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Effect of Dexmedetomidine IV on the Duration of Spinal Anesthesia with Prilocaine: A Double-Blind, Prospective Study in Adult Surgical Patients

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ABSTRACT

Background: The duration of spinal anesthesia with prilocaine has been poorly documented and no English-language study has been published regarding the effects of dexmedetomidine on the duration of anesthesia with spinal prilocaine.

Objective: The aim of this study was to assess the effects of dexmedetomidine IV on the duration of action of prilocaine and its associated adverse events (AEs) in spinal anesthesia.

Methods: In this double-blind, prospective study, patients classified as American Society of Anesthesiologists grade I to II who were to undergo lower abdominal, anorectal, or extremity surgery with a spinal anesthetic were assigned to 1 of 2 groups. All patients were administered prilocaine 2% for spinal anesthesia. Within 10 minutes after spinal anesthesia was initiated, group 1 received a loading dose of dexmedetomidine 1 μg/kg IV, followed by a maintenance dose of 0.4 μg/kg · h for 50 minutes; group 2 (control) received the same amount of physiologic saline in the same time frame. Mean arterial pressure (MAP), heart rate (HR), duration of sensory and motor blockade, and sedation scores were tracked. Patients were observed for 4.5 hours after surgery, with follow-ups occurring up to 96 hours after surgery.

Results: Eighty-three patients were assessed for study inclusion, 23 of whom were excluded. Sixty patients (42 men, 18 women; mean [SD] age, 40.56 [16.86] years) were included in the study. MAP was similar in the 2 groups throughout the study. Mean (SD) HR was significantly lower in group 1 compared with group 2 at 20 minutes (70.43 [19.28] vs 77.63 [18.14] beats per minute, respectively; $P = 0.02$). The mean (SD) duration of the persistence of sensory anesthesia (ie, the time required for the maximal level of anesthesia to regress 2 dermatomes) was significantly longer in group 1 compared with group 2 (148.33 [21.18] vs 122.83 [18.73] minutes; $P < 0.001$). The mean (SD) time to complete abolishment of motor blockade was also significantly longer in group 1 than in group 2 (215.16 [25.10] vs 190.83 [18.57] minutes; $P < 0.001$). The average sedation score in group 1 was significantly higher than in group 2

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($P < 0.001$) during anesthesia. Significantly more patients in group 1 required atropine than those in group 2 (9 vs 2 patients; $P < 0.001$) to treat bradycardia. There was no significant between-group difference in the number of patients who received ephedrine to treat hypotension. One patient in each group reported waist and back pain; 2 patients in each group reported nausea. Shivering occurred in 0 and 5 patients in groups 1 and 2, respectively; the between-group difference in AEs was not statistically significant. Paresthesia, postdural puncture headache, allergic reactions, total spinal anesthesia, urinary retention, or vomiting—AEs commonly associated with spinal anesthesia—were not observed or reported by either group.

Conclusions: The results of this study suggest that dexmedetomidine IV significantly prolonged the duration of spinal anesthesia and provided a significantly higher level of sedation compared to placebo in this group of adult surgical patients. The treatment was generally well tolerated in all patients. (*Curr Ther Res Clin Exp.* 2007;68:313–324)

Key words: dexmedetomidine, prilocaine, spinal anesthesia.

INTRODUCTION

Spinal anesthesia has several advantages, including spared spontaneous respiration, low cost, reduced risk for pulmonary aspiration secondary to vomiting in patients whose stomach is full, facilitation of surgery by relaxing the intestines and abdominal wall, elimination of intubation, minimal disruption of blood chemistry, reduced hemorrhaging during surgery, and earlier return of intestinal motility.[1,2] However, spinal anesthesia also has complications and contraindications, including refusal by the patient, the inability to estimate the duration of surgery, postdural puncture headache (PDPH), urinary retention, waist and back pain, paresthesia, allergic reactions, total spinal anesthesia, shivering, and vomiting.[1,2]

In order to prolong the duration of spinal anesthesia, sodium bicarbonate, carbon dioxide, or vasoconstrictor agents have been added to the local anesthetic, as well as IV clonidine, an α_2-agonist drug.[2,3] A prospective, double-blind study[4] was conducted in 2006 in 60 patients undergoing transurethral resection of prostate or bladder tumor. The objective of that study was to determine the effects of low-dose dexmedetomidine (3 μg) or clonidine (30 μg) on the duration of bupivacaine spinal block. The results suggested that dexmedetomidine or clonidine, when added to intrathecal bupivacaine, produced similar prolongation of the duration of the motor and sensory block with preserved hemodynamic stability and lack of sedation.

The duration of spinal anesthesia with prilocaine has been poorly documented, and no English-language study has been published regarding the effects of dexmedetomidine on the duration of anesthesia with spinal prilocaine according to a literature search of MEDLINE (1965–2007) using key words *prilocaine, spinal anesthesia,* and *dexmedetomidine.* In this study, the effects of dexmedetomidine IV on the duration of action of prilocaine and its associated adverse events (AEs) were investigated in spinal anesthesia.

PATIENTS AND METHODS

Patients categorized as American Society of Anesthesiologists (ASA) physical status I or II[5] who were to undergo lower abdominal, anorectal, or extremity surgery under spinal anesthesia were eligible for this double-blind, prospective study after providing written informed consent. The study was conducted in 6 months in accordance with the principles of the Declaration of Helsinki[6] and Good Clinical Practice.[7] Institutional ethics committee approval was obtained before starting the study.

Patients with pregnancy, hypovolemia, coagulation disorders, or local infection at the surgical site; a history of headache, heart disease, allergy, chronic alcohol use or abuse, anemia, congenital heart disease, bundle block, congestive heart failure, or arrhythmia; and patients who had recently received sedative drugs or who were receiving antidepressant treatment were not eligible for the study.

Consecutive patients were allocated into 2 groups by the lead study investigator (M.T.) according to the last digit (odd or even) of their admission number. One investigator (Y.T.), who was not blinded to the treatment groups, prepared the 2 study solutions—dexmedetomidine and physiologic saline. Both of the solutions were identical in appearance to maintain blinding. The patients and the other investigators who were responsible for administering the study solutions, perioperative patient care, and study follow-up were blind to the treatment groups. Patients in group 1 received a maintenance dexmedetomidine infusion, whereas those in group 2 (control) received physiologic saline at the equivalent dose and duration.

One day before surgery, each patient was visited and their physical status and laboratory data were assessed by the anesthesiologist (Y.T.) participating in the study. All patients were informed about spinal anesthesia and signed informed consent. None of the patients received premedication.

On the day of surgery, each patient was admitted to the preoperative preparation unit and was hydrated with lactated Ringer solution containing 5% dextrose (10 mL/kg) through a venous catheter inserted in the dorsum of the hand. After admission to the operating room, electrocardiography and monitoring of blood pressure (BP), heart rate (HR), and peripheral oxygen saturation (SpO_2) were initiated (KMA 800, PETAS, Ankara, Turkey). Lumbar puncture was performed using aseptic techniques in the sitting position through the L4 to L5 interspace in the midline using a 25-G Quincke needle (Spinocan, B-Braun Melsungen AG, Melsungen, Germany), the tip of which was held parallel to the dural fibers. When clear cerebrospinal fluid was observed, 80 mg of prilocaine 2% solution was administered into the subarachnoid space. Each patient was then brought to the supine position, their head was elevated, and oxygen 3 L/min was administered. The duration of surgery for all study patients was estimated to be 60 to 90 minutes. Based on the $t_{1/2}$ of dexmedetomidine (~2 hours),[8] the duration of the infusion was to be 60 minutes for both the active drug and the control solution. Within 10 minutes after spinal anesthesia was initiated, group 1 received

a loading dose of dexmedetomidine 1 μg/kg IV, followed by a maintenance dose of 0.4 μg/kg · h for 50 minutes. In group 2, physiologic saline was administered in the same manner. The same anesthesiologist (M.T.), who was experienced in spinal anesthesia, provided anesthesia to all of the study patients.

Sensory blockade was determined using the pin-prick test, and motor blockade was determined using the Bromage scale[9] (0 = free movement of the legs and feet; 1 = just able to flex the knees, with free movement of the feet; 2 = unable to flex the knees, but with free movement of the feet; 3 = unable to move legs or feet) by a second anesthesiologist (I.K.), who was blinded to administration. The level of sedation was assessed according to the Ramsay sedation scale[10] (1 = patient is anxious and agitated or restless or both; 2 = patient is cooperative, oriented, and tranquil; 3 = patient responds to commands only; 4 = patient exhibits a brisk response to light glabellar tap or loud auditory stimulus; 5 = patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus; 6 = patient exhibits no response).

During anesthesia, BP, HR, and SpO_2 were recorded at 5-minute intervals for the first 10 minutes, at 10-minute intervals for the remainder of the first hour, at 20-minute intervals for the second hour, and at 30-minute intervals for the remainder of the recording period (4.5 hours). The levels of sensory and motor blockade were assessed at 2-minute intervals until the maximal level of anesthesia was achieved and at 5-minute intervals thereafter. *Hypotension* was defined as a decrease >30% in BP compared with the initial preoperative value, and *bradycardia* was defined as HR <50 beats per minute. Patients who developed hypotension were to be administered fluid replacement treatment and ephedrine IV at bolus doses of 5 mg; those who developed bradycardia were treated with atropine 0.01 mg/kg IV. The time to achieve maximal sensory blockade and the duration of motor blockade were also recorded. The *duration of the persistence of sensory anesthesia* was defined as the time required for the maximal level of anesthesia to regress 2 dermatomes. The *duration of motor blockade* was defined as the time required to completely eliminate the motor blockade (ie, Bromage scale score = 0).

Tolerability

AEs, particularly those associated with spinal anesthesia (eg, paresthesia, headache, allergy, hypotension, bradycardia, nausea, vomiting, shivering, waist and back pain, total spinal anesthesia, and difficulty urinating), were also recorded.

The patients were observed and asked about AEs for 4 hours in the recovery room and were then discharged to their wards. The patients were observed at 4-hour intervals for the first 24 hours and then at 8-hour intervals for 96 hours in their wards by another anesthesiologist and surgeon (Y.T., E.K.).

Statistical Analysis

The Student *t* test (independent samples) was used to compare the data (hemodynamic parameters, age, weight, height, time to the regression by 2 der-

matomes of sensory blockade [TDRT], and time to complete abolishment of motor blockade [CAMB]). Demographic data, AEs, sedation, and sensory blockade level were analyzed using the χ^2 test. A power analysis indicated that 27 patients were needed in each group ($\alpha = 0.05$, $\beta = 0.81$); consequently, the study was designed with 30 patients in each group. $P < 0.05$ was considered statistically significant.

RESULTS

Eighty-three patients were assessed for study inclusion, 23 of whom were excluded according to the exclusion criteria. The 60 patients (42 men, 18 women; mean [SD] age, 40.56 [16.86] years) included in the study were divided equally into 2 groups. The 2 groups were similar in terms of demographic data, ASA grade, and the duration of surgery (**Table**). HR was significantly lower in group 1 compared with group 2 at 20 minutes after the initiation of spinal anesthesia (70.43 [19.28] vs 77.63 [18.14] beats per minute, respectively; $P = 0.02$) (**Figure 1**). There were no significant between-group differences in regard to mean arterial pressure (MAP) (**Figure 2**) or SpO_2 (**Figure 3**).

Mean (SD) time to reach peak sensory level was similar in the 2 groups (group 1, 13.50 [6.41] vs group 2, 13.16 [5.49] minutes). Median (range) peak sensory level was similar in the 2 groups according to the pin-prick test (group 1, T10 [T4–T10]; group 2, T10 [T4–T11]). The TDRT was significantly longer in group 1 than in group 2 (148.33 [21.18] vs 122.83 [18.73] minutes; $P < 0.001$) (**Figure 4**).

Table. Baseline demographic characteristics, ASA grade, and duration of surgery in patients receiving prilocaine 2% for spinal anesthesia and maintenance anesthesia with dexmedetomidine (group 1) or physiologic saline (group 2) (N = 60).*

Variable	Group 1 (n = 30)	Group 2 (n = 30)
Age, mean (SD), y	40.63 (18.56)	40.50 (15.29)
Sex, no. (%)		
Male	22 (73.3)	20 (66.7)
Female	8 (26.7)	10 (33.3)
Weight, mean (SD), kg	71.03 (13.58)	69.10 (14.04)
Height, mean (SD), cm	169.70 (5.35)	167.10 (7.14)
ASA grade, no. (%)		
I	21 (70.0)	22 (73.3)
II	9 (30.0)	8 (26.7)
Duration of surgery, mean (SD), min	71.02 (11.79)	72.50 (14.84)

ASA = American Society of Anesthesiologists.
*No significant between-group differences were found.

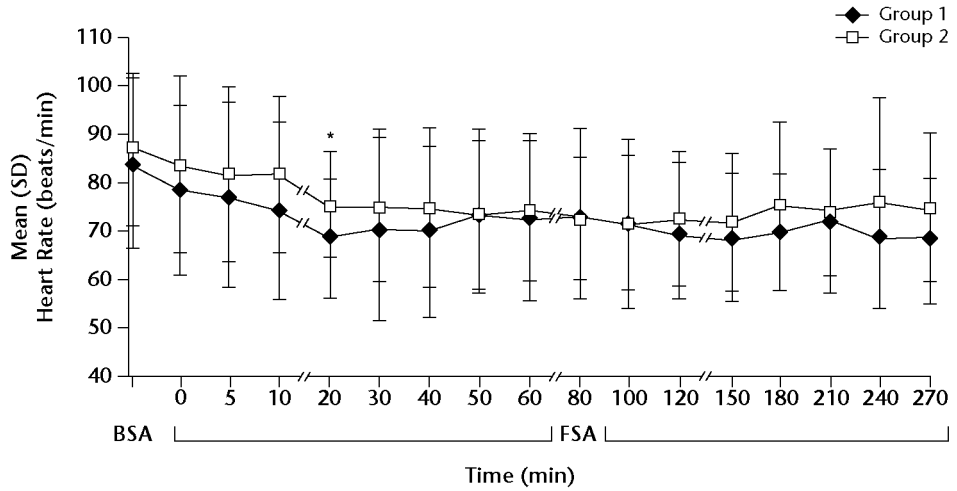

Figure 1. Mean (SD) heart rate by treatment group in adult surgical patients randomized to IV dexmedetomidine (group 1) or normal saline (group 2). BSA = before spinal anesthesia; FSA = following spinal anesthesia. *$P = 0.02$.

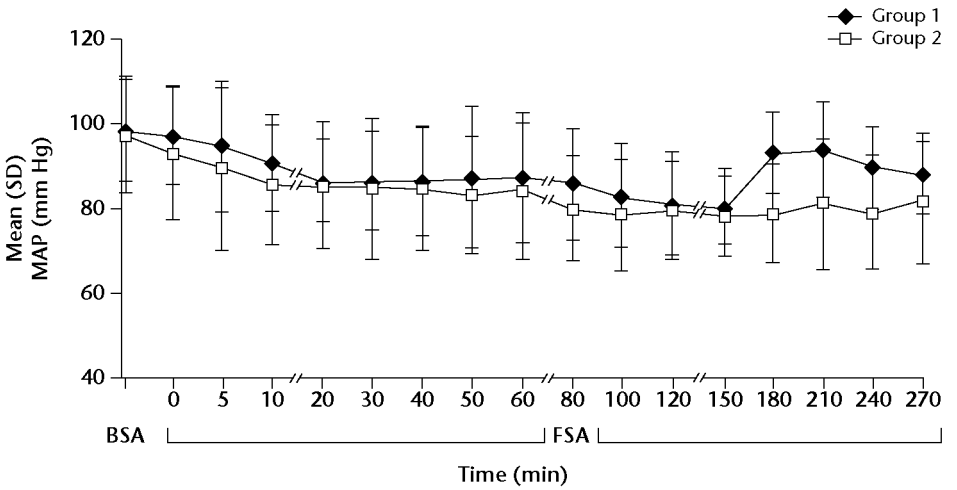

Figure 2. Mean (SD) arterial pressure (MAP) by treatment group in adult surgical patients randomized to IV dexmedetomidine (group 1) or normal saline (group 2). BSA = before spinal anesthesia; FSA = following spinal anesthesia.

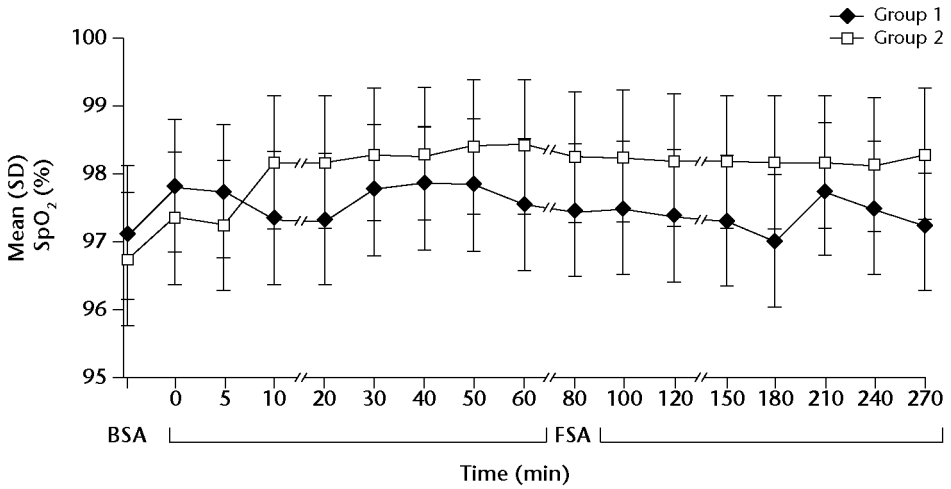

Figure 3. Mean (SD) peripheral oxygen saturation (SpO_2) by treatment group in adult surgical patients randomized to IV dexmedetomidine (group 1) or normal saline (group 2). BSA = before spinal anesthesia; FSA = following spinal anesthesia.

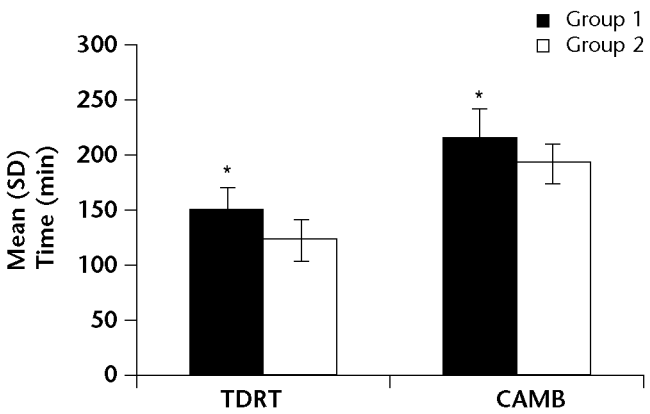

Figure 4. The time required for the maximal level of anesthesia to regress 2 dermatomes and for complete abolishment of the motor blockade in adult surgical patients randomized to IV dexmedetomidine (group 1) or normal saline (group 2). TDRT = time to the regression by 2 dermatomes of sensory blockade; CAMB = time to complete abolishment of motor blockade. *$P < 0.001$.

The CAMB was significantly longer in group 1 than in group 2 (215.16 [25.10] vs 190.83 [18.57] minutes; $P < 0.001$) (**Figure 4**). Median (range) sedation level was significantly greater in group 1 than in group 2 (3 [2–4] vs 2 [1–2]; $P < 0.001$). The number of patients who received ephedrine was similar in group 1 (3 [10.0%]) and group 2 (2 [6.7%]). A significantly greater number of patients in group 1 received atropine compared with those in group 2 (9 [30.0%] vs 2 [6.7%]; $P = 0.042$).

Tolerability

Waist and back pain were reported in 1 (3.3%) patient in each group. Nausea was reported in 2 (6.7%) patients in each group. No patient in group 1 experienced shivering, while shivering occurred in 5 (16.7%) patients in group 2; however, the between-group difference was not statistically significant. None of the patients in either group reported paresthesia, PDPH, allergy, vomiting, total spinal anesthesia, or difficulty urinating.

DISCUSSION

Spinal anesthesia has certain advantages. It can be administered rapidly and it provides good abdominal relaxation. The blockade caused by spinal anesthesia is well controlled, and the toxic effects of the local anesthetics used are less frequent and severe than general anesthesia. The onset of spinal anesthesia is rapid, and its effects on mental status are minimal. Blood loss is lower with this type of anesthesia, and spinal anesthesia has been found to have protective effects against thromboembolism.[1,2]

When a single-dose injection is used for spinal anesthesia, the duration of anesthesia is directly associated with the duration of effect of the local anesthetic administered. Prolonging the duration of spinal anesthesia would be ideal for surgical interventions with longer durations. Various additives have been used to prolong the duration of spinal anesthesia, including vasoconstrictive agents, such as epinephrine, phenylephrine, and clonidine.[1,2] Opioids and neostigmine have also been used.[2,11,12] Clinically, α_2-agonists, such as clonidine and dexmedetomidine, are being used as adjuvants in anesthesia.[13,14] The α_2-agonists used in regional anesthesia have been reported to alter the characteristics of anesthetic solutions by inducing vasoconstriction, potentiating the blockade of C-fibers, or augmenting the effects of local anesthetics by positively influencing slow retrograde axonal transport along the nerves at the spinal cord level.[15,16]

Subtype-specific α_2-agonists probably provide analgesia and anesthesia without causing any hemodynamic effects by stimulating only the intended receptor population. The α_2-adrenergic receptors in the nerve endings may contribute to the analgesic effect by preventing norepinephrine release.[16–19]

Prilocaine has been used for spinal anesthesia for >30 years.[20] However, until 2000, prilocaine and its duration of action had been poorly documented for use in spinal anesthesia. Ostgaard et al,[21] in a randomized study of 100 patients

scheduled for short urologic procedures under spinal anesthesia, reported that the mean (SD) duration of sensory blockade and motor blockade with lidocaine 80 mg and prilocaine 80 mg were 123 (42) and 197 (42) minutes, respectively. The double-blind, randomized study by de Weert et al[22] reported the mean (SD) duration with isobaric 2% lidocaine 4 mL or isobaric 2% prilocaine 4 mL intrathecally, to be 127 (59) and 166 (45) minutes, respectively. We found these durations to be 122.83 (18.73) and 190.83 (18.57) minutes in the control group, which are in agreement with the literature. In the treated group, dexmedetomidine IV significantly prolonged both the time required for the maximal level of the sensory blockade to regress 2 dermatomes and the time for complete reversal of motor blockade compared with the control group. These findings may be due to the adjunct effect of dexmedetomidine. Dexmedetomidine did not affect the time to the onset of the sensory block. Kanazi et al[4] reported that intrathecal dexmedetomidine did not produce a significant difference in the time to reach peak sensory level.

The hemodynamic effects of dexmedetomidine are biphasic; when it is administered IV, it induces hypotension and bradycardia until the central sympatholytic effect is established, after which it causes decreases in MAP and HR. This restricts the use of dexmedetomidine in outpatient surgery patients, since hypotension and bradycardia may occur in the postoperative period.[23–25] The prevalence of hypotension after spinal anesthesia, which has been reported to be 30% to 40%, has been attributed to sympathetic blockade.[2,26] The prevalence of decreased MAP after dexmedetomidine infusion was found to be 14%, 17%, 23%, and 27% at infusion doses of 0.25, 0.5, 1.0, and 2.0 μg/kg, respectively.[24] In our study, the prevalence of hypotension requiring the administration of ephedrine was 10.0% in the treatment group and 6.7% in the control group, although the between-group difference was not significant. The hypotension was attributed to spinal anesthesia reaching its maximal sensory level. Hypotension might have been augmented by the added hypotensive effect of dexmedetomidine. However, the low prevalence of hypotension in our study may be attributed to providing sufficient preoperative hydration.

In the literature, the prevalence of bradycardia after spinal anesthesia was reported to be 10% to 15%.[24] The prevalence of reduced HR following dexmedetomidine infusion was reported to be 25%. We observed a significant reduction in HR in group 1 compared with group 2 at 20 minutes after the initiation of anesthesia. Nine patients in the dexmedetomidine group and 2 patients in the control group required atropine. This difference was attributed to the bradycardia-inducing effect of dexmedetomidine.

Sedation is frequently required during regional anesthesia for the comfort of both the patient and the surgeon. Propofol, midazolam, clonidine, and dexmedetomidine are frequently used with this purpose.[27,28] In studies of dexmedetomidine, the intended level of sedation was reported to be achieved at doses of 0.2 to 0.7 μg/kg · hr. Sedation was also reported to be deepened with larger doses.[23,25] In our study, deeper sedation was induced in group 1 than group 2,

indicating that dexmedetomidine may reduce the need for extra sedative agents.

One of the main goals in using sedative agents is to avoid respiratory depression. In a previous study, the α_2-adrenergic agonists were found to cause no respiratory depression or only minimal depression.[18] In our study, respiratory depression was not observed in any of the patients, and no significant between-group difference was found in SpO_2 because all patients were administered oxygen 3 L/min during the procedures.

The prevalence of back pain secondary to spinal anesthesia has been found to range between 2.5% and 54.0%.[29–31] In our study, the prevalence of back and waist pain was 3.3%, which is similar to other reports in the literature. The prevalence of shivering after spinal anesthesia has been reported to range between 10% and 40%.[32,33] The absence of shivering in group 1 in our study may be associated with dexmedetomidine use. In group 2, we observed shivering in 16.7% of the patients, which is in agreement with the literature.

After spinal anesthesia, the prevalence of nausea has been reported to range between 2% and 18%, whereas that of vomiting ranged between 0% and 7%.[26] In our study, the prevalences of nausea were 6.7% and 0% in group 1 and group 2, respectively; these findings are similar to the literature. Complications such as paresthesia, PDPH, allergy, total spinal anesthesia, vomiting, and difficulty in voiding were not observed in any of our patients.

Limitations

The study sample size was small; only 30 patients were included in each group. More than one local anesthetic might have been included in the study design to give more comparative data. Finally, the patients were not randomly assigned to the study groups. Consecutive patients were allocated into groups according to the last digit (odd/even) of their admission number by the study supervisor, who was not blinded to the treatment group. A strictly randomized blinded patient allocation to the groups might have made the results of this study more valuable.

CONCLUSION

We found that dexmedetomidine IV prolonged the duration of sensory and motor blockade, provided a higher level of sedation, and was well tolerated compared with placebo.

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