2; T40 = 40 min after T2; T60 = 60 min after T2; T80 = 80 min after T2. MAP = mean arterial blood pressure; HR = heart rate; SpO_2 = oxygen saturation; RR = respiratory rate; BIS = bispectral index; OAA/S = Observer's Assessment of Alertness/Sedation Scale.

viding the same level of sedation during surgery.

Midazolam has been used frequently for sedation but it is associated with hypotension, and over-sedation with accompanying respiratory depression and upper airway obstruction [3, 9]. In surgical settings, a continuous infusion of midazolam for sedation is not a common practice. Usually midazolam is given in small boluses for sedation which does not guarantee continuous satisfactory sedation during surgery. Dexmedetomidine provides excellent sedation with minimal respiratory depression but the initial loading dose of dexmedetomidine is known to cause cardiovascular adverse drug reactions, such as hypertension, hypotension, or bradycardia [10, 11]. Comparative studies on

Table 3. Post-operative recovery data

	Dex 0.5 group	Dex 1.0 group	P
5 OAA/S (min)	36.9 ± 21.5	43.6 ± 20.1	0.195
Discharge (min)	57.3 ± 13.6	61.8 ± 13.0	0.181
Hemodynamics			
MAP			
At arrival	79.8 ± 11.7	79.3 ± 10.2	0.850
At discharge	79.0 ± 10.3	75.7 ± 8.9	0.169
SpO_2			
At arrival	98.6 ± 1.6	98.5 ± 1.6	0.905
At discharge	99.5 ± 0.9	99.3 ± 1.0	0.555
HR			
At arrival	61.8 ± 7.1	61.9 ± 8.5	0.961
At discharge	60.7 ± 10.1	61.0 ± 8.7	0.894
OAA/S			
At arrival	3.4 ± 0.8	3.6 ± 0.7	0.451
At discharge	5	5	

Data are mean ± SD. 5 OAA/S = the time required to recover to the OAA/S score of 5; Discharge = the time required to discharge from the post-anesthesia care unit; MAP = mean arterial blood pressure; SpO_2 = oxygen saturation; HR = heart rate; OAA/S = Observer's Assessment of Alertness/Sedation Scale.

sedation showed that midazolam sedation was associated with a lower incidence of bradycardia compared to dexmedetomidine sedation [3, 12]. Moreover, there have been reports of the synergistic enhancement of their sedative effects when midazolam and dexmedetomidine are used in combination [13]. Hence, midazolam and dexmedetomidine both in low doses might prevent respiratory depression and bradycardia while providing an optimal level of sedation.

A series of studies comparing sedatives reported more frequent bradycardia in the patients receiving dexmedetomidine [3, 14, 15]. Dexmedetomidine being a α_2-adrenergic agonist causes an α_2-adrenoceptor-induced vasoconstrictive response in the peripheral vasculature which increases the blood pressure initially. Then due to both centrally and peripherally mediated sympatholytic action, hypotension follows [16]. This decrease in the sympathetic outflow and circulating catecholamine levels [5-7] as well as the vagal mimetic effect [17] of dexmedetomidine cause a decrease in the HR and BP. Bradycardia during spinal anesthesia is believed to result from the decreased venous return to the heart and the blockade of sympathetic cardio-accelerator fibers [18, 19]. Therefore, aggravated bradycardia can occur when spinal anesthesia and dexmedetomidine sedation are combined in a patient.

The first ten minutes of the initial loading period of dexmedetomidine was critical in managing bradycardia because atropine was administered in both the Dex 1.0 and the Dex 0.5 groups during the initial loading period of dexmedetomidine. The usual loading dose is 1.0 μg/kg which is given for a 10 min period followed by 0.2-0.7 μg/kg/h. Hypotension and bradycardia are known to be related to the dose, route of administration, and infusion rate of dexmedetomidine [5]. Mizrak et al. [20] reported that a loading dose of 0.5 μg/kg dexmedetomidine did not cause clinically major adverse effects when the patient was premedicated during general anesthesia. But this loading dose alone is probably not enough to provide adequate sedation during regional anesthesia. In this study, the incidence of bradycardia was significantly lower in the Dex 0.5 group compared to the Dex 1.0 group probably because the sympatholytic action of dexmedetomidineas well as the vagal mimetic effect is reduced due to the low dose and slow infusion rate of dexmedetomidine. 45.5% of the patients who received a 1.0 μg/kg bolus dexmedetomidine required atropine. But one must understand that we provided a strict requirement that atropine was to be administered when the HR was lower than 50 beat/min. In the clinical setting, in the case of healthy young patients, even a lower HR is allowed to occur without the giving of any medication. Therefore, the need for atropine in the clinical setting might be different from this study. Still, 45.5% of the patients required atropine, and therefore, it is essential to find a way to lower the incidence of bradycardia during dexmedetomidine infusion without having a detrimental effect on the level of sedation.

Arain and Ebert [21] reported that more time was required to achieve optimal sedation with dexmedetomidine. To evaluate differences in sedation time among the groups, we assessed the BIS and OAA/S score. In our study, the BIS and OAA/S score were significantly low at T5 and T10 in the Dex 0.5 group. Afterwards, there was no statistical difference in the BIS and OAA/S score between the groups. At T5, the

OAA/S score was 3.8±1.1 and 4.7±0.6 in the Dex 0.5 and the Dex 1.0 groups, respectively. Since an OAA/S score of 4 or less is considered to indicate adequate sedation, low dose midazolam and the halved initial loading dose of dexmedetomidine provided faster onset of action for sedation. At T10, the OAA/S score was 2.7±0.9 and 3.6±1.3 in the Dex 0.5 and the Dex 1.0 groups, respectively. Both groups provided adequate sedation at T10. No side effects were found in either group. These findings suggest that the earlier sedation effect after the start of dexmedetomidine was achieved as a result of the administration of low dose midazolam until later sedation was achieved by dexmedetomidine. Also, both dexmedetomidine and midazolam complemented each other intraoperatively, enabling an optimal level of sedation to be achieved and maintained. More time was required to achieve optimal sedation with dexmedetomidine alone. Also the finding provide us with this information: the dexmedetomidine loading dose could be further reduced in the Dex 0.5 group after T5 for adequate sedation.

Midazolam 0.025 mg/kg with a halved loading dose of dexmedetomidine was superior in terms of producing sedation and lower incidence of bradycardia than with dexmedetomidine alone, without causing respiratory depression or hemodynamic instability. However, whether the dosage of midazolam in the present study was adequate pharmacodynamically remains unclear. Further investigations of the dosage of midazolam will be required.

Disclosure of conflict of interest

None.

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