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Original article

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

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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.



## 1. Introduction

The $\alpha_2$-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 $\alpha = 0.05$. 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

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