Anesthesiology
1999; 90:971–7

Hyperbaric Spinal Ropivacaine

A Comparison to Bupivacaine in Volunteers

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Background: **Ropivacaine is a newly introduced local anesthetic that may be a useful alternative to low-dose bupivacaine for outpatient spinal anesthesia. However, its relative potency to bupivacaine and its dose–response characteristics are unknown. This double-blind, randomized, crossover study was designed to determine relative potencies of low-dose hyperbaric spinal ropivacaine and bupivacaine and to assess the suitability of spinal ropivacaine for outpatient anesthesia.**

Methods: **Eighteen healthy volunteers were randomized into three equal groups to receive one spinal administration with bupivacaine and a second with ropivacaine, of equal-milligram doses (4, 8, or 12 mg) of 0.25% drug with 5% dextrose. The duration of blockade was assessed with (1) pinprick, (2) transcutaneous electrical stimulation, (3) tolerance to high tourniquet, (4) electromyography and isometric force dynamometry, and (5) achievement of discharge criteria. Differences between ropivacaine and bupivacaine were assessed with linear and multiple regression. $P < 0.05$ was considered significant.**

Results: **Ropivacaine and bupivacaine provided dose-dependent prolongation of sensory and motor block and time until achievement of discharge criteria (R^2 ranges from 0.33–0.99; P values from < 0.001 through 0.01). Spinal anesthesia with ropivacaine was significantly different from bupivacaine and was approximately half as potent for all criteria studied. A high incidence of back pain (28%; $P = 0.098$) was noted after intrathecal ropivacaine was given.**

Conclusion: **Ropivacaine is half as potent and in equipotent doses has a similar profile to bupivacaine with a higher incidence of side effects. Low-dose hyperbaric spinal ropivacaine does not appear to offer an advantage over bupivacaine for use in outpatient anesthesia. (Key words: Ambulatory; potency; spinal anesthesia.)**

ROPIVACAINE, an amide local anesthetic similar to bupivacaine in chemical structure, is the first new local anesthetic to be introduced in more than 25 yr. Ropivacaine may be a suitable replacement to bupivacaine because it is considered to be less cardiotoxic on a milligram basis.[1] Although clinical trials suggest that ropivacaine may be less potent,[2–4] direct potencies of ropivacaine *versus* bupivacaine in humans are unknown and should be determined before recommending ropivacaine as a substitute for bupivacaine.

The suggestion that epidural ropivacaine may have a lesser potency than bupivacaine has intriguing implications for spinal anesthesia. Spinal bupivacaine has a low incidence of postoperative complaints,[5] but in doses that provide reliable anesthesia (7.5 mg or greater) it may delay patient discharge after outpatient surgery.[6,7] Lesser doses may produce a faster recovery but are associated with a high failure rate (approximately 25%).[7,8] If spinal ropivacaine proves less potent, it may allow for more reliable spinal anesthesia than bupivacaine with a shorter recovery time. This potential profile, combined with less intense motor block, may make ropivacaine well suited for the outpatient setting.

We performed this randomized, double-blind volunteer study with two objectives: (1) to directly determine relative potencies of intrathecal bupivacaine and ropivacaine in humans to allow direct evaluation of ropivacaine as a substitute for bupivacaine, and (2) to create a dose–response curve for low-dose hyperbaric 0.25% spinal ropivacaine to determine its suitability for outpatient spinal anesthesia.

Methods

After Institutional Review Board approval and informed consent were obtained, 18 healthy volunteers

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Received from the Department of Anesthesiology, Virginia Mason Medical Center and University of Washington School of Medicine, Seattle, Washington. Submitted for publication April 21, 1998. Accepted for publication November 12, 1998. Supported by the Department of Anesthesiology, Virginia Mason Medical Center.

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(aged 27–51 yr; 11 female, 7 male) were enrolled in this randomized, double-blind, crossover study. Each volunteer received two spinal anesthetics, separated by at least 24 h and at most 6 weeks, one with bupivacaine and the second with an equal-milligram dose of ropivacaine. Hyperbaric study solutions were created by combining 0.5% bupivacaine (Sensorcaine®-MPF, ASTRA USA Inc., Westborough, MA) or 0.5% ropivacaine (Naropin™, ASTRA USA Inc.) with an equal volume of 10% dextrose, resulting in final drug and dextrose concentrations of 0.25% and 5%, respectively. The drug solutions were made by one investigator who did not have subsequent involvement in the data collection. The solutions were then administered, and the subjects tested by another blinded author. The volunteers were randomly assigned to one of three groups of six subjects, each group receiving one of three doses (4, 8, or 12 mg; 1.6, 3.2, and 4.8 ml, respectively). All subjects had fasted for 6 h and received no sedatives during the study. Before subarachnoid block, a 20-gauge peripheral intravenous line was placed, and an intravenous bolus of lactated Ringer's solution (6 ml/kg) was administered, followed by an infusion of 8 ml · kg^{-1} · h^{-1} for the first hour and 2 ml · kg^{-1} · h^{-1} thereafter.

Spinal anesthesia was administered with the volunteers in the left lateral decubitus position. Under sterile conditions and after local infiltration of the skin with 1% lidocaine, the subarachnoid space was entered at the L2–L3 interspace *via* the midline approach using a 19-gauge introducer and a tapered 22/24-gauge Safetap™ spinal needle (Kendall Healthcare Products Co., Mansfield, MA). With the spinal needle orifice facing cephalad, 0.2 ml of the cerebrospinal fluid was aspirated, followed by injection of the study solution at a rate of 0.25 ml/s. After drug administration, a second 0.2 ml aspiration and reinjection of cerebrospinal fluid was used to confirm intrathecal injection. Volunteers were immediately laid in the supine position and kept horizontal for the remainder of the study. The duration of blockade was assessed using the following modalities: (1) sensory block to pinprick, (2) tolerance to transcutaneous electrical stimulation, (3) tolerance to thigh tourniquet, and (4) motor block by electromyography (EMG; abdomen), isometric force dynamometry (quadriceps), and modified Bromage scale (lower extremity).

Bilateral sensory block to pinprick was tested in a cephalad-to-caudad direction with a disposable dermatome tester (a plastic pin; B. Braun Medical Inc., Bethlehem, PA) every 5 min after injection for the first 60 min, then at 10-min intervals until complete resolution of sensory anesthesia. The right C5–C6 dermatome was used as an unblocked reference point.

Tolerance to transcutaneous electrical stimulation (TES),[9] was determined at six common surgical sites: at the lateral ankle (S1) bilaterally, at the medial knee (L3) bilaterally, at the pubis midline (T12), and at the umbilicus midline (T10). TES was performed with a peripheral nerve stimulator (Model NS252, Fisher & Paykel, Auckland, New Zealand) using 50-Hz tetanus for 5 s initially at 10 mA and then with increasing increments of 10 mA to a maximum of 60 mA. This maximum limit was chosen because previous studies have shown TES at 60 mA to be equivalent to the intensity of stimulation caused by surgical incision.[10,11] Testing began in a systematic cephalad-to-caudad order at 4 min after injection and continued at 10-min intervals until the volunteer could no longer tolerate 60 mA on two successive tests. If the volunteer was never able to tolerate 60 mA, the testing was terminated at 34 min.

Duration of the tolerance to a left thigh tourniquet was assessed.[9] Thirty minutes after injection, a standard 34-inch pneumatic cuff was inflated to 300 psi after exsanguination by gravity, in a manner similar to the tourniquet application used in lower extremity orthopedic procedures at our institution. Volunteers were instructed to request deflation of the tourniquet when the discomfort level reached a pain score of 5/10 or at a maximum time limit of 120 min.

Motor block of the abdominal and lower extremity muscles was assessed using EMG, isometric force dynamometry, and modified Bromage scale.[9] To test abdominal muscle strength, an EMG lead was placed at the mid-clavicular line to the left of the umbilicus. A restraining strap was placed across the body at the level of the xiphoid, and the volunteer attempted an isometric maximal contraction of abdominal muscle flexion (a sit-up) against the strap. Using a commercially available surface electromyograph (MyoTrac2, Thought Technology Ltd., Montreal, Quebec, Canada), an averaged, rectified measurement was taken during the middle 2 s of a 6-s maximal effort. Muscle strength of the right lower extremity was measured using a commercially available isometric force dynamometer (Micro FET, Hoggan Health Industries, Draper, UT) during a 5-s maximal force contraction of the right quadriceps muscle (straight leg lift against resistance). Measurements for both tests were performed in triplicate and averaged at baseline and at 10-min intervals after injection until $\geq$ 90% of baseline strength returned. Modified Bromage scores (no block [0], able to bend the knee [1], able to

dorsiflex the foot [2], and complete motor block [3]) were recorded every 10 min after injection until the resolution of the motor block or until 40 min if no motor block was achieved.

Each volunteer met simulated discharge criteria before completion of the study. On recovery of S2 dermatome to pinprick, volunteers attempted ambulation without assistance. If ambulation was successful, they then attempted to void. If they were unable to either ambulate or void, then they repeated their attempts at 15-min intervals until these endpoints were achieved. Volunteers were later questioned regarding possible side effects (including headache, back pain, neurologic deficits) on the following day and at 1 week after administration of their spinal anesthetics. Volunteers were asked to provide detailed descriptions of any back pain according to its location, any radiating quality, severity (mild, moderate, or severe), any therapy administered, and its duration.

Statistical Analysis

Multiple and linear regression was used to determine dose–response relationships and to compare ropivacaine with bupivacaine for TES tolerance, EMG, isometric force dynamometry, Bromage scores, and achievement of discharge criteria. Analysis of quadratic effect was also used to determine that the dose–response curves were linear in the dose range studied (data not shown). Mean and 95% confidence intervals of the slope of the regression line were used to calculate the per-milligram increments of predicted durations of sensory and motor block and time until achievement of discharge criteria for ropivacaine and bupivacaine. All bilateral measurements were averaged for each volunteer. In addition, all dermatome levels blocked to pinprick were averaged for each dose of each drug to determine estimated time course of sensory anesthesia to pinprick. Significance was defined as $P < 0.05$.

Results

Subject demographics were similar in the three groups (table 1), and spinal anesthesia was successful in all participants. Increasing doses of ropivacaine and bupivacaine resulted in increasing duration of sensory and motor blocks (figs. 1–4). Multiple regression indicated that ropivacaine was significantly different from bupivacaine for all measurements ($P < 0.05$). Dose–response relationships were determined for ropivacaine and bupivacaine in sensory block to pinprick, tolerance to TES, tolerance to tourniquet, motor block, and time until achievement of discharge criteria and are reported as minutes of duration per milligram-dose (table 2). Tolerance to TES was not achieved for the lower doses of ropivacaine at the ankle, pubis, and umbilicus (table 3).

Table 1. Subject Demographics

	4-mg Group	8-mg Group	12-mg Group
Age (year)	36 ± 10	37 ± 5	38 ± 8
Height (cm)	168 ± 10	175 ± 10	163 ± 8
Weight (kg)	71 ± 14	74 ± 17	61 ± 10
Sex (M/F)	2/4	4/2	1/5

Values are mean ± SD.

Side effects were few. One volunteer required intravenous atropine, 0.4 mg, for both 12-mg spinal anesthetics because of bradycardia (heart rate < 50 beats/min) and hypotension (systolic blood pressure < 85 mmHg). A second volunteer received intravenous atropine, 0.4 mg, for the treatment of nausea without hemodynamic instability during a 12-mg bupivacaine spinal anesthetic. Both volunteers had sensory blocks higher than T4; both drugs were represented. Two volunteers had mild postdural puncture headaches after one of their two anesthetics. Neither required treatment, and both resolved within 48–72 h.

Six episodes of backaches occurred in six volunteers, with five of these episodes occurring after administration of intrathecal ropivacaine (5 of 18 *vs.* 1 of 18; $P = 0.098$, Fisher exact test). The backaches occurred in the lumbosacral area and lasted 3–5 days. All six incidents were described as mild to moderate in intensity, requiring only heat, stretching exercises, or nonsteroidal antiinflammatory drugs for treatment. Only one volunteer complained of symptoms radiating to her left buttock, after receiving a 12-mg dose of bupivacaine. The remaining five volunteers developed back pain only after their ropivacaine spinal anesthetics, and all denied radiating symptoms. All doses of ropivacaine were represented, and there was no relationship between the back pain and the order in which the drugs were administered.

Discussion

The dose–response data for bupivacaine and ropivacaine in this study demonstrates an approximate relative potency of 2:1. This relative potency is well illustrated by the dermatome regression curves (fig. 1) and from the linear regressions in table 2. In figure 1, the resolution of

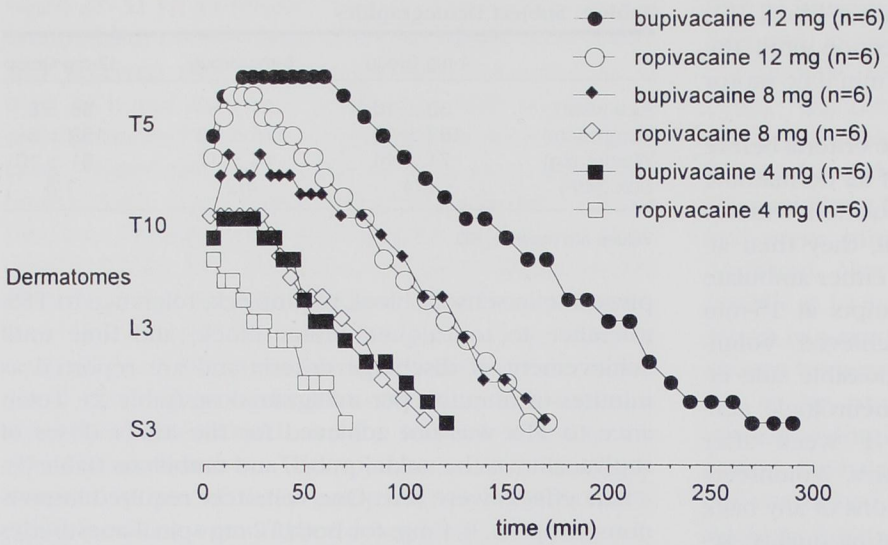

Fig. 1. Time course of dermatome regression to pinprick for three doses of bupivacaine and ropivacaine.

4 mg of bupivacaine is similar to 8 mg of ropivacaine. Table 2 illustrates that the durations of anesthesia per milligram dose for ropivacaine and bupivacaine are consistently near a 2:1 ratio. To our knowledge, no previous studies have directly determined the relative potencies of spinal ropivacaine and bupivacaine.

A second unique aspect of this study is the development of dose–response relationships for low doses of these drugs. These relationships help to determine if ropivacaine is a better alternative to bupivacaine for outpatient spinal anesthesia. Ropivacaine might be considered a preferred alternative if, for example, equipotent doses provided surgical anesthesia similar to bupivacaine but with a faster recovery profile. Our data do not indicate that ropivacaine offers an advantage over bupivacaine because equipotent doses of hyperbaric spinal ropivacaine provide similar sensory and motor block and time until achievement of discharge criteria as bupivacaine.

Our study also raises the question of potential side effects. A relatively high incidence of back pain (5 of 18 volunteers; 28%) with intrathecal ropivacaine administration was found in this study. Although the number of volunteers tested was not large enough to suggest significance, the occurrence is nonetheless concerning. Because spinal bupivacaine offers a lower incidence of transient radiating back pain than lidocaine, we would expect any alternative to bupivacaine to offer at least the

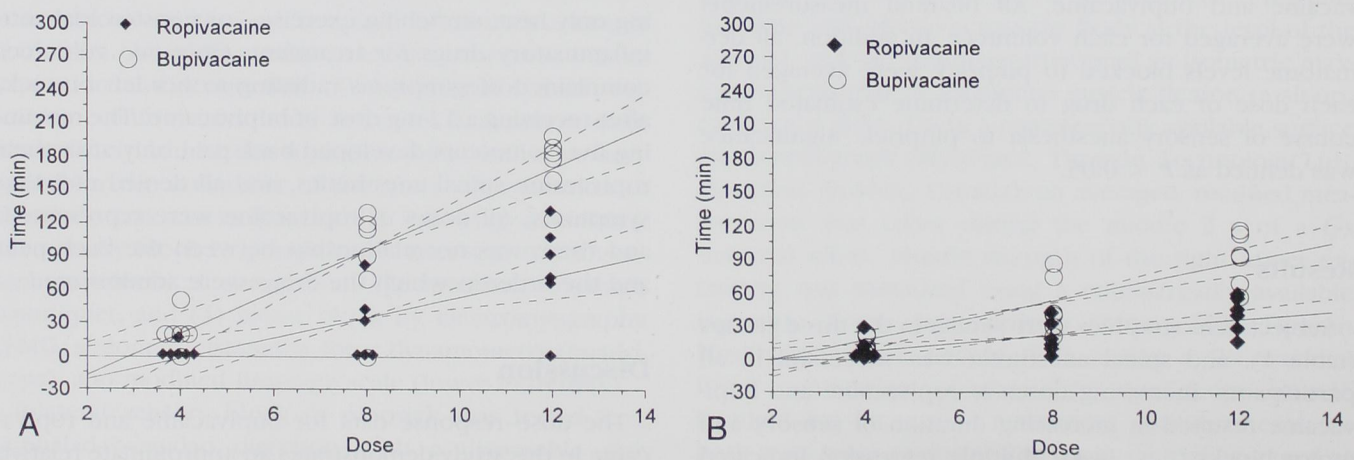

Fig. 2. Dose-related increases in duration of tolerance (*A*) to transcutaneous electrical stimulation (TES) at the knee (L3 dermatome) equivalent to surgical stimulation (bupivacaine, $R^2 = 0.90$; $P < 0.0001$; ropivacaine, $R^2 = 0.63$; $P < 0.0001$) and (*B*) to pneumatic thigh tourniquet at 300 psi (bupivacaine, $R^2 = 0.89$; $P < 0.0001$; ropivacaine, $R^2 = 0.77$; $P < 0.0001$). Mean and 95% confidence intervals of the slope of linear regression are plotted for bupivacaine and ropivacaine. For all doses, n = 6.

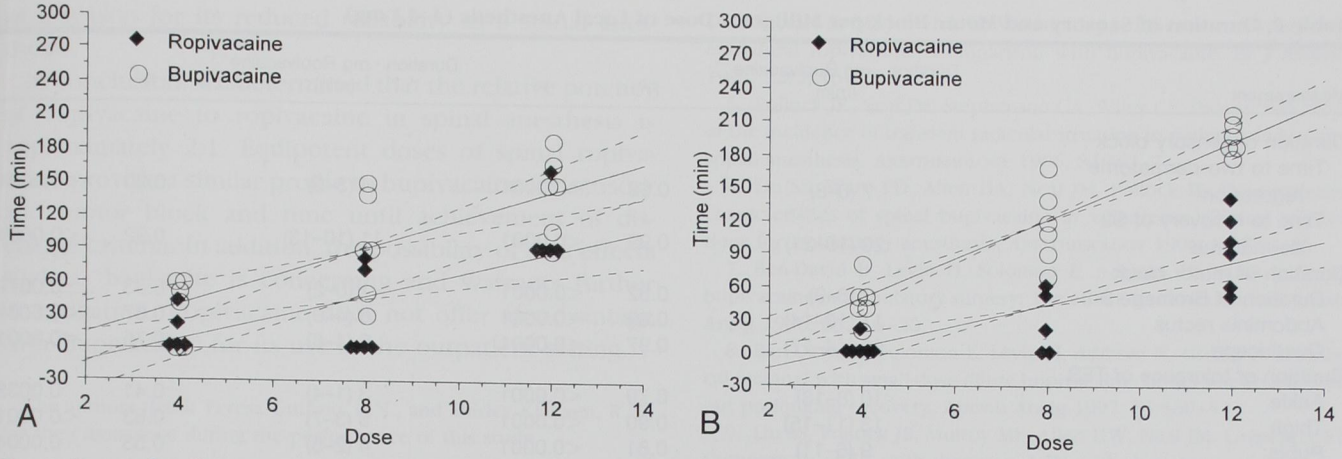

Fig. 3. Dose-related increases in the duration of motor block of the (*A*) abdominal muscles as assessed by electromyography (bupivacaine, $R^2 = 0.89$; $P < 0.0001$; ropivacaine, $R^2 = 0.67$; $P < 0.0001$) and (*B*) the right quadriceps muscle as assessed by isometric force dynamometry (bupivacaine, $R^2 = 0.97$; $P < 0.0001$; ropivacaine, $R^2 = 0.75$; $P < 0.0001$). Mean and 95% confidence intervals of the slope of linear regression are plotted for bupivacaine and ropivacaine. In *A*, for the 4-mg and 12-mg dose, n = 5; for the 8-mg dose, n = 6. In *B*, n = 6 for all doses.

same complication-free profile. If spinal ropivacaine is associated with backache, much like lidocaine, then there exists another reason for ropivacaine to be considered unsuitable as an alternative to bupivacaine.

There have been a few previous studies that have involved spinal ropivacaine. These investigations, however, used large doses (15 and 22.5 mg) of glucose-free ropivacaine, which provided long-lasting anesthesia for up to 6 h in sensory and motor block.[12,13] Furthermore, their studies did not directly compare ropivacaine with any other known spinal anesthetic, such as bupivacaine. Although these studies demonstrated that ropivacaine was safe and efficacious in high doses, their data are not applicable to ropivacaine's use in the ambulatory setting.

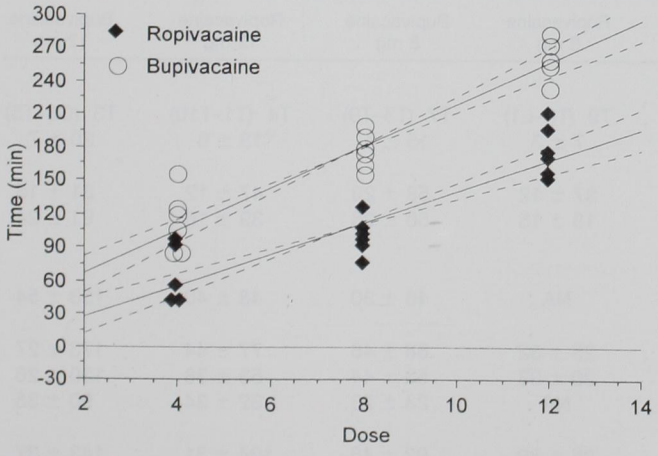

Fig. 4. Dose-related increases in time until achievement of discharge criteria: regression of S2 sensory block to pinprick, ambulation without assistance, and ability to void (bupivacaine, $R^2 = 0.98$; $P < 0.0001$; ropivacaine, $R^2 = 0.97$; $P < 0.0001$). Mean and 95% confidence intervals of the slope of linear regression are plotted for bupivacaine and ropivacaine. For all three doses, n = 6.

Previous clinical studies of ropivacaine have largely focused on epidural anesthesia and analgesia. These studies typically used large doses (100–200 mg) of ropivacaine in varying concentrations. In comparing these doses with similarly large doses of bupivacaine, they found that the motor block was less profound with ropivacaine but that the sensory anesthesia was equally long in duration.[2–4] The relative potencies that were suggested in the informal pooled analysis of data from the files of ASTRA Pain Control, Sweden,‖ were closer to 1:1 for ropivacaine *versus* bupivacaine. Thus our findings, when compared with the current literature, are somewhat unexpected because we directly derived an approximate potency of 2:1 for ropivacaine *versus* bupivacaine. Our study, however, is the first and only direct determination of relative potencies presently available between spinal ropivacaine and bupivacaine. Furthermore, a direct comparison for ropivacaine between epidural and spinal anesthesia cannot be made.

There are limitations to this study. The anesthetics were performed on healthy volunteers and not on surgical patients. The stimulation (TES) used could only mimic the intensity of surgical incision, even though previous studies have shown their correlation.[10,11]

‖ Finucane, BT. Ropivacaine: Epidural anesthesia for surgery. Am J Anesth 1997; Sept/Oct(suppl):22–5.

Table 2. Duration of Sensory and Motor Block per Milligram Dose of Local Anesthetic (4–12 mg)

Measurement	Duration · mg Bupivacaine^{-1} (min)	R^2	*P*	Duration · mg Ropivacaine^{-1} (min)	R^2	*P*
Duration of sensory block						
Time to two-dermatome regression	7 (6–8)	0.92	<0.0001	4 (3–5)	0.90	<0.0001
Time to recovery of S2 dermatome	20 (19–21)	0.99	<0.0001	11 (10–13)	0.92	<0.0001
Duration of motor block						
Duration of Bromage 3	7 (6–9)	0.82	<0.0001	1 (0–2)	0.33	0.0077
Abdominis rectus	11 (10–14)	0.89	<0.0001	6 (4–9)	0.67	<0.0001
Quadriceps	16 (14–17)	0.97	<0.0001	6 (4–8)	0.75	<0.0001
Duration of tolerance of TES						
Ankle	10 (8–13)	0.79	<0.0001	3 (1–4)	0.41	0.0033
Thigh	13 (11–15)	0.90	<0.0001	5 (3–7)	0.63	<0.0001
Pubis	9 (6–11)	0.81	<0.0001	4 (2–5)	0.53	0.0004
Umbilicus	6 (4–8)	0.72	<0.0001	2 (0–3)	0.33	0.0108
Duration of tolerance to tourniquet	7 (6–8)	0.89	<0.0001	3 (2–4)	0.77	<0.0001
Discharge criteria	22 (21–24)	0.98	<0.0001	14 (13–15)	0.97	<0.0001

Values are derived from linear regression and are the mean (95% confidence interval). *P* value is significance of linear regression.

Therefore discrepancies to our findings may be possible in a true surgical setting, although good clinical correlation with previous studies using this model suggests otherwise.[6,7] Another concern is the use of a 0.25% concentration of local anesthetic and whether it may have diluted the effects of spinal ropivacaine. It is possible that a higher concentration may produce different findings, but if we compare our dose–response curves of 0.25% hyperbaric bupivacaine in this study with those previously developed for low-dose 0.75% hyperbaric bupivacaine,[6] they are nearly identical. Such similarity would minimize the concern of diluting the ropivacaine

Table 3. Characteristics of Spinal Anesthesia for Ropivacaine and Bupivacaine

Drug Dose	Ropivacaine 4 mg	Bupivacaine 4 mg	Ropivacaine 8 mg	Bupivacaine 8 mg	Ropivacaine 12 mg	Bupivacaine 12 mg
Sensory block						
Peak block height [mean (range)]	T12 (T7–L3)	T10 (T7–L1)	T9 (T6–L1)	T7 (T3–T9)	T4 (T1–T10)	T3 (C8–T5)
Time to peak block height	9 ± 4	9 ± 4	7 ± 3	15 ± 4	13 ± 6	20 ± 7
Time to two-dermatome regression	25 ± 13	35 ± 10	37 ± 12	58 ± 29	47 ± 12	81 ± 15
Duration of tourniquet tolerance	7 ± 10	13 ± 8	18 ± 15	50 ± 26	39 ± 16	91 ± 24
Motor block						
Duration of TES tolerance at ankle	1 ± 2	19 ± 17	NA	46 ± 30	48 ± 40	153 ± 54
Duration of TES tolerance at thigh	3 ± 6	22 ± 16	25 ± 32	88 ± 48	77 ± 44	173 ± 27
Duration of TES tolerance at T12	NA	10 ± 24	20 ± 33	53 ± 44	53 ± 38	120 ± 26
Duration of TES tolerance at T10	NA	3 ± 8	NA	23 ± 23	32 ± 34	90 ± 35
Time until 90% recovery—abdomen	12 ± 18	35 ± 28	25 ± 39	92 ± 48	104 ± 31	143 ± 37
Time until 90% recovery—quadricep	3 ± 8	47 ± 20	30 ± 27	117 ± 36	93 ± 34	198 ± 15
Duration of Bromage 3 motor block	NA	1 ± 2	NA	41 ± 29	26 ± 27	112 ± 18
Discharge criteria achievement						
Time until micturition	63 ± 24	113 ± 27	98 ± 17	178 ± 16	176 ± 23	258 ± 20
Time to S2 dermatome recovery	38 ± 32	82 ± 24	80 ± 33	148 ± 14	143 ± 23	246 ± 21

Values are mean ± SD (min).

NA = dose did not achieve complete block.

as a reason for its reduced reliability as a spinal anesthetic.

In conclusion, we determined that the relative potency of bupivacaine to ropivacaine in spinal anesthesia is approximately 2:1. Equipotent doses of spinal ropivacaine provide a similar profile to bupivacaine for sensory and motor block and time until achievement of discharge criteria. In addition, the possibility of side effects such as backache is concerning and warrants further investigation. Ropivacaine does not offer an advantage over bupivacaine for its use in the outpatient setting.

The authors thank Teresa Guthrie, R.N., and Shirley Klakken, R.N., for their assistance during the performance of this study.

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