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ORIGINAL ARTICLE

Epinephrine decreases the dose of hyperbaric bupivacaine necessary for tourniquet pain blockade during spinal anesthesia for total knee replacement arthroplasty

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Abstract
Purpose We quantified the dose-sparing effect of epinephrine by comparing the median effective dose (ED_{50}) of intrathecal hyperbaric bupivacaine co-administered with epinephrine with the ED_{50} of intrathecal hyperbaric bupivacaine alone.
Methods Three groups were randomly generated from 162 patients undergoing total knee replacement arthroplasty under combined spinal and epidural anesthesia: Group B (bupivacaine), Group BE1 (bupivacaine plus epinephrine 100 μg), and Group BE2 (bupivacaine plus epinephrine 200 μg). Each group was further divided by bupivacaine doses of 6, 7, 8, 9, 10, or 11 mg. The anesthesia was defined as successful if a bilateral T12 sensory block occurred within 15 min, and no intraoperative epidural supplement was required. The ED_{50} and ED_{95} for successful anesthesia and successful tourniquet pain blockade were determined separately by probit regression analysis.
Results The ED_{50} and ED_{95} of intrathecal hyperbaric bupivacaine for successful anesthesia were not different among the groups: the ED_{50} values were 7.1 mg [95 % confidence interval (95 % CI) 6.0–8.0 mg] in Group B, 6.2 mg (95 % CI 4.8–7.2 mg) in Group BE1, and 6.3 mg (95 % CI 4.9–7.2 mg) in Group BE2. However, the ED_{50} and ED_{95} values for tourniquet pain control were significantly smaller in Groups BE1 and BE2 than in Group B: the ED_{50} values were 7.2 mg (95 % CI 6.3–7.9 mg), 5.5 mg (95 % CI 4.1–6.3 mg), and 5.3 mg (95 % CI 3.7–6.2 mg) in Groups B, BE1, and BE2, respectively. The incidence of tourniquet pain was significantly lower in Groups BE1 and BE2 than in Group B. The time to patients' requests for supplemental analgesia was significantly longer in Groups BE1 and BE2 than in Group B.
Conclusions Intrathecal epinephrine did not decrease the dose of intrathecal hyperbaric bupivacaine required for successful anesthesia. However, it reduced the dose required for tourniquet pain blockade.

Keywords Intrathecal epinephrine · Hyperbaric bupivacaine · Spinal anesthesia · Dose-sparing effect · ED_{50}

Introduction

For many years, the addition of epinephrine to local anesthetic solutions was assumed to prolong spinal nerve block through vasoconstriction, which decreases vascular absorption and prolongs drug contact with the nervous system [1]. However, it has been demonstrated that subarachnoid epinephrine, injected alone or in combination with lidocaine, does not constrict the vessels supplying the lumbar region of the spinal cord or decrease vascular uptake [2–7]. Rather, intrathecal epinephrine was demonstrated to have direct antinociceptive activity [8, 9]. Clinically, epinephrine has been reported to prolong the duration of spinal block or labor analgesia and to increase the quality of anesthesia [10–18]. However, other studies have shown that epinephrine has no effect of prolongation on spinal anesthesia or labor analgesia [19–22]. Furthermore, it has not been fully elucidated whether the addition

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of epinephrine can reduce the local anesthetic dose, and to our knowledge, the dose-sparing effect of epinephrine on spinal bupivacaine has never been quantified by dose–response curve analysis.

Therefore, we conducted a prospective, double-blind, dose–response study to: (1) determine the median effective dose (ED_{50}) and ED_{95} of intrathecal hyperbaric bupivacaine alone, and the ED_{50} and ED_{95} of intrathecal hyperbaric bupivacaine co-administered with epinephrine; and (2) compare anesthetic duration and quality between bupivacaine alone and co-administration of bupivacaine with epinephrine in patients undergoing total knee replacement arthroplasty (TKRA) under combined spinal and epidural anesthesia (CSEA).

Subjects, materials, and methods

This study was approved by the Institutional Review Board of our institution and all patients provided written informed consent. Patients with American Society of Anesthesiologists (ASA) physical status classification I–III, scheduled for TKRA surgery under CSEA during the period between December 2009 and January 2011 were enrolled in this prospective, randomized, double-blind study. Patients with previous spine surgery, diabetes or other neuropathies, skin infection at the site of injection, allergy to bupivacaine, or other common contraindications for spinal anesthesia were excluded. Patients shorter than 140 cm or taller than 160 cm, or those with a body mass index (BMI) of less than 20 or greater than 35 were also excluded. Using the computer program http://www.randomizer.org, patients were randomized into three groups: Group B ($n = 54$), Group BE1 ($n = 54$), and Group BE2 ($n = 54$); then into subgroups of bupivacaine doses of 6, 7, 8, 9, 10, or 11 mg ($n = 9$ for each subgroup). Thus, 18 study groups were defined (B6-11; B6-11E1; and B6-11E2).

No patients received premedication. Standard monitoring was applied, including continuous pulse oximetry and electrocardiogram. Non-invasive blood pressure was measured at 2-min intervals for 20 min from the start of anesthesia, and at 5-min intervals until the end of surgery. All patients were rapidly administered 8 ml/kg of lactated Ringer's solution in the first 10 min of spinal anesthesia, followed by 4 ml/kg/h of a maintenance dose and 8 ml/kg of Voluven® (Fresenius Kabi, Bad Homburg, Germany) at 4 ml/kg/h during surgery. Oxygen was given at 5 l/min via facial mask during surgery. No urinary catheter was inserted initially. CSEA, using a double-space technique, was performed with the patients in the sitting position. An 18-G Tuohy needle (Perican®; B. Braun, Melsungen, Germany) was inserted into the epidural space by loss of resistance to air at the $L_{3–4}$ interspace, and an epidural catheter (Perifix®; B. Braun) was threaded 2–3 cm into the epidural space. The catheter was gently aspirated and checked for blood or cerebrospinal fluid. No local anesthetic test dose was administered. Spinal puncture was performed at the $L_{4–5}$ interspace using a 25-G pencil-point Whitacre spinal needle (Kimberly-Clarke, Roswell, GA, USA). After the free flow of cerebrospinal fluid was confirmed, freshly prepared anesthetic solutions were injected over a period of 20 s. The needle bevel was headed cephalad during injection. Patients in Group B received only bupivacaine (Marcaine Spinal®; AstraZeneca, Sodertalje, Sweden), at doses of 6, 7, 8, 9, 10, or 11 mg ($n = 9$ for each dose). Patients in Group BE1 received these 6 different doses of bupivacaine with 100 μg epinephrine, and those in Group BE2 received the 6 different doses of bupivacaine with 200 μg epinephrine. Patients were placed in the supine position immediately after the spinal injection. Once the intrathecal injection was completed, another anesthesiologist, blind to the bupivacaine dosage, entered the operating room to manage the patient and record data. Patients were treated by an unchanging group of surgeons, using identical surgical techniques.

The endpoint of the success or failure of the spinal anesthesia was defined according to a previous study, with modification [23]. Successful induction, which was defined differently from successful anesthesia, was defined as a bilateral T12 sensory level with a sensory anesthesia scale greater than 2 (perception of a pinprick as touch but not sharp) 15 min after the intrathecal drug administration [24]. Successful anesthesia was defined as successful induction with no additional epidural anesthetics required during surgery. Failed anesthesia was recorded when induction failed or supplemental epidural analgesia was required to complete surgery because either a patient reported a score on the verbal rating scale of pain (VRS) of ≥ 2, where 0 represented "no pain" and 10 represented "worst pain imaginable" or a patient requested additional analgesia, despite initial attainment of the T12 sensory level. Successful tourniquet pain blockade was defined as no tourniquet pain reported by the patient during the tourniquet time. Subjects with failed induction were included in the calculation of the ED_{50} but excluded from further measurements of time to first request for supplemental analgesia and time to self-voiding. Those subjects who underwent urinary catheterization after surgery were excluded from the measurement of time to first self-voiding. Successful anesthesia or tourniquet pain blockade was considered as a final endpoint for calculating the ED_{50} of spinal bupivacaine. In cases of failed induction, anesthesia, or tourniquet pain blockade, supplemental epidural anesthesia with 2 % lidocaine plus 1:200,000 epinephrine was administered through the epidural catheter incrementally (5 ml each time) at 10-min intervals.

Sensory level to pinprick was assessed by the following scale: 0 = ability to appreciate a pinprick as sharp; 1 = perception of a pinprick as less sharp than in unblocked areas; 2 = perception of a pinprick as touch but not sharp (analgesia); or 3 = inability to feel a pinprick (anesthesia) [24]. Surgery was allowed to start when the patient showed a grade greater than 2 at or above T12. Sensory changes were recorded bilaterally along the midclavicular line by assessing changes in pinprick sensation using a 25-G needle. Time to highest level of block (min) was recorded from the above measurements.

Motor block in the lower limbs was graded according to the Bromage scale: 0 = able to lift extended knee at hip; 1 = able to flex knee but not lift extended leg; 2 = able to flex toes only; or 3 = unable to move hip, knees, or toes [25]. Sensory and motor block assessments were made for the first 2, 5, 10, 15, 20, and 30 min after spinal injection.

In all patients, the time to first request for supplemental analgesia was measured. For cases defined as successful anesthesia, patient-controlled epidural analgesia was not started until patients requested supplemental analgesia. During surgery, a patient complaint of tourniquet pain was recorded with onset time and VRS score. Tourniquet pain was not considered as anesthesia failure.

Hypotension was defined as a decrease in systolic blood pressure of more than 20 % relative to baseline or a mean blood pressure of <55 mmHg. When hypotension occurred, the patient was administered repeated intravenous ephedrine bolus doses of 5 mg. Bradycardia was defined as a heart rate of <60 beats/min, and atropine 0.5 mg was administered to treat bradycardia. Events of nausea and vomiting were recorded to obtain incidence.

Using a Cochrane–Armitage test for trend in proportions, a sample size of nine patients per group was obtained based on six groups with bupivacaine doses of 6, 7, 8, 9, 10, or 11 mg and proportions of success equal to 0.5, 0.6, 0.7, 0.8, 0.9, and 0.99. Our calculation indicated that a total sample size of 54 subjects would give 85 % power to detect a linear trend, using a two-sided Z test with continuity correction and a significance level of 0.05 (PASS® 11.0.2; NCSS, LCC, Kaysville, UT, USA) [26]. Comparison between the ED_{50} of bupivacaine alone and those of bupivacaine with two doses of epinephrine required a total of 162 subjects.

SPSS software (version 12.0; SPSS, Chicago, IL, USA) was used for statistical analysis. Data were analyzed using one-way analysis of variance or the Kruskal–Wallis test with a post-hoc test according to the normality of data. Fisher's exact test or the χ^2 test was used for incidence data. A value of $p < 0.05$ was considered statistically significant. Probit regression analysis, based on the success of anesthesia or tourniquet pain blockade for each patient, was performed to obtain the ED_{50} and ED_{95} values of bupivacaine, using SPSS software. A dose–response curve was drawn using the Calcusyn 2.1 program (BIOSOFT, Cambridge, UK). The ED_{50} and ED_{95} values of the groups were compared using the ED_{50} ratio test [27].

Results

All one hundred and sixty-two patients enrolled completed the study according to the protocol and were included in the analysis. Demographic and perioperative data were similar in all groups (Table 1).

There was no case of induction failure even at the low dose range. The ED_{50} and ED_{95} values are shown in Table 2. There were no differences in the ED_{50} and ED_{95} values of successful anesthesia among the groups. However, the ED_{50} and ED_{95} values for tourniquet pain blockade in Groups BE1 and BE2 were significantly smaller than those in Group B. Post-hoc analysis revealed that there was no significant difference between Groups BE1 and BE2.

Logistic plots were drawn for the probability of anesthetic success (Fig. 1) and the probability of tourniquet pain blockade (Fig. 2) for all groups. The incidence of tourniquet pain was also significantly lower in Groups BE1 and BE2 than in Group B ($n = 16$, 29.6 % for Group B, $n = 6$, 11.1 % for Group BE1 vs. $n = 5$, 9.3 % for Group BE2, $p = 0.030$, Table 2). Post-hoc analysis revealed that there was no significant difference between Groups BE1 and BE2.

The characteristics of the spinal anesthesia are shown in Table 3. In Groups BE1 and BE2, 12 patients felt pain (VRS ≥2) at various times during the surgery and received an epidural top-up, and 17 patients in Group B felt pain (VRS ≥2) during surgery and received an epidural top-up ($p = 0.486$). The overall time to patient's first request for supplemental analgesia was significantly different among the three groups (160.7 ± 43.7 min for Group B vs. 176.5 ± 36.5 min for Group BE1 vs. 179.3 ± 39.6 min for Group BE2, $p = 0.036$). Post-hoc analysis revealed that this time was significantly longer in Groups BE1 and BE2 than in Group B ($p = 0.044$ and $p = 0.040$, respectively), but there was no difference between Groups BE1 and BE2. Time to the first request for supplemental analgesia according to each dose subgroup is presented in Fig. 3. The duration of analgesia was significantly longer in Group BE2 than in Group B in the dose subgroups of 7, 8, and 10 mg ($p = 0.031$, 0.046, and 0.018, respectively). The duration was also significantly longer in Group BE1 than in Group B in the dose subgroups of 9 and 10 mg ($p = 0.048$ and 0.045, respectively). There was no difference in the duration of analgesia in each subgroup between Groups BE1 and BE2. The peak level of the sensory block and the

Table 1 Patient characteristics and perioperative values

	Group B ($n = 54$)	Group BE1 ($n = 54$)	Group BE2 ($n = 54$)	p value
Age (years)	67.4 ± 9.5	68.8 ± 7.4	69.3 ± 7.7	0.773
Height (cm)	152.3 ± 7.9	152.2 ± 5.3	152.1 ± 8.7	0.625
Weight (kg)	62.5 ± 11.5	64.1 ± 8.9	63.3 ± 11.9	0.405
Gender (male/female; *n*)	6/48	6/48	11/43	0.327
ASA PS (I/II/III; *n*)	11/33/10	8/36/10	12/34/8	0.883
Poorly controlled hypertension	5	6	2	0.439
Stable angina	2	1	1	0.999
Chronic obstructive lung disease	2	3	4	0.910
Renal failure on dialysis	1	0	1	0.999
Duration of surgery (min)	107.0 ± 12.4	108.2 ± 13.3	107.2 ± 10.1	0.959
Duration of tourniquet time (min)	95.9 ± 13.1	97.1 ± 13.7	92.8 ± 13.5	0.226

Values are means ± SD, or the numbers of patients per category

ASA PS American Society of Anesthesiologists physical status, *B* varying dose (6, 7, 8, 9, 10, or 11 mg) of intrathecal bupivacaine only, *BE1* varying dose of bupivacaine with 100 μg of epinephrine, *BE2* varying dose of bupivacaine with 200 μg of epinephrine

Table 2 ED_{50} and ED_{95} values for successful anesthesia and successful tourniquet pain blockade

	Group B	Group BE1	Group BE2
ED_{50} for successful anesthesia	7.1 mg (6.0–8.0)	6.2 mg (4.8–7.2)	6.3 mg (4.9–7.2)
ED_{95} for successful anesthesia	10.9 mg (9.8–12.8)	10.0 mg (8.9–11.8)	10.0 mg (9.0–11.8)
ED_{50} for successful tourniquet pain blockade	7.2 mg (6.3–7.9)	5.5 mg (4.1–6.3)[a]	5.3 mg (3.7–6.2)[a]
ED_{95} for successful tourniquet pain blockade	9.9 mg (9.0–11.5)	8.2 mg (7.2–9.5)[a]	7.9 mg (7.0–9.3)[a]

Numbers in parenthesis are 95 % confidence intervals of each ED_{50} and ED_{95} value

B varying dose (6, 7, 8, 9, 10, or 11 mg) of intrathecal bupivacaine only, *BE1* varying dose of bupivacaine with 100 μg of epinephrine, *BE2* varying dose of bupivacaine with 200 μg of epinephrine, ED_{50} median effective dose, ED_{95} 95 % effective dose

[a] Different from Group B

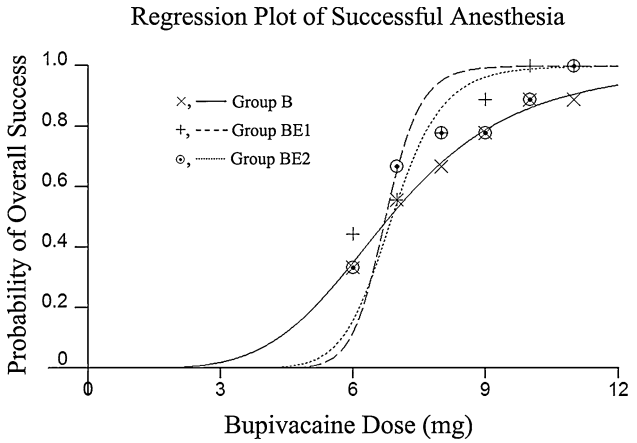

Fig. 1 Regression plot of the probability of success of spinal anesthesia as a function of the dose of bupivacaine (*Group B*), bupivacaine with epinephrine 100 μg (*Group BE1*), or bupivacaine with epinephrine 200 μg (*Group BE2*). *X* axis, intrathecal dose of 0.5 % hyperbaric bupivacaine; *Y* axis, probability of overall success. Successful spinal anesthesia was defined as a bilateral T12 sensory block to pinprick within 15 min of intrathecal drug administration with no additional epidural anesthetic during surgery

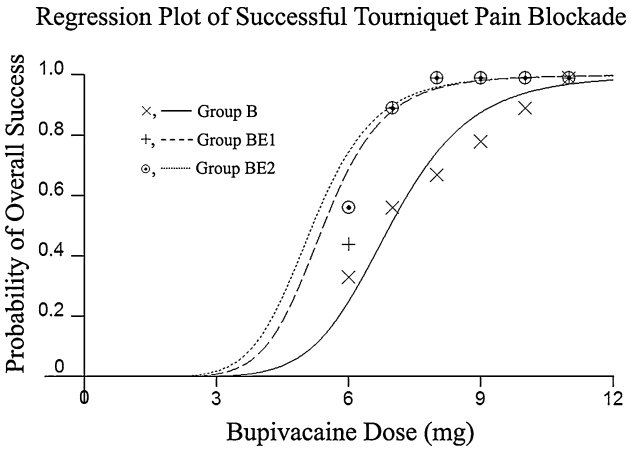

Fig. 2 Regression plot of the probability of success of tourniquet pain blockade as a function of the dose of bupivacaine (*Group B*), bupivacaine with epinephrine 100 μg (*Group BE1*), or bupivacaine with epinephrine 200 μg (*Group BE2*). *X* axis, intrathecal dose of 0.5 % hyperbaric bupivacaine; *Y* axis, probability of success of tourniquet pain blockade. Successful tourniquet pain blockade was defined as no tourniquet pain reported by the patient during the tourniquet time

Table 3 Characteristics of spinal anesthesia

	Group B ($n = 54$)	Group BE1 ($n = 54$)	Group BE2 ($n = 54$)	p value
Total numbers of successful cases/failures (n/n)	37/17	42/12	42/12	0.486
Quality of anesthesia (excellent/good/poor)	30/7/17	29/13/12	32/10/12	0.553
Peak level of sensory block	T10 (T4–T12)	T10 (T4–T12)	T10 (T4–T12)	0.685
Time to peak sensory block (min)	13.0 ± 3.2	12.9 ± 2.5	12.1 ± 2.5	0.189
Maximum Bromage scale 0–1–2–3 (n)	2–15–29–8	1–9–30–14	1–11–25–17	0.400
Time to the patient's first request for supplemental analgesia (min)	160.7 ± 43.7	176.5 ± 36.5[b]	179.3 ± 39.6[b]	0.036[a]
Incidence of tourniquet pain (n, %)	16 (29.6 %)	6 (11.1 %)[b]	5 (9.3 %)[b]	0.030[a]
Time to first self-voiding in successful cases (min)	334.9 ± 37.8	333.8 ± 33.8	339.1 ± 31.7	0.799

Values are means ± SD (ranges), or the numbers of patients per category

B varying dose (6, 7, 8, 9, 10, or 11 mg) of intrathecal bupivacaine only, *BE1* varying dose of bupivacaine with 100 μg of epinephrine, *BE2* varying dose of bupivacaine with 200 μg of epinephrine

[a] Different among the three groups

[b] Different from Group B by post-hoc analysis

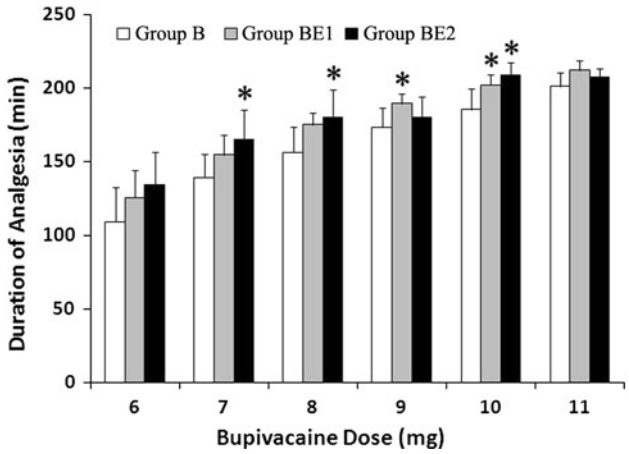

Fig. 3 Times to the first request for supplemental analgesia at different doses of hyperbaric bupivacaine in all dose subgroups. *White* bupivacaine only (Group B); *Gray* bupivacaine with epinephrine 100 μg (Group BE1); *black* bupivacaine with epinephrine 200 μg (Group BE2). *$p < 0.05$ compared with Group B

time to peak level were similar in all groups. Motor block intensity was not different among groups. The time to first self-voiding in successful anesthesia cases was not different among Groups B, BE1, and BE2. No significant differences among Groups B, BE1, and BE2 were observed in the total dose of ephedrine or in the incidence of hypotension, bradycardia, nausea, vomiting, shivering, or pruritus (Table 4).

Discussion

In this prospective, double-blind, randomized study, we compared the ED_{50} and ED_{95} values of intrathecal hyperbaric bupivacaine without epinephrine or co-administered with 100 or 200 μg of epinephrine using probit regression analysis. This is the first study to have proven the tourniquet pain blockade effect of epinephrine quantitatively by dose–response study. There was no significant difference in the ED_{50} and ED_{95} values for successful anesthesia between the group with bupivacaine alone and the groups with different doses of epinephrine added, although the

Table 4 Frequency of adverse events

	Group B ($n = 54$)	Group BE1 ($n = 54$)	Group BE2 ($n = 54$)	p value
Incidence of hypotension (n, %)	6 (11.1 %)	3 (5.6 %)	5 (9.3 %)	0.688
Total dose of ephedrine (mg)	8.5 ± 4.4	6.0 ± 1.7	6.8 ± 1.6	0.509
Lowest MBP (mmHg)	64.2 ± 8.7	64.1 ± 7.7	64.4 ± 8.8	0.991
Incidence of bradycardia (n, %)	6 (11.1 %)	8 (14.8 %)	10 (18.5 %)	0.600
Incidence of nausea (n, %)	8 (14.8 %)	6 (11.1 %)	7 (13.0 %)	0.956
Incidence of vomiting (n, %)	3 (5.6 %)	4 (7.4 %)	2 (3.7 %)	0.910
Incidence of shivering (n, %)	10 (18.5 %)	9 (16.7 %)	7 (13.0 %)	0.801
Incidence of pruritus (n, %)	0 (0 %)	0 (0 %)	0 (0 %)	–

Values are means ± SD, or the numbers of patients per category

MBP mean blood pressure, *B* varying dose (6, 7, 8, 9, 10, or 11 mg) of intrathecal bupivacaine only, *BE1* varying dose of bupivacaine with 100 μg of epinephrine, *BE2* varying dose of bupivacaine with 200 μg of epinephrine

duration of analgesia was significantly longer in Groups BE1 and BE2 than in Group B. However, the ED_{50} and ED_{95} values for blocking tourniquet pain were significantly smaller in Groups BE1 and BE2 than in Group B, and the incidence of tourniquet pain was significantly lower in Groups BE1 and BE2 than in Group B.

Previous studies have reported that intrathecal epinephrine has a dose-sparing effect in spinal anesthesia or labor analgesia [10–18] which was proven by prolonging the duration of analgesia. However, none of these studies quantified the sparing effect of intrathecal epinephrine by determining the ED_{50} and ED_{95} values for successful anesthesia or for blocking tourniquet pain. The present study showed that the addition of epinephrine 100 or 200 μg did not decrease the ED_{50} and ED_{95} values of intrathecal bupivacaine for successful anesthesia, even though the duration of analgesia measured by time to the patient's first request for supplemental analgesia was significantly prolonged. However, the incidence of tourniquet pain was significantly lower with the addition of epinephrine, and both the ED_{50} and ED_{95} for blocking tourniquet pain was significantly reduced with this addition. As the successful anesthesia is more important than the duration of analgesia alone, it would be more reasonable to judge the dose-sparing effect of epinephrine by comparing the ED_{50} and ED_{95} values for successful anesthesia than by comparing the duration of analgesia.

The results on prolongation of analgesia by epinephrine in the previous studies are conflicting. Some studies have supported the prolongation of the analgesia [10–18], but others have dismissed it [19–22]. Our results are in line with the prolongation of the duration of analgesia by epinephrine. The mechanism of this prolongation is though to be via the direct suppression of wide dynamic range (WDR) neuron activity in the dorsal horn of the spinal cord and via a direct agonistic effect on alpha 2 adrenergic receptor of epinephrine [8, 9, 28]. Previously, epinephrine was assumed to prolong spinal nerve block through vasoconstriction [1], but subarachnoid epinephrine was demonstrated not to constrict spinal cord vessels or decrease the vascular uptake of local anesthetics [2–7].

We found that patients in Groups BE1 or BE2 had a lower incidence of tourniquet pain and lower ED_{50} and ED_{95} values for tourniquet pain blockade than those in Group B; this finding was in accordance with a previous study [13], which showed a lower tourniquet pain score with the addition of epinephrine. Even when the sensory block is adequate, some patients still experience tourniquet pain during spinal or epidural anesthesia [29, 30]. This type of pain is thought to be mediated by C fibers [31, 32], while the sensations of pinprick, touch, and cold are mediated through Aδ and C fibers [33]. Gissen et al. [34] demonstrated the differential sensitivity of nerve fibers to lidocaine by showing that C fibers and Aβ fibers were more resistant to lidocaine-induced conduction block than Aδ fibers. This means that C fiber-mediated tourniquet pain may still occur when Aδ fibers are blocked. However, this problem seems to be overcome by combining epinephrine with bupivacaine. As previously mentioned, epinephrine has a direct antinociceptive effect [8, 9, 28]. But this effect of epinephrine was not present in a dose-dependent manner in the present study.

In regard to the doses of epinephrine, Chambers et al. [16] compared the effect of three different doses (100, 200, 300 μg) of epinephrine added to 1.5 ml of 5 % lidocaine in 7.5 % dextrose for spinal anesthesia. A significant difference in the time to the recovery from sensory anesthesia was seen between groups with and without epinephrine. However, no difference was seen between the three doses of epinephrine. Gurbet et al. [10] compared four doses (12.5, 25, 50, and 100 μg) of spinal epinephrine added to 0.5 % hypobaric bupivacaine 2.5 mg with fentanyl 25 μg for labor analgesia and found that the addition of epinephrine 12.5 μg prolonged analgesia, with no advantages for higher doses. Collins et al. [8] conducted a study in a spinal cord-transected cat, and found that 50 and 100 μg intrathecal epinephrine suppressed noxiously evoked activity in a dose-dependent manner in WDR neurons in the dorsal horn of the spinal cord. In the present study, we could not see any difference in the duration of analgesia between the two different doses of epinephrine used.

We found no differences between our groups in time to peak sensory block, in contrast to the findings of Leight and Carlson [15], but our results were similar to the results of other studies [17, 21], which also found no reduction in the time of onset. The highest level of sensory block was not different among groups in our study, in accordance with previous studies. Different methodologies used in the studies, such as sensory block assessment, might have led to different results among the studies, but epinephrine does not seem to induce a more cephalad spread of hyperbaric bupivacaine. No difference was seen among our groups in the incidence of complications, in accordance with previous findings [18].

There are several limitations of this study. First, we used a double-space technique in CSEA, in which first a loss of resistance is performed at a higher level, to be followed by spinal anesthesia at a lower level. The dura would be pushed forward and the spread of the anesthetics might be impaired owing to the injection of air at a higher level, and this could influence the estimation of ED_{50} and ED_{95}. A single-space technique might have reduced this effect. Second, we used CSEA instead of single-shot spinal anesthesia. It is possible that the attending anesthesiologist tends to administer an epidural rescue dose at a lower degree of patient discomfort under CSEA than under spinal

anesthesia, and would then regard such a case as a failure. Therefore, the estimated ED_{50} and ED_{95} values under CSEA may have been higher than those under spinal anesthesia. Third, we did not investigate the effect of a full range of intrathecal epinephrine doses. In this study, we only used 100 and 200 μg of epinephrine, which were the most common doses of epinephrine used in previous studies [10, 11, 14, 16–19, 21, 22, 24]. Although further advantages may occur with doses higher than 200 μg, the present study could represent contemporary practice. Further studies with various doses are required to find the ideal dose of intrathecal epinephrine.

In conclusion, in the present study we shed some light on the old controversy regarding epinephrine's dose-sparing effect by showing that the ED_{50} and ED_{95} values of bupivacaine for successful anesthesia were not decreased by the addition of epinephrine. However, the duration of analgesia, defined as the time to the patient's first request for supplemental analgesia, was significantly prolonged by the addition of epinephrine. Moreover, the addition of epinephrine reduced the incidence of tourniquet pain and reduced the ED_{50} and ED_{95} values of bupivacaine for tourniquet pain blockade. No definitive advantages existed with the higher dose of epinephrine. From our results we conclude that the addition of epinephrine is necessary to reduce the bupivacaine dose required to block tourniquet pain in patients undergoing TKRA.

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