Original Article

Postoperative Analgesic Effect of Intrathecal Dexmedetomidine Compared to Morphine in Bupivacaine Spinal Block

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Background: Intrathecal dexmedetomidine has been reported to potentiate the effect of local anesthetics.

Objective: To compare post-operative analgesic effect of 5 μg dose of dexmedetomidine or 0.2 mg dose of morphine added with intrathecal bupivacaine.

Materials and Methods: Fifty-six patients undergoing hip or knee arthroplasty under spinal anesthesia were randomized into two groups. Each patient received a 12.5 mg dose of bupivacaine for spinal anesthesia. A 0.2 mg dose of morphine or a 5 μg dose of dexmedetomidine was diluted in an equivalent volume and administered intrathecally in the control (M) and intervention (D) group, respectively. Post-operative morphine patient control analgesia (PCA) was used in every patient. The primary objective was to determine the time to the first analgesic requirement. The time to reach the T10 sensory level, time to regression to S1 sensory level and motor levels, the 24-post-operative-hour morphine requirement, verbal numerical rating pain scale, and adverse effects were recorded.

Results: Patients in group M had a significantly longer analgesic duration of the time to the first analgesic requirement; 468.50 and 302.46 minutes in groups M and D, respectively, (p-value 0.006). The morphine requirement during the first 24 post-operative hours was smaller in group M (19.14 mg) than in group D (37.58 mg) (p-value 0.003). Pruritus was significantly higher in group M. Post-operative pain score, nausea and vomiting, and sedation score were not different between the two groups.

Conclusion: Intrathecal dexmedetomidine provided significantly lower post-operative analgesia in 24 hours after hip or knee arthroplasty compared to morphine.

Keywords: Intrathecal dexmedetomidine, Morphine, Bupivacaine, Spinal block

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Post-operative pain management is a major challenge to enhance the patient outcome after surgery. The hyperbaric bupivacaine, a local anesthetic agent commonly used for spinal anesthesia, has a limited duration of analgesia of approximately two to three hours. Morphine (0.1 to 0.2 mg) is the most common adjuvant added to the intrathecal hyperbaric bupivacaine because it significantly increases post-operative analgesia to 12 to 24 hours and decrease the local anesthetic dose[1]. However, pruritus, nausea, and vomiting are common adverse effects of intrathecal morphine. Respiratory depression or sleep apnea is also the major concern for opioid administration. Dexmedetomidine and clonidine which are an α-2 receptor agonists have also analgesic property, decrease sympathetic tone, attenuate neuroendocrine response to injury, reduce intraoperative anesthetic drugs, reduce perioperative opioid requirement, and produce dose-dependent sedation and analgesia[2,3]. They can be administered intravenously during surgery to synergist the anesthetic drugs. Previous studies reported both clonidine and dexmedetomidine given intrathecally can potentiate the effect of local anesthetics and decrease dose of local anesthetics[4-9]. However, few studies evaluated the post-operative analgesic effect of intrathecal dexmedetomidine[10-12]. The purpose of the present study was to compare post-operative analgesic effect of 5 μg dose of dexmedetomidine to 0.2 mg dose of morphine added

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with intrathecal bupivacaine for lower extremities surgery.

Materials and Methods

The present study design was a prospective, randomized, double-blinded, controlled trial study. The protocol was approved by the Medical Ethics Committee at Prince of Songkla University. Written inform consent was obtained from the 56 patients undergoing elective hip or knee arthroplasty surgery in Songklanagarind Hospital between April 2012 and June 2013. The eligibility criteria were age older than 18 years old and the American Society of Anesthesiologists (ASA) classification physical status 3 or less, anesthetic technique was spinal anesthesia.

Exclusion criteria included preoperative treatment with α-adrenergic antagonists, absolute contraindication for spinal anesthesia, drug allergy to local anesthetics, morphine, and dexmedetomidine, conversion or combination of general anesthetic technique, and inadequate or failed spinal block.

All patients were randomized into two groups according to a computer-generated randomization. The group was in the sequential sealed, opaque envelope. Dexmedetomidine (Precedex® 100 µg/ml; Abbott Laboratories) was prepared by diluting with normal saline to the concentration of 25 µg/ml. The preservative-free morphine (1 mg/ml) was also diluted with normal saline to the concentration of 0.1 mg/ml. The patients in morphine group (group M) and dexmedetomidine group (group D) received a 0.2 mg (0.2 ml) dose of morphine and a 5 µg (0.2 ml) dose of dexmedetomidine, respectively, added to 2.5 ml of 0.5% hyperbaric bupivacaine. All of the admixtures were coded and prepared by the researcher or nurse anesthetists who did not involve in the study. The patients and anesthesiologists who performed the spinal anesthesia and the post-operative pain assessment were also blinded.

All patients were not premedicated. After arriving the operating theater, they were monitored with standard monitoring and preloaded with 500 ml of intravenous crystalloid solution. The spinal block was performed at L3 to L4 level with a 27-gauge Quincke® needle. The systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), oxygen saturation, sensory blockade assessed by pin prick test, and motor blockade assessed by using modified Bromage score (Bromage 0=the patient is able to move the hip, knee and ankle; Bromage 1=the patient is unable to move the hip, but is able to move the knee and ankle; Bromage 2=the patient is unable to move the hip and knee, but is able to move the ankle; Bromage 3=the patient is unable to move the hip, knee and ankle) were recorded at baseline and then at 1, 3, 5, 7, 9, 12, 15, 20, 25, and 30 minutes after spinal anesthesia. The time to T10 sensory level and time to Bromage score of 3 were also recorded. The intraoperative rescue pain was 0.5 mcg/kg of intravenous fentanyl. Hypotension was defined as a decrease in SBP more than 20% from baseline, or a systolic blood pressure lower than 90 mmHg. Hypotension was treated with 6 mg of intravenous ephedrine and if the blood pressure remained low, the 6 mg of intravenous ephedrine were repeated within five minutes. Bradycardia was defined as HR less than 50 beats/minute and was treated with 0.6 mg of intravenous atropine.

In the post-anesthetic care unit (PACU), the patient control analgesia (PCA) with morphine setting at 1 mg bolus dose, five minutes of lockout interval, and 40 mg of 4-hour limit without baseline infusion was started in every patient and continued for at least 24-hour. The vital signs, pin prick sensation, modified Bromage score, time to regression to S1 sensory level, time to Bromage score of 0, and post-operative pain assessed by verbal numerical rating scale (VNRS, range from 0 to10) were recorded every 15 minutes until the patients were discharged from PACU. Paracetamol in the dose of 500 mg was given orally every six hours as a co-analgesic medication. The time to the first morphine requirement, total morphine consumption during the first 24 post-operative hours, verbal numerical rating pain scale (at rest and during movement), and adverse effects (pruritus, post-operative nausea and vomiting, sedation score, and urinary retention) were recorded at 1, 2, 4, 8, 12, and 24 hours post-operatively. Degree of post-operative nausea and vomiting were classified as 0=no nausea or vomiting; 1=mild nausea or vomiting with no initial treatment; 2=moderate nausea or vomiting with responding to initial treatment; or 3=severe nausea or vomiting with requiring repeat treatment. Patient who reported vomiting received intravenous 4 to 8 mg of ondansetron or 10 mg of metoclopramide. The primary outcome was time to first analgesic requirement. The patients were analyzed in term of intention-to-treat.

Statistical analysis

From the previous study[13], 25 patients in each group were required to achieve 80% power and type I error=0.05 and 95% confidence interval (CI). To accommodate for 10% patients drop-out, 28 patients were enroll in each group. The Stata-10 software was

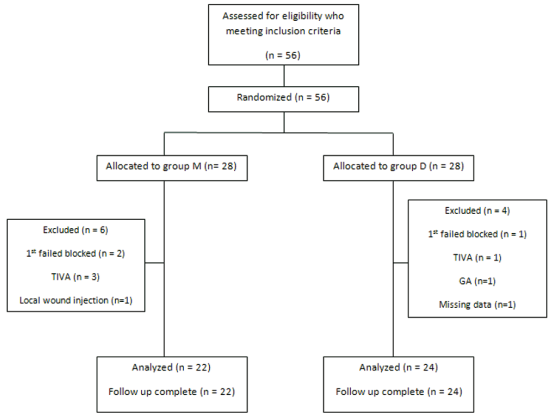

Figure 1. Consort flow diagram describing participant's enrollment, allocation and analysis.

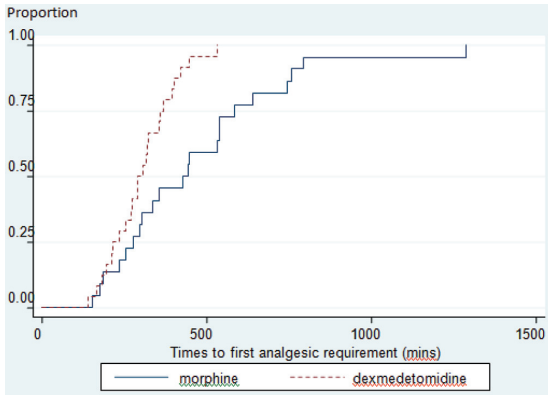

Figure 2. The Kaplan-Meier failure estimates curve of median times to first analgesic requirement.

used to analyze the data. Two-group comparisons of demographic data, baseline variables, primary outcome, and secondary outcomes were analyzed with independent 2-sample t-test for continuous normal distribution data and Mann-Whitney U test for continuous non-normal distribution data including age, height, ASA classification and total morphine consumption in post-operative 24 hours. Time to first analgesic requirement, time to T10 sensory level, time to regression to S1 sensory level, time to Bromage score of 3, and time to Bromage score of 1 were analyzed by means of Kaplan-Meier failure estimate curves. Nominal categorical data between study groups were compared using the Chi-squared test or Fisher's exact test as appropriated. Results were expressed as mean ± standard deviation (SD) for normal distribution data, and median for non-normal distribution data. For all determinations, p-value lower than 0.05 was considered to be statistically significant.

Table 1. Demogaphic data

	Group M (n = 28)	Group D (n = 28)	p-value
Sex, n (%)			0.767
Male	9 (32.1)	7 (25.0)	
Female	19 (67.9)	21 (75.0)	
Age (years), Median (IQR)	63 (53, 69)	68 (56, 73)	0.228
Body weight (kg), Mean±SD	65.5±8.9	61.0±6.3	0.035
Height (cm), Median (IQR)	155 (152, 165)	154 (150, 161)	0.526
BMI (kg/m^2), Mean (SD)	26.2±3.6	24.7±3.3	0.120
ASA class, Median (IQR)	2 (2, 2)	2 (2,2)	0.982
Diabetes mellitus, n (%)	7 (25.0)	2 (7.1)	0.143
Hypertension, n (%)	14 (50.0)	19 (97.9)	0.277
Operation, n (%)			1.000
Hip surgery	12 (42.9)	11 (39.3)	
Knee surgery	16 (57.1)	17 (60.7)	

M=morphine; D=dexmedetomidine; IQR=interquartile range; SD =standard deviation; BMI=body mass index, ASA class=American Society of Anesthesiologists classification

Results

Of the 56 patients, six patients were excluded from group M and four patients were excluded from group D (Figure 1).

The patient baseline demographic data including sex, age, height, body mass index (BMI), ASA classification and the surgical operation were similar in both groups except the body weight. Patients in group M were more obese than in group D (p-value 0.035) (Table 1). However, after performing the regression analysis, the body weight has a hazard ratio 1.02 (p-value 0.217, 95% CI 0.99 to 1.06), which was not significantly different between groups.

According to the post-operative analgesic duration, the time to first analgesic requirement was longer in group M (429 minutes) than in group D (289 minutes) (p-value 0.006) (Figure 2).

There was no difference between the time to reach T10 sensory block of group M and group D, (4 minutes in both groups). The time to reach motor block of Bromage score 3 in group M was longer than in group D (5 and 3 minutes, respectively), but it was not statistically significant (p-value 1.000). The regression time to S1 sensory level was significantly different between groups, which were 225 minutes and 209 minutes in group D and M, respectively (p-value 0.135). The regression times to motor block of Bromage score 0 in group D was longer than in group M (225 and 170 minutes, respectively) (p-value 0.002) (Figure 3).

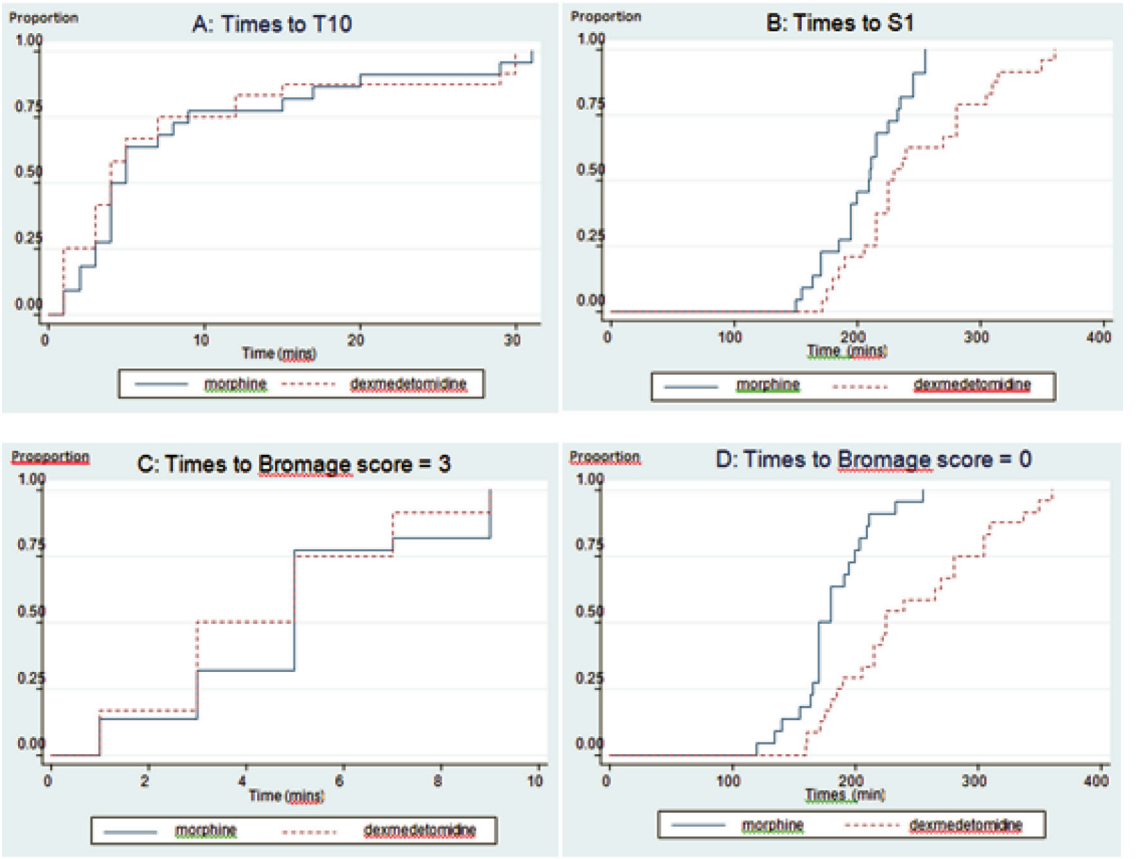

Figure 3. (A) The Kaplan-Meier failure estimates curve of times to reach T10 sensory block. (B) The regression time to S1 sensory level. (C) The time to reach motor block of Bromage score 3. (D) The regression time to motor block of Bromage score 0.

Six patients in group D and four patients in group M developed hypotension that required ephedrine administration. One patient in group D received atropine for the treatment of bradycardia. However, the mean values of MAP and HR were not significantly different between the two groups throughout the intra-operative period (Figure 4). All patients had a peripheral oxygen saturation greater than 96% at all times and did not require additional oxygen therapy after surgery.

The total morphine requirement during the first 24 post-operative hours was less in group M (19.2 mg) than in group D (37.6 mg) (p-value 0.003). Post-operative verbal numerical rating scale at rest and during movement in group D was higher than in group M but was only significantly different between two and eight hours post-operatively (Figure 5).

The incidences of nausea and vomiting were not different between the two groups except that the incidence of vomiting at 4-post-operative hours was significantly higher in group M (18.2%) than in group D (8.3%) (p-value 0.04). However, vomiting of four patients in group M were mild and two patients in group D had moderate symptom (Table 2). The incidences of pruritus at 2, 4, 8, and 12-post-operative hours were significantly higher in group M (Table 2). Every patient in the study had sedation score of 0 to 1 and retained Foley's catheter during post-operative 24 hours.

Discussion

The present study demonstrated that intrathecal morphine had the longer effect of post-operative analgesia compared with intrathecal dexmedetomidine, with the longer time to first analgesic requirement and the lower 24 hours post-operative morphine consumption. Additionally, patients receiving intrathecal morphine reported less VNRS at rest and during movement than those who received intrathecal dexmedetomidine.

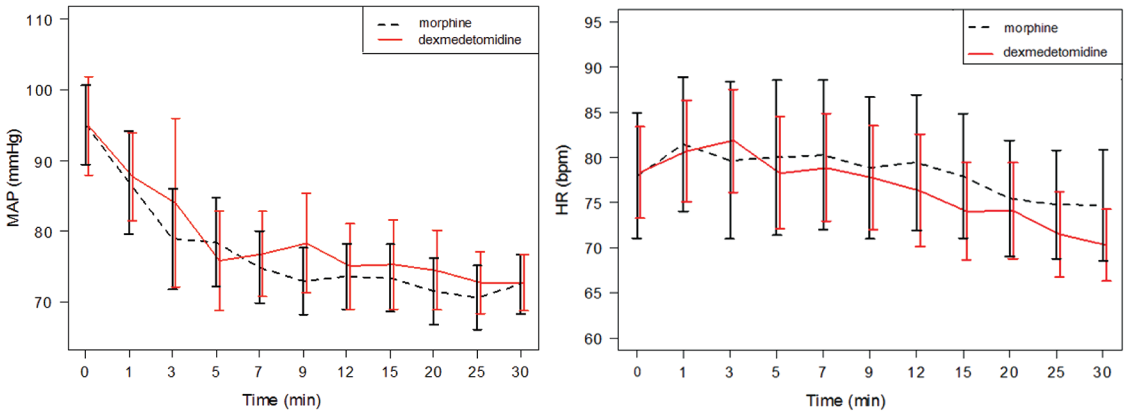

Figure 4. The intra-operative hemodynamic changes of the mean values of mean arterial pressure (MAP) and heart rate (HR) in both groups.

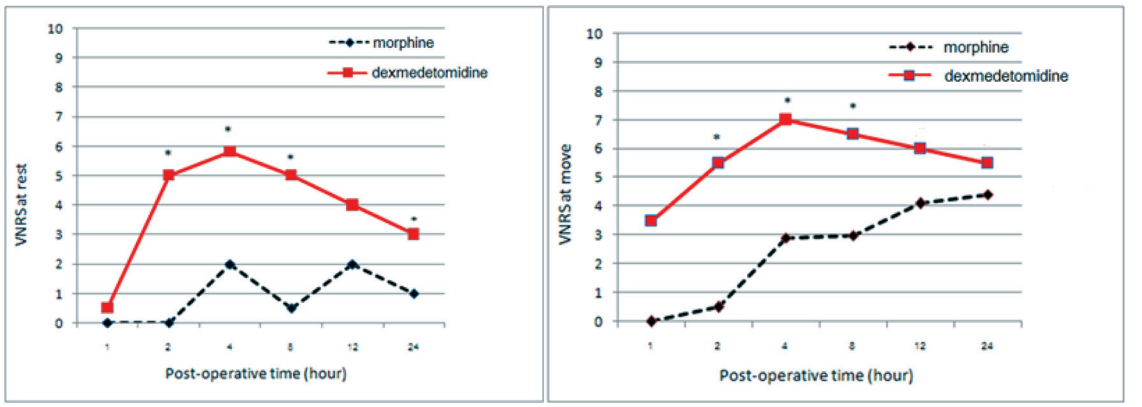

Figure 5. Postoperative verbal numerical rating scale score at rest and during movement.

* Means p-value <0.05

Table 2. The incidences and severity of nausea and vomiting and the incidences of pruritus within 24 hours after surgery in both groups

Side effects	Postoperative hour, n (%)																	
	1			2			4			8			12			24		
	gr. M	gr. D	p-value	gr. M	gr. D	p-value	gr. M	gr. D	p-value	gr. M	gr. D	p-value	gr. M	gr. D	p-value	gr. M	gr. D	p-value
Nausea			0.17			0.35			0.05			0.38			0.51			0.38
Mild	6 (27)	5 (21)		7 (32)	5 (21)		6 (27)	1 (4)		3 (14)	3 (12)		2 (9)	2 (8)		0 (0)	1 (4)	
Moderate	7 (32)	3 (12)		2 (9)	6 (25)		0 (0)	2 (8)		0 (0)	2 (8)		1 (4)	0 (0)		1 (4)	3 (12)	
Severe	0 (0)	0 (0)		1 (4)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Vomitting			0.22			0.81			0.04			0.32			0.26			0.38
Mild	3 (14)	3 (12)		2 (9)	2 (8)		4 (18)	0 (0)		2 (9)	1 (4)		0 (0)	2 (8)		0 (0)	1 (4)	
Moderate	6 (27)	2 (8)		3 (14)	5 (21)		0 (0)	2 (8)		0 (0)	2 (8)		1 (4)	0 (0)		1 (4)	3 (12)	
Severe	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		1 (4)	0 (0)		0 (0)	0 (0)	
Pruritus	5 (23)	1 (4)	0.06	6 (27)	1 (4)	0.03	9 (41)	1 (4)	<0.01	9 (41)	3 (12)	0.03	8 (36)	2 (8)	0.02	5 (23)	4 (17)	0.61

gr. M=morphine group; gr. D=dexmedetomidine group

Data compared by Chi-square test

The principle action of morphine administered intravenously is systemic effect from binding with opioid receptor in the central nervous system (CNS). Intrathecal analgesic effect of morphine could also be explained by binding to the μ-opioid receptors, which are located in the substantia gelatinosa of the dorsal horn of the spinal cord. The hydrophilic nature of morphine also determines its duration of action. Preservative-free morphine is very hydrophilic and poorly lipid soluble, which extends its duration of intrathecal analgesic effect up to 12 to 24 hours[1]. The lipophilicity of opioids is represented by the octanol-water partition coefficient, which is 1.4 for morphine[14].

This study shows comparable results to a previous study by Kanazi et al that reported shorten motor blockade of intrathecal dexmedetomidine in spinal anesthesia[6]. Intrathecal dexmedetomidine in the present study also shortened only the onset of motor blockade but not the sensory blockade. The time to reach motor block of Bromage score 3 in group M was statistically not significant longer than in group D (5 and 3 minutes, respectively) (p-value 1.00), and the time to reach T10 sensory block were four minutes in both groups.

When added to intrathecal bupivacaine, dexmedetomidine demonstrated to produce the longer duration of both sensory and motor blockade of spinal anesthesia[6,9-12]. The effect of 5 μg dose of dexmedetomidine added to bupivacaine for neuraxial anesthesia studied by Al-Mustafa et al confirmed that the intrathecal dexmedetomidine prolonged both of the onset and duration of spinal anesthesia[8]. Similar to the present study, the regression time to S1 sensory level was significantly longer in group D (225 minutes) than in group M (209 minutes) (p-value 0.135). Additionally, the regression time to motor block of Bromage score 0 in group D was longer than in group M (225 and 170 minutes, respectively) (p-value 0.002).

The mechanism by which intrathecal alpha-2 adrenoceptor agonists prolong the motor and sensory block of local anesthetics is not well understood. It may possibly be an additive or synergistic effect secondary to the different mechanisms of action of the local anesthetic and the alpha-2 adrenoceptor agonist. The local anesthetics acts by blocking sodium channels, whereas the alpha-2 adrenoceptor agonist acts by binding to pre-synaptic C-fibers and post-synaptic dorsal horn neurons[11].

For post-operative analgesia, the intrathecal morphine at the dose of 0.1 to 0.2 mg is commonly used in orthopedic surgery. Hanna et al reported that 3 μg intrathecal dexmedetomidine prolong the time to the first analgesic requirement[10]. Gupta et al and Mohamed et al also showed less post-operative analgesic requirement for patients receiving intrathecal dexmedetomidine at a dose of 5 μg[11,15]. However, compared with intrathecal morphine, the time to first analgesic requirement in the present study was longer in group M (429 minutes) than in group D (289 minutes) (p-value 0.006). The total morphine requirement during the first 24 post-operative hours was statistically significant lower in group M (19.2 mg) than in group D (37.6 mg) (p-value 0.003), and the pain scores were lower in group M as well. The post-operative analgesic effect of dexmedetomidine was shorter than morphine in the present study. This may be because of the highly lipid solubility of dexmedetomidine, which lead to more absorption to the systemic circulation and less amount of dexmedetomidine left in the subarachnoid space.

The most significant side effects of intrathecal alpha-2 adrenoreceptor agonists are bradycardia and hypotension[13,16,17]. The high dose (15 μg) intrathecal dose of dexmedetomidine used by Eid et al showed significantly higher sedation, which may be harmful in elderly and high-risk surgical patients owing to the risk associated with excessive sedation and respiratory depression[12]. The small dose (5 μg) of intrathecal dexmedetomidine in the study may be responsible for minimal or no sedation observed in both groups. In the present study, the hemodynamic adverse effects were similar in both groups. Although, hypotension and bradycardia more frequently developed in the dexmedetomidine group than in the morphine group, there were not significantly different in MAP and HR in both groups.

The dose-related nausea and vomiting of intrathecal morphine spreading to the area postrema in the CNS occurred in approximately 15% to 20% of patients[18]. In the present study, the highest incidences of nausea and vomiting were 20.8% in group D and 31.8% in group M. Even though, the incidences of nausea and vomiting were comparable between groups, the incidence of vomiting was statistically significant higher in morphine group at 4-post-operative-hour. This may represent the peak effect of intrathecal morphine. Our post-operative nausea and vomiting from intrathecal dexmedetomidine were higher than those in previous study (3.3%)[11]. The pruritus induced by intrathecal morphine was reported as high as 59.5%[18]. The highest incidence of pruritus in the present study was 40.9% at 4-hour post-

operation in morphine group. The low-dose intrathecal dexmedetomidine reported by the previous studies did not cause the post-operative pruritus[9,11,15]. However, 16.7% of our patients receiving dexmedetomidine developed pruritus. Our patients receiving morphine complained of more pruritus than patients in the dexmedetomidine group. The PCA morphine used in post-operative period maybe produced some degree of nausea, vomiting, and pruritus in the dexmedetomidine group.

There were some limitations of the present study design, first, our sample size was relatively small, and further studies are needed to confirm the conclusion of the present study. The second was that the 24 hours post-operative follow-up time in the present study was not long enough to evaluate any long-term neurological deficits from intrathecal dexmedetomidine. A number of animal studies conducted using intrathecal dexmedetomidine at a dose range of 2.5 to 100 µg did not report any neurologic deficits[10-23]. Similar to the present study, the use of 5 µg of intrathecal dexmedetomidine with hyperbaric bupivacaine in previous human trials did not show the neurologic deficits 24 hours after surgery[9,11,15]. Eid et al also reported that the patients who received intrathecal dexmedetomidine (10 and 15 µg) did not have any neurological deficit after two weeks post-operative follow-up[12]. The third was that the urinary retention was not included in the present study because every patient in the study retained the Foley's catheter in post-operative 24 hours.

In conclusion, 5 µg dose of intrathecal dexmedetomidine provided a significantly lower post-operative analgesic effect in the 24 hours after hip or knee arthroplasty compared to morphine. However, intrathecal morphine had more post-operative adverse effects such as nausea, vomiting, and pruritus.

What is already known on this topic?

Dexmedetomidine is an alpha-2 adrenergic agonist that also has analgesic activity. It has an additive effect to both opioid and anesthetic drugs. Therefore, it can be used for sedation and pain management in operating theater and intensive care unit. However, it is commonly administered in intravenous route. Morphine is a common co-analgesic drug mixed together with local anesthetics to enhance the sensory blockade effect of neuraxial block. However, side effects of morphine are of serious concern especially the respiratory depression. Many medications can be used as local anesthetic adjuvants such as neostigmine, ketamine, midazolam, clonidine, and dexmedetomidine.

What this study adds?

At present, intrathecal dexmedetomidine has limited use in surgical patients but previous trials reported that it enhanced both sensory and motor block of local anesthetic drugs in neuraxial anesthesia. The present study showed that the analgesic effect of low-dose intrathecal dexmedetomidine had some benefit in both intra-operative and post-operative period. Although it had less side effects compared to intrathecal morphine, its post-operative analgesic advantage was not as good as morphine. The off-label use of intrathecal dexmedetomidine is another concern because of the possibility of neurotoxicity, which need further investigations to support for clinical practice.

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Conflicts of interest

The authors declare no conflict of interest.

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