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ORIGINAL ARTICLE

The effects of single-dose intravenous dexmedetomidine on hyperbaric bupivacaine spinal anesthesia

Seung Hwan Jung · Soo Kyung Lee · Kyung Jee Lim · Eun Young Park · Mae Hwa Kang · Jung Min Lee · Jae Jun Lee · Sung Mi Hwang · Sung Jun Hong

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Abstract
Purpose Dexmedetomidine, a selective α2-adrenoceptor agonist, has analgesic and sedative effects. The purpose of this study was to investigate the effects of small, single-dose intravenous dexmedetomidine administration after hyperbaric bupivacaine spinal anesthesia.
Methods Sixty adult patients classified as American Society of Anesthesiologists physical status 1 or 2 and scheduled for lower extremity surgery under spinal anesthesia were studied. Patients were randomly assigned to one of three groups and administered hyperbaric intrathecal bupivacaine 12 mg. 5 min after spinal anesthesia, patients in groups 1, 2, and 3 received normal saline 10 ml, dexmedetomidine 0.25 μg/kg, and dexmedetomidine 0.5 μg/kg, respectively, over 10-min intravenous administration. The onset time, maximum block level, two-dermatome sensory regression time, duration of motor and sensory anesthesia, and side effects were assessed.
Results The two-dermatome sensory regression time was significantly increased in groups 2 and 3. The duration of motor and sensory anesthesia was significantly increased in group 3. Onset time, maximum block level, level of sedation, and incidence of hypotension and treatment-needed bradycardia were no different among the groups.
Conclusion Single-dose intravenous dexmedetomidine 0.25–0.5 μg/kg, administered 5 min after intrathecal injection of hyperbaric bupivacaine, improved the duration of spinal anesthesia without significant side effects. This method may be useful for increasing the duration of spinal anesthesia, even after intrathecal injection of local anesthetics.

Keywords Bupivacaine · Dexmedetomidine · Spinal anesthesia

S. H. Jung
Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul, South Korea

S. K. Lee (✉) · K. J. Lim · E. Y. Park · M. H. Kang · J. M. Lee · J. J. Lee · S. M. Hwang · S. J. Hong
Department of Anesthesiology and Pain Medicine, Hallym University Sacred Heart Hospital, 896, Pyeonchon-dong, Dongan-gu, Anyang 431-070, South Korea
e-mail: agnetask@yahoo.co.kr

Introduction

Hyperbaric bupivacaine is one of the most commonly used agents for spinal anesthesia. Addition of adjuncts, for example epinephrine and opioids, may enhance the quality and/or prolong the duration of spinal anesthesia.

Dexmedetomidine, a highly selective α2-adrenoceptor agonist, provides sedation, and analgesic or anesthetic-sparing effects with little respiratory depression [1, 2]. Dexmedetomidine added to intrathecal bupivacaine resulted in prolongation of the duration of spinal anesthesia [3]. When given intravenously before spinal anesthesia [4] or as a loading dose followed by continuous infusion during surgery [5, 6], it also lengthened the duration of spinal anesthesia.

It is recommended dexmedetomidine is given over 10 min, because rapid administration might produce tachycardia, bradycardia, and hypertension [7]. Side effects, for example hypotension and bradycardia, are dose-dependent and may occur in the postoperative period, because the drug can induce a long-lasting decrease in blood pressure [8]. We hypothesize that small, single-dose intravenous dexmedetomidine after intrathecal injection of hyperbaric

bupivacaine would enhance the quality of spinal anesthesia, for example prolongation of the duration of blockade, with minimal adverse effects.

The purpose of this study was to investigate the effects of small, single-dose intravenous dexmedetomidine administration 5 min after hyperbaric bupivacaine spinal anesthesia, and to find the effective dosage of dexmedetomidine necessary to prolong the duration of spinal anesthesia with minimum adverse effects.

Methods

This study protocol was approved by the Institutional Review Board of our hospital, and written informed consent was obtained from each patient. Sixty patients who were classified as American Society of Anesthesiologists physical status I or II, and undergoing lower extremity surgery of less than 2 h duration under spinal anesthesia were enrolled. Patients were excluded for any of the following reasons: coagulopathy or hypovolemia, pregnancy, obese patients (body mass index >30), height of patients >180 cm or <150 cm, patients with significant cardiovascular, pulmonary, hepatic, renal, neurological, or psychological disease, recent use of any analgesics, sedative drugs, or antidepressants, and history of alcohol abuse.

No premedication was administered. While in the operating room, all patients were monitored by standard limb lead electrocardiography, noninvasive blood pressure measurement, and pulse oximetry to measure peripheral oxygen saturation (SpO_2). Before spinal anesthesia, patients received 6 ml/kg intravenous lactated Ringer's solution or normal saline. Spinal anesthesia was performed with the patient in the lateral decubitus position, by use of a 25-gauge spinal needle inserted in the L3-4 or L4-5 intervertebral space in the midline. After successful puncture, 12 mg 0.5 % hyperbaric bupivacaine was injected and the patient was brought to the supine position. 5 min after intrathecal injection of bupivacaine, the study drugs were administered intravenously over 10 min as a single dose. The study drugs were prepared with a total volume of 10 ml in normal saline. Patients were randomly assigned to three groups by use of the sealed envelope method: patients in group 1 received normal saline only, patients in group 2 received dexmedetomidine (Precedex®; Hospira, Rocky Mount, NC, USA) 0.25 μg/kg in normal saline, and patients in group 3 received dexmedetomidine 0.5 μg/kg in normal saline.

Another investigator who did not know which intravenous drug was administered to the respective groups assessed the sensory level at the mid-clavicular line for each patient by a pinprick test using a blunt 25-gauge needle. The times required to reach loss of sensation at the T10–T12 dermatome (onset time) and the maximum dermatome level, at which sensation was lost, were recorded. The sensory blockade was assessed every minute until the T10–T12 dermatomal level was achieved, then 5, 10, 15, 20, and 30 min after intrathecal injection of bupivacaine, then every 15 min thereafter. The duration of sensory blockade was assessed by time for two-dermatome sensory regression (TDR) and recovery of L2 dermatome sensation (duration of sensory anesthesia, DSA). The duration of motor blockade (DMB) was assessed at 15-min intervals after the immediate end of surgery, by determining the time required to recover knee flexion 10 cm above the surface of the bed.

Vital signs were measured every 2 min for the first 10 min after intravenous injection of the study drug and then every 5 min during surgery. The degree of sedation was assessed by use of the Observer's Assessment Alertness/Sedation (OAA/S) scale [9]: 5, alert; 4, light sedation; 3, moderate sedation; 2, deep sedation; 1, deep sleep/unconscious.

Hypotension was defined as mean arterial pressure (MAP) <65 mmHg or less than 80 % of baseline, and was treated with incremental doses of intravenous ephedrine 5–10 mg. Heart rate <50 beats/min was defined as treatment-needed bradycardia and treated with 0.5 mg intravenous atropine. Hypotension, treatment-needed bradycardia, oxygen desaturation, and excessive sedation (OAA/S scale <3) were recorded.

The sample size was calculated by use of power analysis ($\alpha = 0.05$, $\beta = 0.8$) to detect an increase of 30 min in the two-dermatome sensory regression time with a standard deviation of 30 min, and was found to require at least 16 patients per group. The data obtained were expressed as mean ± standard deviation, median (range), or number of patients. Statistical analysis was performed by use of Student's t test, one-way analysis of variance (ANOVA), the Bonferroni test, the Kruskal–Wallis test, or the chi-squared test. Findings with an associated p value of <0.05 were regarded as statistically significant.

Results

Demographic data were similar among the three groups (Table 1). The spinal anesthesia onset time and the number of injections in each injection site were no different among the groups. The median of the maximum dermatome level of sensory block was T7.5, T6, and T6 in groups 1, 2, and 3, respectively (Table 2).

The median of TDR time was significantly prolonged in group 2 (105 min) and group 3 (120 min) compared with group 1 (75 min), but there was no statistically significant

Table 1 Demographic data

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)
Age (year)	43.2 ± 13.7	48.6 ± 12.3	42.6 ± 11.5
Sex (M/F)	12/8	11/9	12/8
Height (cm)	164.6 ± 7.9	164.4 ± 8.9	166.4 ± 7.7
Weight (kg)	65.1 ± 6.4	65.5 ± 9.7	67.3 ± 10.9
Duration of surgery (min)	69.3 ± 28.3	70.8 ± 27.4	69.8 ± 27.4

Values are expressed as mean ± SD or number of patients

Table 2 Onset time, injection site, and maximum sensory block level

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)
Onset time (min)	2.6 ± 1.1	2.5 ± 1.0	2.3 ± 0.7
Injection site (L3-4/L4-5)	2/18	2/18	1/19
Maximum level	T7.5 (T2–T11)	T6 (T2–T10)	T6 (T4–T12)

Values are expressed as mean ± SD, number of patients, or median (range)

Injection site, inthrathecal bupivacaine injection site; Maximum level, maximum sensory block level; T, thoracic dermatome

Table 3 Duration of spinal anesthesia (min)

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)
TDR	75 (45–120)	105 (75–150)[a]	120 (75–150)[a]
DMB	135 (60–180)	150 (90–210)	165 (90–240)[a]
DSA	165 (90–210)	195 (120–240)	210 (120–270)[a]

Values are expressed as median (range)

TDR, time for two-dermatome sensory regression; DMB, time for recovery of knee flexion; DSA, time for recovery of L2 dermatomal sensation

[a] $P < 0.05$ compared with group 1

difference between groups 2 and 3. DMB was significantly prolonged in group 3 (165 min) compared with group 1 (135 min), but the differences between groups 1 and 2 (150 min) and between groups 2 and 3 were not significant. DSA was significantly prolonged in group 3 (210 min) compared with group 1 (165 min), but the differences between groups 1 and 2 (195 min) and between groups 2 and 3 were not significant (Table 3).

There was no statistically significant difference in the MAP and the SpO_2 among the three groups. Reduction of the heart rate was significant in group 3 at 20, 45, and 60 min compared with group 1 (Table 4). However, there were no differences in the incidence of hypotension and treatment-needed bradycardia among the three groups

Table 4 Heart rate after administration of dexmedetomidine or normal saline

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)
T0	79.3 ± 14.0	73.5 ± 9.3	80.0 ± 13.4
T2	75.4 ± 13.7	72.9 ± 9.1	76.8 ± 14.5
T5	76.9 ± 15.0	73.0 ± 12.9	74.0 ± 14.3
T10	71.3 ± 14.1	68.6 ± 11.2	69.8 ± 15.7
T15	69.8 ± 13.1	67.1 ± 11.0	64.9 ± 13.5
T20	67.9 ± 13.1	64.7 ± 8.1	59.9 ± 10.7[a]
T30	66.1 ± 12.0	63.1 ± 9.7	60.6 ± 11.3
T45	66.4 ± 12.6	60.1 ± 9.5	59.0 ± 8.3[a]
T60	64.8 ± 9.9	62.0 ± 7.9	58.5 ± 7.3[a]
T90	63.5 ± 10.5	62.6 ± 6.4	59.3 ± 6.9

Values are expressed as mean ± SD

T, time (min) after start of dexmedetomidine or normal saline

[a] $P < 0.05$ compared with group 1

Table 5 Adverse events

	Group 1 ($n = 20$)	Group 2 ($n = 20$)	Group 3 ($n = 20$)
Hypotension	3	3	3
Treatment-needed bradycardia	2	3	5

Values are expressed as number of patients

Treatment-needed bradycardia, heart rate <50 beats/min

(Table 5). There was no patient with excessive sedation throughout the procedure in any group.

Discussion

This study proved intravenous administration of 0.25–0.5 μg/kg dexmedetomidine 5 min after intrathecal injection of hyperbaric bupivacaine was effective in increasing the duration of spinal anesthesia. The incidence of adverse events, for example hypotension or treatment-needed bradycardia, did not differ from those of the control group.

It has been reported that intrathecal clonidine and dexmedetomidine result in bupivacaine spinal anesthesia of increased duration without significant adverse effects [3, 10]. It also has been reported that intravenous dexmedetomidine prolongs the duration of regional anesthesia. Intravenous dexmedetomidine 0.5 μg/kg given as premedication prolonged the duration of sensory blockade of bupivacaine-induced spinal anesthesia, and provided sedation and additional analgesia [4]. Intravenous administration of dexmedetomidine as a loading dose followed by maintenance dose until the end of surgery increased the

duration of epidural anesthesia [11] and spinal anesthesia, while providing a competent sedative effect and hemodynamic stability [5].

However, dexmedetomidine causes dose-dependent decreases in blood pressure, heart rate, and plasma catecholamine concentrations [8, 12], and higher concentrations can result in systemic and pulmonary hypertension [13]. These cardiovascular effects might limit the usefulness of dexmedetomidine for a less healthy patient population. After ropivacaine spinal anesthesia, intravenous dexmedetomidine infusion with a loading dose followed by maintenance for 50 min prolonged the duration of sensorial and motor blockade, and provided sufficient sedation. However, the incidence of bradycardia was found to be 30 %, whereas bradycardia was not observed in the control group [6].

Dexmedetomidine as a loading dose was better if given over 10 min [7], and sometimes it was administered without a loading dose [13]. It is necessary to monitor blood pressure even after discontinuation of dexmedetomidine because its infusion for only 2 min induced a long-lasting decrease in mean arterial blood pressure in healthy volunteers, with a maximum decrease of 14–27 % 60 min after discontinuation of the drug, for the dose of 0.25–2.0 μg/kg [8]. Intravenous dexmedetomidine can enhance decreases in blood pressure and heart rate accompanied by spinal anesthesia. In addition, when given intravenously, an analgesic ceiling effect of the drug was apparent at a dose of 0.5 μg/kg [14].

On the basis of these findings we investigated the effect of administration of small, single-dose intravenous dexmedetomidine (0.25 and 0.5 μg/kg) on spinal anesthesia by administering dexmedetomidine 5 min after intrathecal injection of bupivacaine, and found that the duration of spinal anesthesia was prolonged. This method may be useful to increase the duration of spinal anesthesia even after administration of intrathecal local anesthetics. These doses of dexmedetomidine did not provide sufficient sedation, and hemodynamic stability was maintained after administration of dexmedetomidine.

Although the precise mechanism is unknown, it has been suggested that dexmedetomidine provides anesthesia and analgesic action through supraspinal, spinal, and peripheral action; among these, the supraspinal action could explain the prolongation of spinal anesthesia after intravenous administration [13–15]. The mechanism for prolongation of motor block by dexmedetomidine is also uncertain. Possible mechanisms include a synergistic interaction of two drugs from different classes [16] or activation of descending noradrenaline neurons facilitating the motor component of the spinal reflexes [17].

A limitation of this study is that we investigated the effects of dexmedetomidine on spinal anesthesia with only two small doses, 0.25 or 0.5 μg/kg. Therefore, it is difficult to discuss the dose–response relationship for the dose of dexmedetomidine and the duration of spinal anesthesia. However, dexmedetomidine added to ropivacaine increases the duration of sciatic nerve sensory blockade in a dose-dependent fashion in rats [18]. Further studies are required to determine the dose–response relationship.

In conclusion, small, single-dose intravenous administration of dexmedetomidine 5 min after hyperbaric bupivacaine spinal anesthesia prolonged the duration of spinal anesthesia without significant adverse effects. This method can be useful in increasing the duration of spinal anesthesia, even after intrathecal injection of local anesthetics.

References

1. Johnson JO, Grecu L, Lawson NW. Antonomic nervous system. In: Barash PG, Cullen BF, Stoelting RK, Cahalan MK, Stock MC, editors. Clinical anesthesia. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 355.
2. Basar N, Akpinar S, Doganci N. Buyukkocak U, Kaymak C, Sert O, Apan A. The effects of preanesthetic, single-dose dexmedetomidine on induction, hemodynamic, and cardiovascular parameters. J Clin Anesth. 2008;20:431–6.
3. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, Bulbul M, Baraka AS. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anaesthesiol Scand. 2006;50:222–7.
4. Kaya FN, Yavascaoglu B, Turker G, Yildirim A, Gurbet A, Mogol EB, Ozcan B. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. Can J Anaesth. 2010;57:39–45.
5. Al-Mustafa MM, Badran IZ, Abu-Ali HM, Al-Barazangi BA, Massad IM, Al-Ghanem SM. Intravenous dexmedetomidine prolongs bupivacaine spinal analgesia. Middle East J Anesthesiol. 2009;20:225–31.
6. Elcicek K, Tekin M, Kati I. The effects of intravenous dexmedetomidine on spinal hyperbaric ropivacaine anesthesia. J Anesth. 2010;24:544–8.
7. Grant SA, Breslin DS, Macleod DB, Gleason D, Martin G. Dexmedetomidine infusion for sedation during fiberoptic intubation: a report of three cases. J Clin Anesth. 2004;16:124–6.
8. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology. 1992;77:1134–42.
9. Chernik DA, Gilling D, Laine H, Hendler J, Siler JM, Davidson AB, Schwam EM, Siegel JL. Validity and reliability of the Observer's Assessment of Alertness/Sedation scale: study with intravenous midazolam. J Clin Psychopharmacol. 1990;10(244–51):126.
10. Kaabachi O, Zarghouni A, Ouezini R, Abdelaziz AB, Chattaoui O, Kokki H. Clonidine 1 microg/kg is a safe and effective adjuvant to plain bupivacaine in spinal anesthesia in adolescents. Anesth Analg. 2007;105:516–9.
11. Coskuner I, Tekin M, Kati I, Yagmur C, Elcicek K. Effects of dexmedetomidine on the duration of anaesthesia and wakefulness in bupivacaine epidural block. Eur J Anaesthesiol. 2007;24:535–40.
12. Kallio A, Scheinin M, Koulu M, Ponkilainen R, Ruskoaho H, Viinamäki O, Scheinin H. Effects of dexmedetomidine, a

selective alpha 2-adrenoceptor agonist, on hemodynamic control mechanisms. Clin Pharmacol Ther. 1989;46:33–42.
13. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology. 2000;93:382–94.
14. Jaakola ML, Salonen M, Lehtinen R, Scheinin H. The analgesia action of dexmedetomidine -a novel alpha 2-adrenoceptor agonist-in healthy volunteer. Pain. 1991;46:281–5.
15. Jorm CM, Stamford JA. Actions of the hypnotic anaesthetic, dexmedetomidine, on noradrenaline release and cell firing in rat locus coeruleus slices. Br J Anaesth. 1993;71:447–9.
16. Calasans-Maia JA, Zapata-Sudo G, Sudo RT. Dexmedetomidine prolongs spinal anaesthesia induced by levobupivacaine 0.5% in guinea-pigs. J Pharm Pharmacol. 2005;57:1415–20.
17. Strahlendorf JC, Strahlendorf HK, Kingsley RE, Gintautas J, Barnes CD. Facilitation of lumbar monosynaptic reflexes by locus coeruleus stimulation. Neuropharmacology. 1980;19:225–300.
18. Brummett CM, Padda AK, Amodeo FS, Welch KB, Lydic R. Perineural dexmedetomidine added to ropivacaine causes a dose-dependent increase in the duration of thermal antinociception in sciatic nerve block in rat. Anesthesiology. 2009;111:1111–9.