Original article

Clinical evaluation of combination of dexmedetomidine and midazolam vs. dexmedetomidine alone for sedation during spinal anesthesia

Ze-yu Zhao [a],[*],[#], Jian-hui Gan [b],[#], Jian-bo Liu [a], Qing Cheng [a]

[a] Department of Anesthesiology, Sichuan 81 Rehabilitation Center (Sichuan Provincial Rehabilitation Hospital), Chengdu 611135, China
[b] Department of Anesthesiology, The Affiliated Tangshan People Hospital of North China University of Science and Technology, Tangshan 06300, China

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ABSTRACT

Background: Dexmedetomidine is a useful sedative agent for spinal anesthesia. However, it has been reported to decreases heart rate in a dose-dependent manner. In the present study, we compared the bolus dose of midazolam and bolus loaded dexmedetomidine over 10 min to determine additional sedation methods.
Methods: A total of 100 patients who were classified as American Society of Anesthesiologists physical status I–II undergoing spinal anesthesia were randomly divided into two groups. In the combination of midazolam and dexmedetomidine group (group MD), 10 min after bolus loading of 0.05 mg/kg midazolam, 0.5 μg/kg/h dexmedetomidine was infused. In the dexmedetomidine group (group D), 1 μg/kg bolus dose of dexmedetomidine was infused over 10 min, and then 0.5 μg/kg/h dexmedetomidine was infused continuously.
Results: At 10 min, the sedation depth of the two groups was approximately the same. In both groups, the bispectral index (BIS) was within the optimal range of 55–80 and the Ramsay Sedation Scale score was within the optimal range of 3–5. Both patient and surgeon satisfaction with sedation did not differ between groups. At 10 min, heart rate (beats/min) was significantly lower (P < .01) in group D and mean blood pressure (mm Hg) was significantly lower (P < .01) in group MD. The prevalence of bradycardia (P = .714), hypotension (P = .089), and hypoxia (P = .495) did not differ statistically between the two groups.
Conclusions: Midazolam bolus and dexmedetomidine continuous infusion may be a useful additional sedation method for patients who have severe bradycardia.
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1. Introduction

The α$_2$-adrenoceptor agonist dexmedetomidine acts on the locus coeruleus to induce sedation. It also has an analgesic effect without causing respiratory depression (Gerlach and Dasta, 2007; Chiu et al., 1995). In addition, intravenous (IV) administration of dexmedetomidine prolongs the duration of spinal anesthesia (Elcicek et al., 2010). Therefore, it has been used successfully for the sedation of patients during surgery.

However, several studies have reported that dexmedetomidine induces severe bradycardia and sinus arrest or pause, which is usually related to the infusion of a large-dose (Vuyk et al., 2015; Riker and Fraser, 2005; Ingersoll-Weng et al., 2004). Therefore, we devised a new method that replaces the bolus loading of 1.0 μg/kg of dexmedetomidine over 10 min with 0.05 mg/kg of midazolam and only utilizes dexmedetomidine for sedation with a maintenance infusion of 0.5 μg/kg/h.

In this study, we examined whether the combination of dexmedetomidine and midazolam could achieve an ideal depth of sedation compared to the traditional dexmedetomidine alone method, and whether the combination method could have advantages regarding maintaining hemodynamic stability.

2. Materials and methods

A total of 90 patients who were aged 18–75 and classified as American Society of Anesthesiologists (ASA) physical status I or II were enrolled in this prospective, randomized, double-blind study.

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All of them were scheduled to undergo surgery under spinal anesthesia between March 2015 and December 2015. They were randomly assigned to the combination of midazolam and dexmedetomidine group (group MD) and the dexmedetomidine alone group (group D). This study was approved by the hospital's ethics committee, and all subjects provided written informed consent.

On arrival to the operating room, routine monitoring for with an electrocardiogram, a pulse oximeter, a noninvasive blood pressure cuff, and a bispectral index (BIS) monitor (Model A 3000, Aspect Medical Systems, Inc., Natick, MA, USA) was performed. Patients' initial vital signs, BIS, and Ramsay Sedation Scale (RASS) scores were monitored and recorded. End-tidal CO_2 ($ETCO_2$) and respiratory rate (RR) were monitored while 5 L/min of oxygen was administered via an oxygen mask. Spinal anesthesia was performed in the lateral decubitus position with a 25-gauge Quincke needle by using a midline approach at the L2–3 or L3–4 interspace. 0.5% bupivacaine was infused intrathecally, whose amount was determined in accordance with the patient's age and height to reach a target sensory level.

The time point at which the patient arrived in the operating room was defined as T0. Then, the time points 10 min, 30 min, 60 min, and 90 min after the initiation of sedation were defined as T1, T2, T3, and T4, respectively.

For the patients in group MD, 10 min after they received a bolus dose of 0.05 mg/kg of midazolam (T2), the IV infusion of dexmedetomidine (Precedex®; Hospira, Rocky Mount, NC, USA, 200 µg/2 ml) at 0.5 µg/kg/h as a maintenance dose was initiated. For the patients in group D, 1 µg/kg of dexmedetomidine was IV-loaded via an infusion pump for 10 min, then the IV infusion of dexmedetomidine at 0.5 µg/kg/h as a maintenance dose was initiated. The vital signs, BIS and RASS scores, hypoxia, bradycardia, hypotension, and paradoxical events were monitored and recorded at 30-min intervals. After the surgery, both surgeons and patients satisfaction with sedation was evaluated using a numeric rating scale of 0–10.

Hypotension was defined as a mean blood pressure (MBP) of less than 60 mmHg, and 4 mg of ephedrine was IV-infused upon detection of hypotension. Bradycardia was defined as a heart rate (HR) of less than 45 beats/min, and 0.5 mg of atropine was IV-infused upon incidence of bradycardia. Hypoxia was defined as a SpO2 of below 90%, and the mouth was opened and the neck was extended upon observance of hypoxia. Patient wakefulness during surgery was defined as a BIS score > 90 and RSS $\leq$ 2.

Based on the pilot studies, we estimated the sample size to detect differences in HR between the groups, with a power of 80% and α = 0.05. In a pilot study the response within each subject group was normally distributed with a standard deviation of 9. If the true difference in HR between the experimental and control means is 5.73, we will need to study 40 experimental subjects and 40 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. Ninety patients were required to allow for possible incomplete data collection or patient dropout.

For statistical analysis of the collected data, SPSS 21.0 (IBM Corp., Armonk, NY, USA) was used. Age, weight, height, heavy Marcaine use, and the level of sensory block were analyzed and compared using Student's t-test. The Mann-Whitney U test was used to analyze non-parametric variables, including scores of ASA, RASS, and satisfaction in surgeons and patients. The BIS, HR, MBP, RR, $ETCO_2$, and saturation in both groups were compared using repeated measures analysis of variance (ANOVA). In the case of a significant difference on repeated measures ANOVA, a Bonferroni-corrected Student's t-test was used for post-hoc testing. The chi-squared test or Fisher's exact test was performed for

categorical variables. Statistical significance was defined as a $P < .05$.

3. Results

Ninety patients undergoing surgery between March 2015 and December 2015 were recruited in the present study. No significant differences were found with the patients' age, gender, height, weight, BMI, ASA score, heavy usage of Marcaine, or level of sensory block (Table 1).

The HR and MBP had a decreasing trend during surgery, and demonstrated differences at T2 in both groups (Figs. 1 and 2). The HR and MBP for group D was 59.2 ± 9.1 beats/min and 77 ± 1 2.8 mmHg respectively, which were significantly lower than those of group MD (66.2 ± 13.7 beats/min and 89 ± 14.1 mmHg) (P < .010) (Figs. 1 and 2). A total of 12 patients in group MD and 13 patients in group D had bradycardia, which was resolved after the IV administration of 0.5 mg atropine (Table 2). A total of 13 patients in group MD and 6 patients in group D had hypotension, which was corrected after the IV administration of 4 mg ephedrine (Table 2).

At 10 min after sedation (T1), there were no significant differences in the BIS and RASS scores between the two groups (P = .711, P = .956) (Fig. 3, Table 3). At 60 min after sedation (T3), the BIS scores of group MD was 68.8 ± 11.8 which was significantly higher than that of group D (57.0 ± 14.7) (P < .010) (Fig. 3). However, there were no significant differences regarding RASS scores, which was 5 for both group MD and group D (P = .392) (Fig. 3 and Table 3).

There were no significant changes and no significant differences between the two groups regarding $ETCO_2$ and O_2 saturation (Fig. 4). However, there was a decreasing trend with time but no significant difference between the groups regarding RR (Fig. 5). A total of 2 patients in group MD had hypoxia, which was relieved by position changes including mouth opening and neck extension (Table 2).

There were no significant differences regarding both patients' and surgeons' satisfaction with the sedation during surgery. Similarly, sedation-related status during surgery and after surgery such as awake and paradoxical behaviors was not statistically significant (Table 2).

4. Discussion

Dexmedetomidine is a selective α2-adrenoceptor agonist. The α2-adrenoceptor includes three subtypes which are α2A, α2B, and α2C. The α2A-adrenergic receptors are mostly located in the periphery while α2B and α2C-adrenergic receptors are distributed throughout the central nerve system including brain and the spinal cord. As a selective α2-adrenoceptor agonist, dexmedetomidine has effects on the brain locus ceruleus and the α2-adrenergic receptors of the spinal cord to result in sedation, sympatholysis, analgesia, and antinociceptive effects. Initially, it has effects on the peripheral blood vessels to cause vasoconstriction and bradycardia. Then, it gradually takes effects on brain and the spinal cord presynaptic α2-adrenergic receptors, reducing norepinephrine release and causing hypotension later (Kallio et al., 1989; Paris and Tonner, 2005). Previous studies have shown that dexmedetomidine results in bradycardia in a significantly large proportion of patients undergoing cardiac surgery. However, there is no significant differences regarding hospital mortality, and therefore it is a safe and effective sedative agent compared with other sedative agents (Lin et al., 2012).

In the present study, the HR of patients in group D at T1 which was the time point of 10 min after the initiation of sedation was

Table 1
Characteristics of Study Subjects.

	Group MD (n = 46)	Group D (n = 44)	*p* value
Gender (n,%)			
Male	16 (55.2)	13 (44.8)	0.595
Female	30 (49.2)	31 (50.8)	
Age (yr)	58.7 ± 15.7	61.5 ± 11.7	0.125
Weight (kg)	63.8 ± 9.7	62.5 ± 10.5	0.535
Height (cm)	165.5 ± 9.5	169.3 ± 8.8	0.956
BMI	23.5 ± 2.5	22.7 ± 3.7	0.345
Heavy Marcaine use (mg)	11.3 ± 2.5	10.5 ± 1.5	0.115
Level of sensory block (T10 = 10, L1 = 12+1)	9.28 ± 2.15	8.75 ± 2.27	0.127
ASA (I/II)	7/39	13/31	0.359

Values are mean ± SD or median (Q1, Q3). Gender is presented as number (%). Levels of sensory block are presented as T10 = 10, L1 = 12 + 1, L2 = 12 + 2. ASA: American Society of Anesthesiologists physical status.
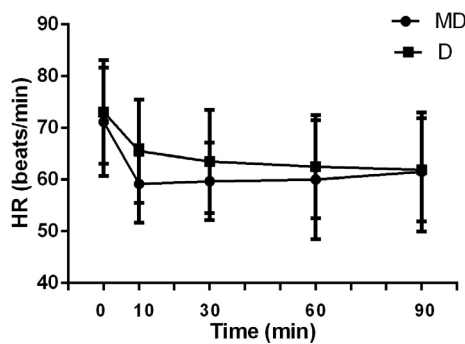
Fig. 1. Changes in HR. Graphs show the mean values and standard deviations. Significant effect of time (P < .010) and significant interaction of time and group (P = .025, Greenhouse-Geisser adjusted) are shown. 0: arrival in operating room, 10, 30, 60, 90: 10, 30, 60, 90 min after sedation.
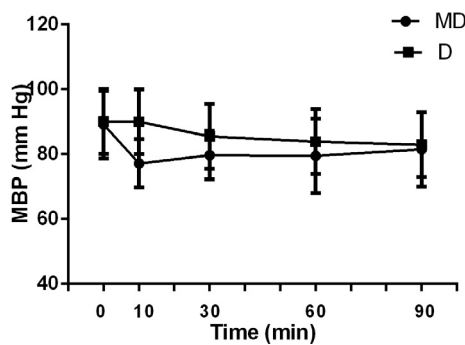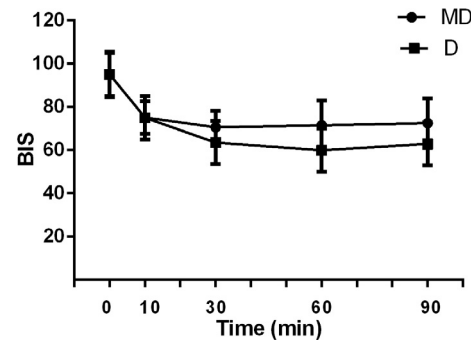

Fig. 2. Changes in MBP. Graphs show the mean values and standard deviations. Significant effect of time (P < .010) and significant interaction of time and group (P = .022, Greenhouse-Geisser adjusted) are shown. T0: arrival in operating room, 10, 30, 60, 90: 10, 30, 60, 90 min after sedation.

significantly lower compared to that of patients in group MD (P < . 010), and the MBP of patients in group MD at T1 was also significantly lower compared to that of patients in group D (P < .010). The reason why bradycardia happened with a significantly higher rate among patients in group D at T2 and rapid hypotension did not happen compared to patients in group MD is that bolus loading of dexmedetomidine for 10 min takes effects on the selective α2-adrenergic receptors and causes vasoconstriction and reflex bradycardia (Kallio et al., 1989). On the other hand, there was no significant difference in the overall incidence rate of bradycardia until T4 which was the time point of 90 min after the initiation

Table 2
Sedation-related Status during Surgery and after Surgery.

	Group MD (n = 46)	Group D (n = 44)	*p* value
Awake (BIS > 90 or RASS ≤ 2)	1 (2.2)	1 (2.3)	1.000
Hypoxia (SpO₂ < 90%)	2 (4.4)	0 (0.0)	0.495
Bradycardia (HR < 45)	12 (26.1)	13 (29.6)	0.714
Hypotension (MBP < 60)	13 (28.3)	6 (13.6)	0.089
Delirium	0 (0.0)	0 (0.0)	N/A
Nausea	4 (8.7)	4 (9.1)	1.000
Vomiting	0 (0.0)	0 (0.0)	–
Paradoxical behavior	0 (0.0)	0 (0.0)	–

Fig. 3. Changes in BIS during sedation. Graphs show the mean values and standard deviations. Significant effect of time (P < .010) and significant interaction of time and group (P < .010, Greenhouse-Geisser adjusted) are shown. T0: arrival in operating room, 10, 30, 60, 90: 10, 30, 60, 90 min after sedation.

**Table 3**
Ramsay Sedation Scale (RASS) Score.

	Group MD (n = 46)	Group D (n = 44)	*p* value
T0	2 (1–2)	2 (1–2)	0.362
T1	4 (3–4)	4 (3–4)	0.956
T2	5 (4–5)	4 (4–5)	0.564
T3	5 (4–5)	5 (4–5)	0.392
T4	4 (4–5)	5 (4–5)	0.275

Mann-Whitney *U* tests were performed for RASS scores and the values are presented as median (interquartile range). There were no significant differences between the two groups. Group MD: midazolam 0.05 mg/kg bolus, Group D: dexmedetomidine 1.0 μg/kg loading infusion over 10 min; in both groups, 0.5 μg/kg/h dexmedetomidine was infused continuously. T0: arrival in operating room, T1, 2, 3, 4: 10, 30, 60, 90 min after sedation.

of sedation (Table 3), and bradycardia was resolved and did not happen again after the IV administration of 0.5 mg atropine.

The MBP for the patients in group MD rapidly decreased after a bolus IV administration of midazolam. However, hypotension was rapidly hemodynamically stabilized after T1 which was the time point of 10 min after the initiation of sedation after the one-time IV administration of 4 mg ephedrine. On the other hand, the MBP for the patients of group D continuously decreased with time in smaller increments (Fig. 2). For patients in group MD, the bolus IV administration of midazolam induced more rapid alleviation of sympathetic hypertension compared with the rate at which sympathetic hypertension was alleviated in patients in group D, which is presumed to be due to a lack of the vasoconstrictive effect of dexmedetomidine for the first 10 min. In the present study, hypotension in group MD could be corrected instantly using the IV administration of inotropics and vasoconstrictors.

The suggested clinical loading dose of dexmedetomidine is 0.5–1.0 μg/kg for 10 min and the suggested clinical maintenance dose is 0.2–0.7 μg/kg/min (Wang et al., 2013). A recent study discovered
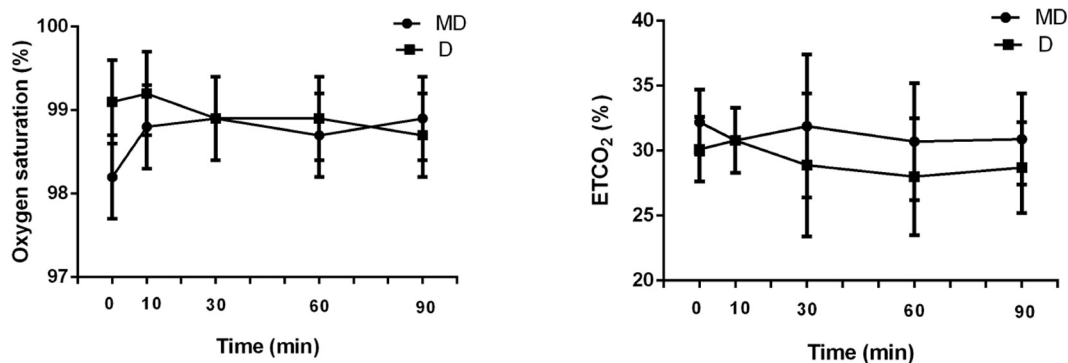
Fig. 4. Changes in O_2 saturation, $ETCO_2$ during sedation. Graphs show the mean values and standard deviations. $ETCO_2$: No significant effect of time (P = .100) and no significant interaction of time and group (P = .631, Greenhouse-Geisser adjusted) are shown. Saturation: No significant effect of time (P = .232) and no significant interaction of time and group (P = .122, Greenhouse-Geisser adjusted) are shown. T0: arrival in operating room, 10, 30, 60, 90: 10, 30, 60, 90 min after sedation.
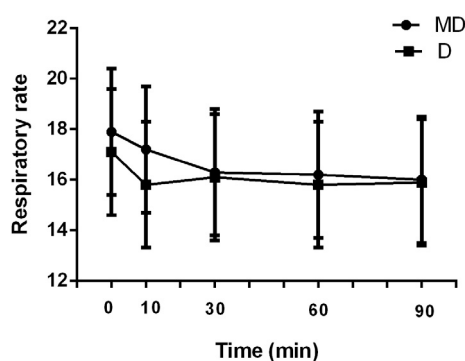
Fig. 5. Changes in RR during sedation. Graphs show the mean values and standard deviations. Significant effect of time (P < .010) and no significant interaction of time and group (P = .440, Greenhouse-Geisser adjusted) are shown. T0: arrival in operating room, 10, 30, 60, 90: 10, 30, 60, 90 min after sedation.

that the IV infusion of 1.0 µg/kg of dexmedetomidine for 10 min achieved a higher sedation score without decreasing oxygen saturation compared with the infusion of 0.5 µg/kg of dexmedetomidine. In addition, it was also more effective regarding prolonging the duration of spinal anesthesia (Lee et al., 2014; Sim et al., 2014). Furthermore, it was approximately similarly effective on elderly patients who were aged 60 years or more and did not result in significant hemodynamic instability (Park et al., 2014). Based on these results, we used the loading dose of dexmedetomidine as 1.0 µg/kg and the maintenance dose as 0.5 µg/kg/h.

In 2014, Bell et al. (2004) reported that there was a significant positive correlation between BIS and RASS (P < .010), which was demonstrated as that BIS scores of 87.2 and 80.9 corresponded to RASS scores of 3 and 4, respectively. The previous studies have shown that the optimal BIS scores for sedation is between 65 and 85 points and the optimal RASS scores is between 3 and 4 points (Monitoring, 2010; Strøm, 2012). In the present study, BIS scores ranged from 55 to 80 points and RASS scores ranged from 3 to 5 points from T1 to T4 which were the time points from 10 min to 90 min after the initiation of sedation. In addition, the BIS and RASS scores reached their optimal ranges at 10 min after the initiation of sedation which was T1 in both groups, suggesting that the patients were sufficiently sedated. The maximum RSS score was achieved at T3 which was the time point of 60 min after the initiation of sedation, meaning that the maximum depth of sedation was reached approximate one hour after the initiation of sedation. The initial bolus loading was performed with midazolam for group MD and with dexmedetomidine for group D, and this is

presumed to be due to the fact that the bolus dose effect is gradually reduced 60 min after the initiation of sedation.

In 2009, Kasuya et al. (2009) reported that BIS values were significantly lower in patients who had the IV administration of dexmedetomidine than those who had the IV administration of propofol at an equal depth of sedation. In the present study, the BIS scores of group D were significantly lower than those of group MD at T3 which was the time point of 60 min after the initiation of sedation, but there were no significant differences between the RSS scores of the two groups, and we then verified that the BIS scores of patients sedated by dexmedetomidine could be lower than those of patients sedated using midazolam. More research needs to be done to determine the relationship between the BIS scores and the depth of sedation of patients who were sedated using dexmedetomidine.

In addition, we evaluated the both surgeons and patients satisfaction with sedation during and after surgery respectively using a numeric rating scale of 0 to 10. The satisfaction of patients with sedation after surgery and the satisfaction of surgeons with sedation during surgery were all higher than 90 points, signifying that the method of sedation utilized in both groups granted satisfaction for both patients and surgeons.

In a comparison of sedation induced by dexmedetomidine (0.2–1.4 µg/kg/h) vs. midazolam (0.02–0.10 mg/kg/h) until extubation in intubated patients undergoing mechanical ventilation in the intensive care unit, dexmedetomidine resulted in a lower incidences of delirium, tachycardia, and hypertension but significantly higher bradycardia (42.2%) than midazolam (18.9%) (Riker et al., 2009).

Midazolam can cause hypoxia even in healthy individuals by reducing hypoxic ventilator responses and inducing upper airway obstruction (Alexander and Gross, 1988; Nozaki-Taguchi et al., 1995). On the other hand, even a high dose of dexmedetomidine can maintain a normal $ETCO_2$ and is rarely associated with respiratory problems (Alexander and Gross, 1988). In the present study, a total of two patients in group MD had hypoxia while no patients in group D had hypoxia (Table 3), and upper airway obstruction was the cause of hypoxia for the two patients; hypoxia did not recur after a mouth opening and neck extension, and the $ETCO_2$ of all patients in both groups was maintained in a range between 28 and 31 (Table 3, Fig. 4). If patients' mouth opening and neck extension were appropriately maintained during surgery, hypoxia could be prevented in advance.

The previous studies have shown that approximatley 10.2% of elderly patients aged 65 years or older treated with midazolam have been found to experience paradoxical events such as confusion, violent behaviors, and restlessness; these symptoms occurred when the mean cumulative dose of midazolam was 7 mg or greater

(Weinbroum et al., 2001). There were no incidences of paradoxical events in the present study, which is presumed to be due to the fact that midazolam was not repeatedly infused but instead was administered as a maximum bolus of 4 mg (0.05 mg/kg) only once.

In conclusion, the HR in group D and the MBP in group MD were changed remarkably after a bolus loading infusion, but these changes were not severe and were able to be controlled. A sufficient sedation depth was reached within 10 min and maintained during surgery in both groups. Dexmedetomidine is a good sedative agent for patients with regional anesthesia, and the midazolam and dexmedetomidine combined method would be an additional sedation method for patients with severe bradycardia.

Acknowledgment

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