Can J Anesth/J Can Anesth (2010) 57:39–45
DOI 10.1007/s12630-009-9231-6

REPORTS OF ORIGINAL INVESTIGATIONS

Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia

La dexmédétomidine, mais pas le midazolam, en intraveineuse prolonge la rachianesthésie réalisée avec de la bupivacaïne

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Received: 8 December 2008 / Accepted: 6 October 2009 / Published online: 29 December 2009

Abstract

Purpose *Midazolam has only sedative properties. However, dexmedetomidine has both analgesic and sedative properties that may prolong the duration of sensory and motor block obtained with spinal anesthesia. This study was designed to compare intravenous dexmedetomidine with midazolam and placebo on spinal block duration, analgesia, and sedation in patients undergoing transurethral resection of the prostate.*

Methods *In this double-blind randomized placebo-controlled trial, 75 American Society of Anesthesiologists' I and II patients received dexmedetomidine 0.5 $\mu g \cdot kg^{-1}$, midazolam 0.05 $mg \cdot kg^{-1}$, or saline intravenously before spinal anesthesia with bupivacaine 0.5% 15 mg ($n = 25$ per group). The maximum upper level of sensory block and sensory and motor regression times were recorded. Postoperative analgesic requirements and sedation were also recorded.*

Results *Sensory block was higher with dexmedetomidine (T 4.6 ± 0.6) than with midazolam (T 6.4 ± 0.9; $P < 0.001$) or saline (T 6.4 ± 0.8; $P < 0.001$). Time for sensory regression of two dermatomes was 145 ± 26 min in the dexmedetomidine group, longer ($P < 0.001$) than in the midazolam (106 ± 39 min) or the saline (97 ± 27 min) groups. Duration of motor block was similar in all groups. Dexmedetomidine also increased the time to first request for postoperative analgesia ($P < 0.01$ compared with midazolam and saline) and decreased analgesic requirements ($P < 0.05$). The maximum Ramsay sedation score was greater in the dexmedetomidine and midazolam groups than in the saline group ($P < 0.001$).*

Conclusion *Intravenous dexmedetomidine, but not midazolam, prolonged spinal bupivacaine sensory blockade. It also provided sedation and additional analgesia.*

Résumé

Objectif *Le midazolam n'a que des propriétés sédatives. En revanche, la dexmédétomidine a des propriétés analgésiques et sédatives, lesquelles pourraient prolonger la durée du bloc sensitif et moteur obtenu par rachianesthésie. Cette étude a été conçue pour comparer l'administration intraveineuse de dexmédétomidine avec du midazolam et un placebo en termes de durée du bloc, d'analgésie, et de sédation de patients subissant une résection transurétrale de la prostate.*

Méthode *Dans cette étude randomisée en double aveugle et contrôlée par placebo, 75 patients ASA (American Society of Anesthesiologists) I et II ont reçu une solution intraveineuse de dexmédétomidine 0,5 $\mu g \cdot kg^{-1}$, de midazolam 0,05 $mg \cdot kg^{-1}$, ou de sérum physiologique (placebo) avant la réalisation d'une rachianesthésie avec de la bupivacaïne 0,5 % 15 mg ($n = 25$ par groupe). Le niveau le plus élevé de bloc sensitif et les temps de régression des blocs sensitif et moteur ont été enregistrés. Les besoins analgésiques postopératoires et la sédation ont également été enregistrés.*

Résultats *Le bloc sensitif était plus élevé avec la dexmédétomidine (T 4,6 ± 0,6) qu'avec le midazolam (T 6,4 ± 0,9; $P < 0,001$) ou le placebo (T 6,4 ± 0,8; $P < 0,001$). Le temps jusqu'à régression du bloc sensitif de deux*

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dermatomes était de 145 ± 26 min dans le groupe dexmédétomidine, soit plus long (P < 0,001) que dans les groupes midazolam (106 ± 39 min) ou placebo (97 ± 27 min). La durée du bloc moteur était similaire dans les trois groupes. La dexmédétomidine a également prolongé le temps requis jusqu'à la première demande d'analgésie postopératoire (P < 0,01 par rapport aux groupes midazolam et placebo) et a réduit les besoins analgésiques (P < 0,05). Le score maximal de sédation sur l'échelle de Ramsay était plus élevé dans les groupes dexmédétomidine et midazolam que dans le groupe placebo (P < 0,001).

Conclusion *La dexmédétomidine intraveineuse prolonge le bloc sensitif rachidien réalisé avec de la bupivacaïne, mais pas le midazolam. Elle procure également une sédation et une analgésie supplémentaire.*

Introduction

Different adjuvants have been used to prolong spinal anesthesia, with the possible advantages of delayed-onset of postoperative pain and reduced analgesic requirements. Dexmedetomidine, a highly selective α_2-adrenoreceptor agonist, has been used for premedication and as an adjunct to general anesthesia. Intravenous dexmedetomidine premedication before general anesthesia provides preoperative sedation, analgesia, and hemodynamic stability and reduces requirements for intraoperative inhalational agents and postoperative analgesics.[1–3] Also, it has been used safely as premedication or as a sedative agent in patients undergoing surgical procedures under regional anesthesia.[4,5] Although a synergistic interaction between intrathecal dexmedetomidine and local anesthetics has been observed in previous studies,[6–9] there are no clinical data regarding the effect of intravenous dexmedetomidine premedication on the duration of sensory and motor block during spinal anesthesia.

In this randomized double-blind placebo-controlled clinical study, we assessed the effects of intravenous dexmedetomidine premedication on spinal block duration as well as on sedation and postoperative analgesia in patients undergoing transurethral resection of the prostate (TURP). To isolate dexmedetomidine's analgesic effects from its sedative effects, a comparison was made with benzodiazepine, midazolam, and placebo.

Methods

The study protocol was approved by our Institutional Medical Ethics Committee, and written informed consent was obtained from each patient. Seventy-five patients who were classified as American Society of Anesthesiologists' (ASA) physical status I–II and undergoing TURP under spinal anesthesia were included. Exclusion criteria included use of any opioid or sedative medications in the week prior to surgery, a history of alcohol or drug abuse, known allergy to any of the test drugs or contraindication to spinal anesthesia (e.g., coagulation defects, infection at puncture site, pre-existing neurological deficits in the lower extremities), and cardiovascular, respiratory, neurological, psychological, hepatic, or renal disease.

After intravenous insertion of an 18-G catheter in the operating room, all patients received 500 mL of lactated Ringer's solution intravascular volume loading before spinal anesthesia. Monitors included electrocardiography, noninvasive blood pressure measurement, pulse oximetry to measure peripheral oxygen saturation (SpO_2), and capnography to measure end-tidal carbon dioxide concentration ($Et\text{-}CO_2$). Using a computer-generated randomization schedule, the patients were randomly divided into three groups: the first group received dexmedetomidine 0.5 $\mu g \cdot kg^{-1}$ ($n = 25$); the second group received midazolam 0.05 $mg \cdot kg^{-1}$ ($n = 25$), and the third group received physiologic saline ($n = 25$). Each group was premedicated 5 min before spinal anesthesia. The study drugs were premixed to a total volume of 5 mL in the 5 mL syringe and were administered intravenously over a 10 min period as a single dose. Five minutes after the end of the infusion, the patient was placed in the lateral position and dural puncture was performed at the L3-4 interspace using a standard midline approach with a 25-G Quincke needle (Spinocan, Braun Melsungen AG, Germany). Bupivacaine 0.5% 3 mL was injected intrathecally, and the patients received oxygen 4 $L \cdot min^{-1}$ via a facemask throughout the procedure. Both the patient and the anesthesiologist were blinded to the treatment group, and all recordings were performed by an anesthesiologist blinded to group allocation. Sensory blockade was assessed using pinprick and cold (iced tube) in the mid-axillary line. Recovery time for sensory blockade was defined as two-dermatome regression of anesthesia from the maximum level. Motor block was assessed immediately after sensory block assessment using a Modified Bromage Scale[10] (0 = no paralysis; 1 = unable to raise extended leg; 2 = unable to flex knee; 3 = unable to flex ankle). Motor block duration was the time for return to Modified Bromage Scale 1. Sensory and motor block were assessed every 2 min for the first 10 min and thereafter every 10 min during surgery and postoperatively. The highest sensory block level and recovery time of both sensory and motor block were recorded. Postoperative pain was assessed by the patient using the visual analogue scale (VAS; 0 = no pain; 10 = worst possible pain) at 4, 8, 12, and 24 hr. In addition, the overall 24-hr pain VAS was evaluated by the overall pain impression of the patient for

24 hr postoperatively. Patients with a VAS score of 3 or more received diclofenac 75 mg intramuscularly. The time for the first request for postoperative analgesia and the number of patients who required supplemental analgesia were recorded.

The Ramsay sedation score[11] was used for sedation score (1 = anxious and agitated; 2 = cooperative and tranquil; 3 = drowsy but responsive to command; 4 = asleep but responsive to a glabellar tap; 5 = asleep with a sluggish response to tactile stimulation; and 6 = asleep and no response). The score was re-evaluated every 10 min for up to 120 min. Excessive sedation was defined as a score greater than 4/6.

Heart rate (HR), mean blood pressure (MAP), oxygen saturation (SpO_2), end-tidal CO_2 (Et-CO_2), and respiratory rate (RR) were recorded before premedication, 2 min after end of premedication, immediately before and after dural puncture, and every 5 min for 120 min after spinal anesthesia. Hypotension (defined by a decrease in MAP below 20% of baseline or systolic pressure <90 mmHg) was treated with intravenous ephedrine 5 mg and additional lactated Ringer's solution (200 mL over a 5 min period). Bradycardia (HR < 50 beats/min) was treated with intravenous atropine 0.5 mg. To avoid masking of respiratory problems by administering supplemental oxygen, respiratory depression was defined as an Et-CO_2 > 50 mmHg or RR < 12 breaths $\cdot$ min^{-1}.

After completion of surgery, the surgeon who was blinded as to treatment group was asked to rate the quality of operative conditions using a three-point scale (3 = good; 2 = moderate; and 1 = poor). The anesthesiologist was asked to grade quality of the anesthetic according to the same scale (3 = good; 2 = moderate; and 1 = poor). All operations were performed by the same surgeon. The following day, patients were assessed as to whether they would have the same anesthetic technique should they require the procedure in the future. They were also asked questions about recall of dural puncture. The presence of any complication in the preoperative and postoperative periods was noted, particularly in relation to respiratory or cardiovascular problems, nausea or vomiting, and headache.

Sample size calculation was based on a previous study,[12] for which we assumed a standard deviation (SD) of 24 min in time to sensory regression of two dermatomes, an α-error of 0.05, and a β-error of 0.2. To show a 20% difference in sensory regression of two dermatomes, at least 23 patients per group were needed. The data were analyzed statistically using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). The normality distribution of the variables was tested using the Shapiro–Wilk test. The Kruskal–Wallis test was used to assess differences among the three groups with respect to nonparametric variables. If this revealed significant differences, the Mann–Whitney *U*-test was used to analyze differences between the groups in pairs. Parametric testing was done using analysis of variance. Categorical data were analyzed using the Chi-square test. Data are presented as mean ± SD, median (range), or number of patients (percentage) per category. P values < 0.05 were considered to indicate statistical significance.

Results

Spinal anesthesia was successful in all patients, and all patients completed the study. Patient characteristics were similar among the three groups. The surgeon and anesthesiologist satisfaction scores were similar for the groups (Table 1).

Maximum upper levels of sensory block were higher with dexmedetomidine (T 4.6 ± 0.6) than with midazolam

Table 1 Demographic and intraoperative data

	Dexmedetomidine (n = 25)	Midazolam (n = 25)	Saline (n = 25)
Age (yr)	56.6 ± 8.5	54.8 ± 6.4	57.2 ± 5.2
Weight (kg)	81.1 ± 12.4	78.5 ± 8.9	79.6 ± .6.9
Height (cm)	172 ± 11	170 ± 8	171 ± 5
ASA I/II	5/20	7/18	6/19
Duration of surgery (min)	38.7 ± 5.6	39.2 ± 6.1	40.2 ± 7.1
Fluid infusion (mL)	856 ± 46	842 ± 51	866 ± 59
Baseline HR (beats $\cdot$ min^{-1})	76.0 ± 6.2	73.9 ± 8.2	75.6 ± 7.1
Baseline MAP (mmHg)	104.4 ± 11.5	98.9 ± 10.2	101.9 ± 9.2
Surgeon satisfaction score (1 = poor; 2 = moderate; 3 = good)	3 (2–3)	3 (2–3)	3 (2–3)
Anesthesiologist satisfaction score (1 = poor; 2 = moderate; 3 = good)	3 (2–3)	3 (2–3)	3 (2–3)

Values are expressed as mean ± standard deviation, median (range), or number of patients. ASA = American Society of Anesthesiologists; HR = heart rate; MAP = mean blood pressure

Table 2 Highest sensory level, sensory and motor regression of spinal anesthesia, and data regarding postoperative analgesia

	Dexmedetomidine ($n = 25$)	Midazolam ($n = 25$)	Saline ($n = 25$)
Highest sensory level (thoracic segments)	4.6 ± 0.6**	6.4 ± 0.9	6.4 ± 0.8
Time for two-segment regression of sensory block (min)	145 ± 26**	106 ± 39	97 ± 27
Time for regression of motor block to Bromage 1 (min)	193 ± 27	186 ± 38	180 ± 34
Time to first request for analgesia (min)	216 ± 43**	136 ± 25	122 ± 34
Overall 24-hr pain VAS	2.1 ± 0.6	2.8 ± 0.5	2.9 ± 0.7

Values are expressed as mean ± standard deviation. ** $P < 0.001$ *vs* midazolam and saline with the Mann–Whitney *U*-test. VAS = visual analogue scale

(*T* 6.4 ± 0.9) ($P < 0.001$) or with saline (*T* 6.4 ± 0.8) ($P < 0.001$). Time for sensory regression of two dermatomes was 145 ± 26 min in the dexmedetomidine group, longer than in the midazolam (106.1 ± 38.8 min; $P < 0.001$) or the saline (97.1 ± 26.5 min; $P < 0.001$) groups. The difference in extension or duration of sensory block between the midazolam and saline groups was not statistically different. Duration of motor block was similar in all groups (Table 2). At 20 and 30 min after spinal anesthesia, the sensory block level in the dexmedetomidine group was higher than in the midazolam and saline groups ($P < 0.05$ for both groups, respectively) (Fig. 1).

The overall 24-hr VAS pain scores were similar for the three groups (Table 2). The VAS pain scores did not change over time (postoperative 4, 8, 12, and 24 hr) in the three groups, and were similar among groups at any observation period for up to 24 hr after surgery (Fig. 2). Time to first request for postoperative analgesia was later in the dexmedetomidine group than in the midazolam and saline groups ($P < 0.001$ between the dexmedetomidine group and both the midazolam and saline groups (Table 2). Fewer patients in the dexmedetomidine group required an analgesic (diclofenac Na) during the first 24 hr after spinal block than in the midazolam ($P < 0.05$) and saline ($P < 0.05$) groups (Table 3).

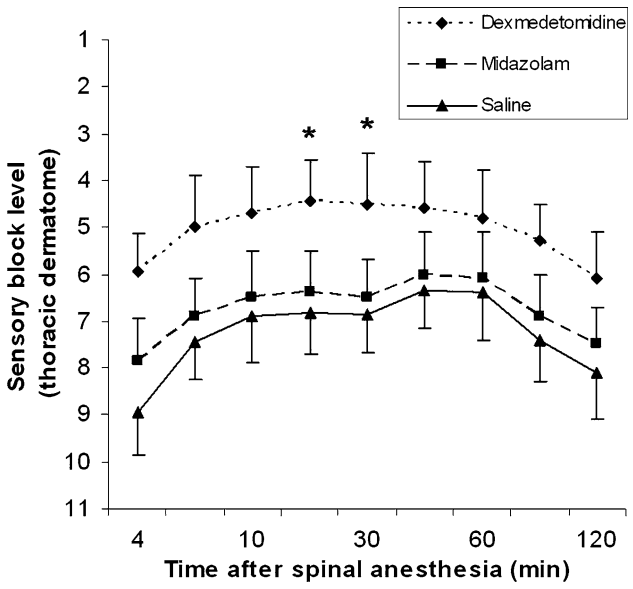

Fig. 1 Sensory block levels after spinal anesthesia in each study group. Values are expressed as means ± SD. * $P < 0.05$ *vs* midazolam and saline with Mann–Whitney *U*-test

The median (range) of the highest Ramsay sedation score was 2 (2–5) in the dexmedetomidine group, 3 (2–5) in the midazolam group, and 1 (1–2) in the saline group. The maximum Ramsay sedation score was greater in the dexmedetomidine and midazolam groups than in the saline group ($P < 0.001$). Excessive sedation (Ramsay sedation score of 5) was observed in two patients of the dexmedetomidine group and in five patients of the midazolam group (Table 3).

The lowest HR and MAP during spinal anesthesia were approximately 20% lower than baseline values and there were no differences among groups. Two patients in the dexmedetomidine group had bradycardia and hypotension needing treatment, while in the saline group, hypotension was observed in four patients and bradycardia was observed in one patient. No other complications attributable to the drugs, and procedure were noted (Table 3). The total amount of fluids administered following spinal anesthesia was similar in the three groups (Table 1).

There were no differences among groups regarding respiratory rate, SpO_2, and Et-CO_2. Respiratory parameters (RR, SpO_2, and Et-CO_2) remained within normal limits throughout the procedure after surgery.

There was no difference among groups regarding the proportion of patients willing to have the same form of anesthesia should they require the same operation in the future (100%, 96%, and 92% in the dexmedetomidine, midazolam, and saline groups, respectively). A similar proportion of patients recalled the dural puncture in the three groups (92%, 80%, and 96%, respectively).

Discussion

Our results indicate that premedication with intravenous dexmedetomidine prolonged the duration of bupivacaine-

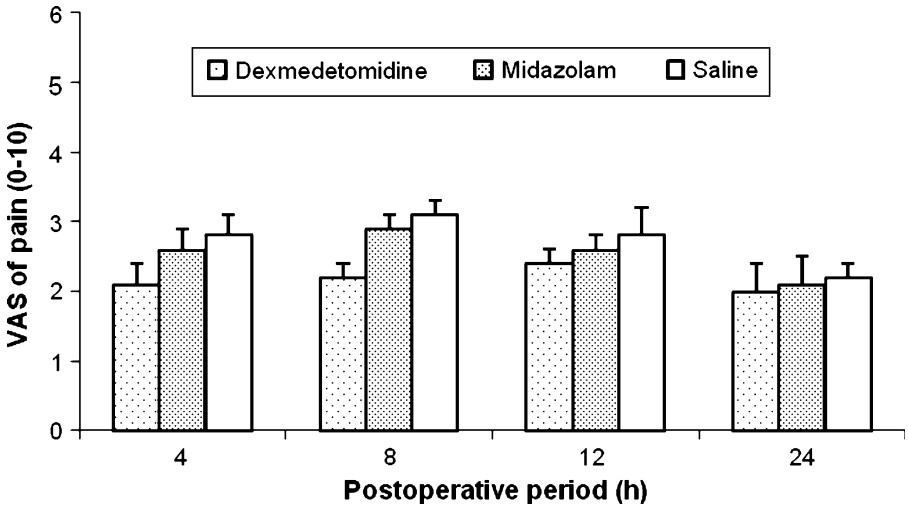

Fig. 2 Visual analogue scale (VAS) scores for the first 24 hr. Values are expressed as mean ± SD. No significant difference found (Mann–Whitney *U*-test)

Table 3 Adverse events and treatments

	Dexmedetomidine ($n = 25$)	Midazolam ($n = 25$)	Saline ($n = 25$)
Lowest heart rate (beats · min^{-1})	61.7 ± 6.2	59.9 ± 6.7	63.1 ± 7.1
Lowest mean arterial pressure (mmHg)	79.9 ± 6.8	82.7 ± 7.4	83.2 ± 7.2
Bradycardia (*n*)	2	0	1
Hypotension (*n*)	2	0	4
Number of patients requiring analgesic (diclofenac Na) for first 24 hr (*n*)	7*	15	16
Excessive sedation (Ramsay sedation score 5/6) (*n*)	2/0	5/0	0/0

Values are expressed as mean ± standard deviation and numbers. * $P < 0.05$ *vs* midazolam and saline with the Chi-square test

induced sensory blockade during spinal anesthesia and increased the maximum upper level of sensory block. In addition, dexmedetomidine increased the time until first request of analgesic for postoperative pain relief and decreased the requirement of supplemental analgesic. It also provided sedation comparable to midazolam premedication.

It is recommended to administer dexmedetomidine over no <10 min, as rapid administration might produce tachycardia, bradycardia, and hypertension.[13] Furthermore, an evaluation of the analgesic effect of different doses of intravenous dexmedetomidine (0.25, 0.5, and, 1 μg · kg^{-1}) on ischemic pain in healthy volunteers demonstrated moderate analgesia with a ceiling effect at 0.5 μg · kg^{-1}.[14] With this in mind, dexmedetomidine, 0.5 μg · kg^{-1} was given over 10 min in this study. Bolus administration of midazolam 0.05 mg · kg^{-1} was reported to give enough sedation and amnesia without any adverse effects on hemodynamics and respiration in patients aged 30–70 yr under spinal anesthesia.[15] Therefore, midazolam 0.05 mg · kg^{-1} was administered to the patients in this study.

Synergistic interaction between dexmedetomidine and local anesthetics has been observed in previous studies. Memiş *et al.*[8] reported that the addition of 0.5 μg · kg^{-1} dexmedetomidine to lidocaine for intravenous regional anesthesia shortened sensory and motor block onset times and prolonged sensory and motor block recovery times without causing side effects. Coşkuner *et al.*[7] have shown that intravenous administration of dexmedetomidine might prolong the recovery time of the sensory blockade of bupivacaine-induced sensorial blockade during epidural anesthesia. Calasans-Maia *et al.*[9] suggested that the duration of motor block induced by spinal injection of levobupivacaine could be prolonged by intrathecal or intraperitoneal administration of dexmedetomidine in guinea pigs. However, there are no clinical data regarding the association of intravenous dexmedetomidine and intrathecal local anesthetic. Although this study showed that the intravenous dexmedetomidine prolonged the duration of sensory block of bupivacaine spinal anesthesia and increased the maximum upper levels of sensory block, the underlying mechanism of this effect remains unclear. The supra-spinal, direct analgesic, and/or vasoconstricting actions of dexmedetomidine are suggested to be involved in this mechanism.[16] In addition, compared with the prolongation of the sensory block, the duration of motor block was not affected by dexmedetomidine. It could be explained that conduction of sensory nerve fiber might be more inhibited than motor nerve fiber at the same

concentration of dexmedetomidine, as similarly reported with clonidine.[17]

Based on present and previous studies, the effect of dexmedetomidine is not dependent on the route of administration. Midazolam has been reported to have an antinociceptive effect through the neuroaxial pathway. However, the effects of midazolam on nociception may depend on the route of administration, with analgesia observed after spinal or epidural application, but not after systemic administration of this agent.[18–20] Also, in our study, intravenous administration of midazolam did not enhance the analgesic effect of intrathecal injection. Finally, the use of dexmedetomidine premedication before spinal anesthesia seems to offer clinical advantages compared with midazolam premedication, since dexmedetomidine provides additional analgesia.

During spinal puncture, it is preferable that patients be able to alert the anesthesiologist of any paresthesia and pain on injection, both of which have been associated with postoperative neurologic deficit. Midazolam may cause restlessness and disinhibition instead of sedation in some patients, and this is referred to as a paradoxical reaction.[21] Thus, surgery will then become extremely difficult. In our study, no patients experienced a paradoxical reaction with midazolam. The sedation produced by dexmedetomidine differs from other sedatives, as patients may be easily aroused and remain cooperative.[22] In this study, excessive sedation was observed in two patients of the dexmedetomidine group compared with five patients in the midazolam group.

Midazolam has a potent anterograde amnesic effect, and dexmedetomidine infusion also may result in impairment of memory and psychomotor performance.[23] However, the amnesic effect of midazolam rapidly diminished with time, and a comparable number of patients in the three groups could remember the spinal puncture.

Rapid or bolus intravenous administration of dexmedetomidine produces sudden hypertension and bradycardia until the central sympatholytic effect dominates, resulting in moderate decreases in both MAP and HR from baseline. We observed no biphasic change or significant cardiovascular variability in this study consisting mainly of healthy patients.[16] This might be attributed to sympathetic blockade associated with spinal anesthesia, slow administration of a low dose, and sufficient preoperative hydration. However, further studies are needed to investigate the efficacy of dexmedetomidine in geriatric patients or medically compromised patient populations.

In previous studies, it has been shown that dexmedetomidine caused no or minimal respiratory depression.[23] However, midazolam is known to cause apnea and arterial desaturation in sedative doses.[24] There was no respiratory depression in any patients and respiratory parameters (respiratory rate, SpO_2, and Et-CO_2) remained within normal limits throughout our procedure.

One limitation of our study is that we used the requirement for rescue analgesic rather than the VAS score to assess the prolongation of analgesia with administration of premedication drug. The primary therapeutic end-point of the current study design was to achieve a VAS score of ≤ 3, and indeed, 24-hr VAS scores were not statistically different among the three groups. Nevertheless, it was concluded within the constraints of the present design that the addition of intravenous dexmedetomidine before spinal block provided similar pain relief with delayed-onset of postoperative pain and significantly less analgesic requirements.

In conclusion, we have shown that a single dose of intravenous dexmedetomidine given as premedication prolonged the duration of sensory blockade of bupivacaine-induced spinal anesthesia. It also provided sedation and additional analgesia.

Conflicts of interest None declared.

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