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Comparison of Ropivacaine and Lidocaine for Intravenous Regional Anesthesia in Volunteers

A Preliminary Study on Anesthetic Efficacy and Blood Level

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Background: Ropivacaine may be useful for intravenous regional anesthesia, but its anesthetic effectiveness and toxicity have not been evaluated.

Methods: Two doses of ropivacaine (1.2 and 1.8 mg/kg) and one dose of lidocaine (3 mg/kg) were compared for intravenous regional anesthesia in 15 volunteers. An arm tourniquet was inflated for 30 min after injection and then deflated in two cycles. Sensory block was measured by response to touch, cold, pinprick, and transcutaneous electric stimulation, and motor function was measured by hand grip strength and muscle power. Median, ulnar, radial, and musculocutaneous nerve functions were tested before local anesthetic injection and then at 5-min intervals until blocks resolved. The plasma ropivacaine and lidocaine concentrations were determined from arterial and venous blood samples drawn from the unanesthetized arm.

Results: Sensory and motor blocks were complete within 25 min and 30 min, respectively, in all three treatment groups. However, recovery of sensory and motor block after tourniquet release was slowest in the high-dose ropivacaine group. Anesthesia to pinprick and transcutaneous electric stimulation was sustained in all the volunteers in the high-dose ropivacaine group for 55 min and 85 min, respectively, whereas complete recovery was observed in the lidocaine group ($P = 0.008$) and partial recovery in the low-dose ropivacaine group ($P < 0.05$) during the same period. Motor block also was sustained in the high-dose ropivacaine group for 70 min, which was significantly longer than in the lidocaine group ($P < 0.05$). All volunteers (five of five) given lidocaine and one volunteer given high-dose ropivacaine reported light-headedness and hearing disturbance during tourniquet release when the arterial plasma lidocaine and ropivacaine concentrations were 4.7 ± 2.1 μg/ml (mean) and 2.7 μ/ml, respectively.

Conclusion: Compared with lidocaine, intravenous regional anesthesia with ropivacaine appears to be comparable but has longer-lasting residual anesthesia. (Key words: Bier's block; local anesthetics; therapeutic use.)

BUPIVACAINE is effective for intravenous regional anesthesia (IVRA)[1,2] and provides sustained analgesia after tourniquet deflation.[3] However, seizures[4] and deaths[5] associated with its use have rendered it unpopular for IVRA. Lidocaine is the most commonly used local anesthetic for IVRA in North America, but postblock analgesia is often short-lived.

Recently, ropivacaine was introduced as a new long-acting amide local anesthetic with physicochemical properties similar to those of bupivacaine.[6] But unlike bupivacaine, ropivacaine is prepared isomerically pure as the S-enantiomer and not as a racemic mixture. In animals[7,8] and humans,[9,10] intravenous injection of ropivacaine results in fewer cardiovascular and central nervous system toxic effects compared to bupivacaine, suggesting that ropivacaine may be more useful for IVRA.

To determine whether ropivacaine is feasible for IVRA, we conducted a preliminary study that compared the anesthetic effects of two doses of ropivacaine with those of a conventional dose of lidocaine (3 mg/kg). We hypothesize that ropivacaine will produce sensory and motor block comparable in onset and magnitude to that of lidocaine but more-enduring residual anesthesia after tourniquet deflation.

Materials and Methods

Study Population

With institutional review board approval and informed consent, we studied 15 healthy volunteers classified as American Society of Anesthesiologists physical status I (10 men, 5 women). Excluded were persons who were

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pregnant or who had a history of seizure or allergy to local anesthetic agents. Volunteers were assigned randomly to undergo IVRA with ropivacaine or lidocaine (Astra Pharma Inc., Mississauga, Ontario, Canada). Both agents were administered using standard techniques.

All volunteers fasted overnight and received no premedication. On the morning of the study, a 20-gauge intravenous cannula was placed in the dorsum of the left hand to permit delivery of the test anesthetic. Immediately after exsanguination with an Esmarch bandage, circulation to the arm was occluded by the proximal cuff of a 13-cm double-cuff pneumatic tourniquet applied to the upper arm and inflated to a pressure of at least 100 mmHg above baseline systolic blood pressure or a minimum of 250 mmHg. In the opposite arm, an 18-gauge cannula was placed in the antecubital vein for venous blood sampling, and a 20-gauge cannula was placed in the radial artery for arterial blood sampling. Volunteers were monitored continuously using electrocardiography, noninvasive automatic blood pressure measurement, and pulse oximetry. Hemodynamic and oxygen saturation data were recorded before anesthesia induction (baseline) and every 5 min during the study.

Study Protocol

Volunteers were randomized to undergo one of three treatments: 1.2 mg/kg ropivacaine (group R1.2), 1.8 mg/kg ropivacaine (group R1.8), or 3 mg/kg lidocaine (group L3). Local anesthetic was injected as a 40-ml bolus over 2 min in the same manner in each volunteer blinded to treatment. The end of injection was taken as time zero. Thirty minutes after time zero, the tourniquet was deflated in two cycles; that is, an initial 30-s deflation was followed by a 60-s inflation and then final deflation.

Measurements

Sensory and motor function were assessed before local anesthetic injection (baseline) and at 5-min intervals thereafter until complete resolution of block. Testing was performed by an investigator blinded to the treatment group. Sensory function was tested in four areas of the anesthetized limb, always in the following sequence: (1) the thenar eminence innervated by the median nerve, (2) the hypothenar eminence innervated by the ulnar nerve, (3) the dorsal first web space innervated by the radial nerve, and (4) the antebrachial portion of the forearm innervated by the musculocutaneous nerve. The sensory modalities tested were touch, cold using ice, response to pinprick using a 23-gauge needle, and tolerance to transcutaneous electric stimulation (TES) using a peripheral nerve stimulator (DualStim NS-2CA; Life-Tech, Houston, TX). A 5-s stimulus of 50-Hz tetanus was delivered in 10-mA increments until the volunteer reported a tingling sensation or we reached a maximum of 60 mA, equivalent to a noxious surgical stimulus.[11] At each assessment time point, sensory testing moved systematically from one site to the next in sequence. The responses to touch, cold, pinprick, and 60-mA TES were recorded as present (+) or absent (−).

Motor function was assessed by testing hand grip strength and muscle power. Hand grip strength was assessed by measuring the pressure generated by squeezing for 5 s a 500-ml normal saline bag connected to a pressure transducer and a recordable printout tracing. Individual muscle groups were tested as follows: thumb opposition (median nerve), little finger flexion and finger abduction–adduction (ulnar nerve), wrist extension (radial nerve), and elbow flexion (musculocutaneous nerve). The power of each muscle group was graded on a scale from 0 to 2, where 0 = absent, 1 = present but weak, and 2 = normal. The times to achieve complete block (grade 0) and complete resolution (grade 2) were recorded.

Blood samples, in 5-ml aliquots, were drawn from arterial and venous cannulae in the unanesthetized arm by a second investigator blinded to the treatment group. Samples were obtained before local anesthetic injection (baseline) and at the following intervals: 10, 20, and 30 min after local anesthetic injection; 30 s after the first tourniquet cuff deflation; and, 30 s and 10, 20, 30, and 60 min after the second (final) cuff deflation. Additional blood samples were drawn whenever the volunteer reported or exhibited symptoms suggestive of local anesthetic toxicity, such as blurred vision, hearing disturbance, or perioral numbness. Blood samples were centrifuged immediately to separate the plasma fraction and frozen at −20°C until the assay. Plasma ropivacaine and lidocaine concentrations were determined by gas chromatography and fluorescence polarization immunoassay, respectively, and the detection sensitivities were 0.01 μg/ml and 0.05 μg/ml, respectively.

Volunteers were monitored for the appearance of systemic local anesthetic-related toxic reactions during local anesthetic injection and tourniquet inflation, and after the first and last cuff deflation. Symptoms monitored in addition to those stated previously included light-headedness, dysarthria, muscle twitching, seizure, blood pressure change, or arrhythmia.

The occurrence of tourniquet pain was also recorded and the severity of pain was graded using a verbal analog

Table 1. Demographic, Local Anesthetic Administration, and Tourniquet Pain Data

	Ropivacaine 1.8 mg/kg (n = 5)	Ropivacaine 1.2 mg/kg (n = 5)	Lidocaine 3 mg/kg (n = 5)
Age (yr)	34.6 ± 3.5	34.4 ± 5.7	29.2 ± 3.5
Weight (kg)	78.6 ± 10.4	73.0 ± 8	69.2 ± 12.3
Height (cm)	175.2 ± 8.4	177.8 ± 4	179.0 ± 11.2
Dose (mg) (range)	142.0 ± 19.2 (120–170)	89.4 ± 11.7 (72–100)	206.0 ± 35.8 (170–260)
Local anesthetic concentration (%) (range)	0.36 ± 0.05 (0.3–0.43)	0.22 ± 0.03 (0.18–0.25)	0.52 ± 0.09 (0.43–0.65)
Incidence of tourniquet pain	2/5	3/5	3/5
Tourniquet pain score	6.0 ± 1.4	4.7 ± 2.1	7.3 ± 1.2

Data are mean ± SD.

scale ranging from 0 to 10, where 0 = no pain and 10 = the worst pain imaginable.

Data Analysis

Data are expressed as the mean ± SD unless otherwise stated. A computer software program (SPSS statistical software, Chicago, IL) was used for statistical analysis. Nominal data were analyzed using the chi-square test and continuous variables were measured by one-way analysis of variance when appropriate. Sensory and motor block progression and resolution were compared among three treatment groups using the Fisher exact test. Blood levels of the high-dose and low-dose ropivacaine groups were compared using two-tailed *t* tests for independent means. Significance was accepted at $P < 0.05$.

Results

Fifteen volunteers successfully completed the study and were equally distributed among the groups. There were no differences in the demographic data and the incidence of tourniquet pain (table 1). The local anesthetic dose and concentration administered for IVRA in each group are summarized in table 1. Compared with baseline, there was no change in heart rate, blood pressure, or oxygen saturation during the study. Cardiac arrhythmia did not occur.

Sensory Anesthesia

The time course to complete sensory block as indicated by the lack of responses to pinprick, cold, touch, and TES was similar among the treatment groups (table 2). In particular, pinprick and TES responses were absent within 20 min of local anesthetic injection in all groups. Recovery of sensory anesthesia was slowest in the high-dose ropivacaine group (fig. 1). Recovery of sensation to touch, cold, pinprick, and TES was complete 80 min, 145 min, 210 min, and 210 min, respectively, after tourniquet deflation at all four test sites in all volunteers receiving high-dose ropivacaine. Analgesia to pinprick and TES was sustained in all five volunteers for 55 min and 85 min, respectively, after tourniquet release compared with complete recovery of the same sensory modalities in the lidocaine group ($P = 0.008$) and partial recovery in the low-dose ropivacaine group during the same time period. Figure 1 shows significant differences of sensory recovery among the groups.

Motor Block

Complete motor block as judged by muscle power, and hand grip strength tests (reduction to 95% of baseline) occurred within 30 min and 25 min, respectively, of local anesthetic injection in all three treatment groups (table 2). Similarly, complete recovery of motor function was most delayed in the high-dose ropivacaine group: 270 min for muscle power and 120 min for hand grip strength to return to baseline in all volunteers. Weakness in muscle power and hand grip strength was sustained for 100 min and 70 min, respectively, in all five volunteers compared with complete recovery in the lidocaine group ($P = 0.008$) and partial recovery in the low-dose ropivacaine group during the same period. Motor recovery of the lidocaine and low-dose ropivacaine groups was not significantly different.

Plasma Anesthetic Concentrations and Toxic Symptoms

Figure 2 shows the mean peak arterial and venous plasma levels (C_{max}) and the time to peak level for

Table 2. Number of Volunteers Showing Sensory and Motor Block after Tourniquet Inflation

	Group	5 min	10 min	15 min	20 min	25 min	30 min
Touch	R 1.8 (n = 5)	0	0	1	4	5	5
	R 1.2 (n = 5)	0	0	4	5	5	5
	L 3 (n = 5)	0	1	2	4	5	5
Cold	R 1.8 (n = 5)	3	4	5	5	5	5
	R 1.2 (n = 5)	1	3	4	5	5	5
	L 3 (n = 5)	0	1	2	4	5	5
Pinprick	R 1.8 (n = 5)	3	4	5	5	5	5
	R 1.2 (n = 5)	2	3	5	5	5	5
	L 3 (n = 5)	1	4	4	5	5	5
TES	R 1.8 (n = 5)	3	4	4	5	5	5
	R 1.2 (n = 5)	1	1	4	5	5	5
	L 3 (n = 5)	0	0	2	5	5	5
Muscle strength	R 1.8 (n = 5)	0	0	1	4	5	5
	R 1.2 (n = 5)	0	0	0	3	4	5
	L 3 (n = 5)	0	0	3	4	5	5
Squeeze test	R 1.8 (n = 5)	0	0	4	4	5	5
	R 1.2 (n = 5)	0	1	3	4	5	5
	L 3 (n = 5)	0	3	3	5	5	5

R 1.8 = ropivacaine 1.8 mg/kg; R 1.2 = ropivacaine 1.2 mg/kg; L3 = lidocaine 3 mg/kg; TES = trancutaneous electrical stimulation.

lidocaine and ropivacaine. Arterial and venous C_{max} for plasma lidocaine were 4.7 ± 2.1 μg/ml (range, 2.1–7.8 μg/ml) and 1.5 ± 0.5 μg/ml (range, 0.8–2.2 μg/ml), respectively. Arterial C_{max} for plasma ropivacaine after cuff release in the high-dose and low-dose groups were 3 ± 0.6 μg/ml (range, 2.1–3.6 μg/ml) and 2.3 ± 1.1 μg/ml (range, 1.3–3.7 μg/ml), respectively. The C_{max} for venous ropivacaine was 1.7 ± 0.5 μg/ml (range, 1.2–2.4 μg/ml) in the high-dose group and 1.1 ± 0.3 μg/ml (range, 0.9–1.5 μg/ml) in the low-dose group. The time to arterial C_{max} was seen within 2 min after cuff deflation in all groups.

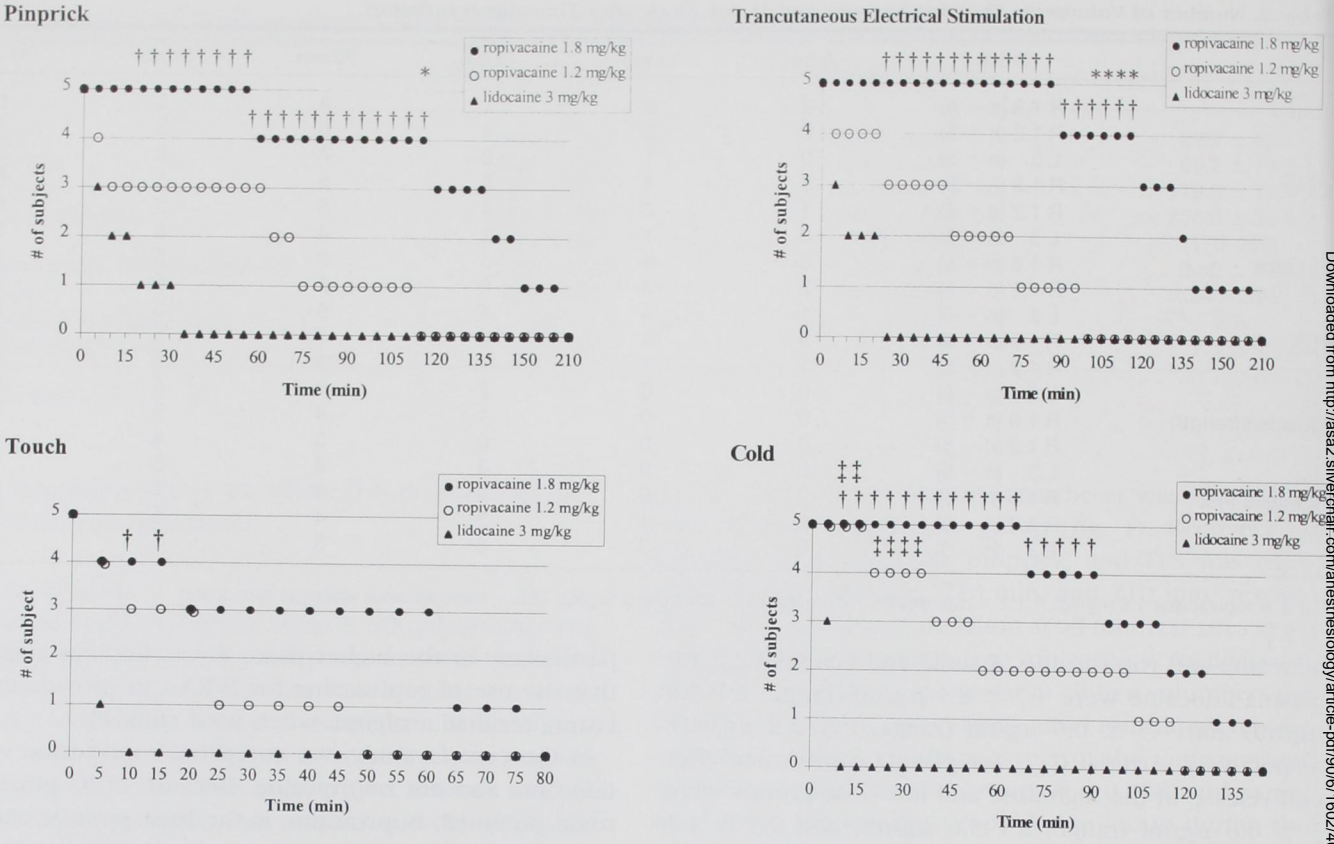
All five volunteers in the lidocaine group reported light-headedness and hearing disturbance at the time of cuff deflation. Similar symptoms were observed in one volunteer in the high-dose ropivacaine group and in none in the low-dose ropivacaine group. The corresponding arterial and venous C_{max} values in this ropivacaine volunteer were 2.7 μg/ml and 2 μg/ml, respectively. The appearance of toxic symptoms coincided with the time to peak arterial plasma lidocaine and ropivacaine levels. Muscle twitching, dysarthria, and seizure were not observed at any time.

Discussion

Data from the current study suggest that 1.2 and 1.8 mg/kg ropivacaine given intravenously produces onset of IVRA comparable to that achieved with a conventional dose of lidocaine, but more enduring anesthesia, particularly at the higher dose. These findings suggest that the use of ropivacaine for IVRA can provide long-lasting residual analgesia when used clinically.

In the current study, we compared ropivacaine with lidocaine and not bupivacaine. Because of its inherent toxic potential, bupivacaine is the least popular agent, whereas lidocaine is the most popular for IVRA in North America. We chose to administer ropivacaine in doses of 1.2 and 1.8 mg/kg, limiting the maximum dose to no more than 180 mg. This is based on previous studies that showed that the optimum dose of bupivacaine recommended for IVRA is 1.5 mg/kg.[12] An intravenous infusion study in humans further showed that the tolerability of central nervous system toxicity is 25% higher with ropivacaine than with bupivacaine.[9] Therefore, the maximum dose of ropivacaine was limited to 1.8 mg/kg in the current study. Furthermore, because the optimal concentration for ropivacaine IVRA has not been determined, we chose to standardize the dose and volume of administration (40 ml). Although variable, the mean ropivacaine concentration was 0.36% in the high-dose group and 0.22% in the low-dose group, which both exceed that recommended for bupivacaine IVRA (0.2%).

Our preliminary data suggest that ropivacaine is effective for use in IVRA. Not only were the times to complete sensory and motor block with ropivacaine and lidocaine similar, the duration of residual sensory anesthesia in volunteers after 1.8 mg/kg ropivacaine was dramatically longer than that achieved with 3 mg/kg lidocaine, as indicated by response to pinprick testing



† p<0.05 Ropivacaine 1.8 mg/kg vs. Lidocaine 3 mg/kg
* p<0.05 Ropivacaine 1.8 mg/kg vs. Ropivacaine 1.2 mg/kg
‡ p<0.05 Ropivacaine 1.2 mg.kg vs. Lidocaine 3 mg.kg

Fig. 1. Recovery of sensation to touch, cold, pinprick, and transcutaneous electric stimulation after tourniquet release is slowest in the high-dose ropivacaine group and is consistently slower than in the lidocaine group. Differences in the recovery of sensation to pinprick and transcutaneous electric stimulation are noted between the high-dose and low-dose ropivacaine groups. Differences in the recovery of touch and cold sensation are found between the low-dose ropivacaine and lidocaine groups.

and TES. Longer-lasting residual anesthesia also has been reported with IVRA using bupivacaine. The duration of postblock analgesia after 50 mg of bupivacaine was 344 ± 28 min compared with 111 ± 27 min after 100 mg lidocaine.[3] The prolonged effect obtained with bupivacaine is attributed to properties of high protein binding and lipid solubility. It is likely that the prolonged effect of ropivacaine is a result of the same properties.

To our knowledge, this is the first study of IVRA ropivacaine in humans to measure plasma ropivacaine concentrations to correlate with the occurrence of symptoms suggesting systemic toxicity. Only one volunteer who received high-dose ropivacaine experienced lightheadedness and hearing disturbance after tourniquet release. Peak arterial and venous plasma concentrations in this volunteer were 2.7 μg/ml and 2 μg/ml, respectively, whereas the respective mean values for the group were 3 ± 0.6 μg/ml and 1.7 ± 0.5 μg/ml. It is interesting to note that, although other volunteers in the ropivacaine groups had higher plasma concentrations, they did not experience symptoms related to toxic effects.

The safety of ropivacaine for IVRA has not been established and cannot be determined from the current study because of our small sample size. Our study merely provides preliminary data on the anesthetic effect of two doses of ropivacaine for IVRA. However, we may speculate that rapid intravenous bolus administration of ropivacaine at 1.8 mg/kg in the absence of a properly functioning arm tourniquet can be dangerous. Scott *et al.*[9] showed that with a slow intravenous infusion of 10 mg/min volunteers could tolerate 124 ± 38 mg ropivacaine before the onset of central nervous system effects

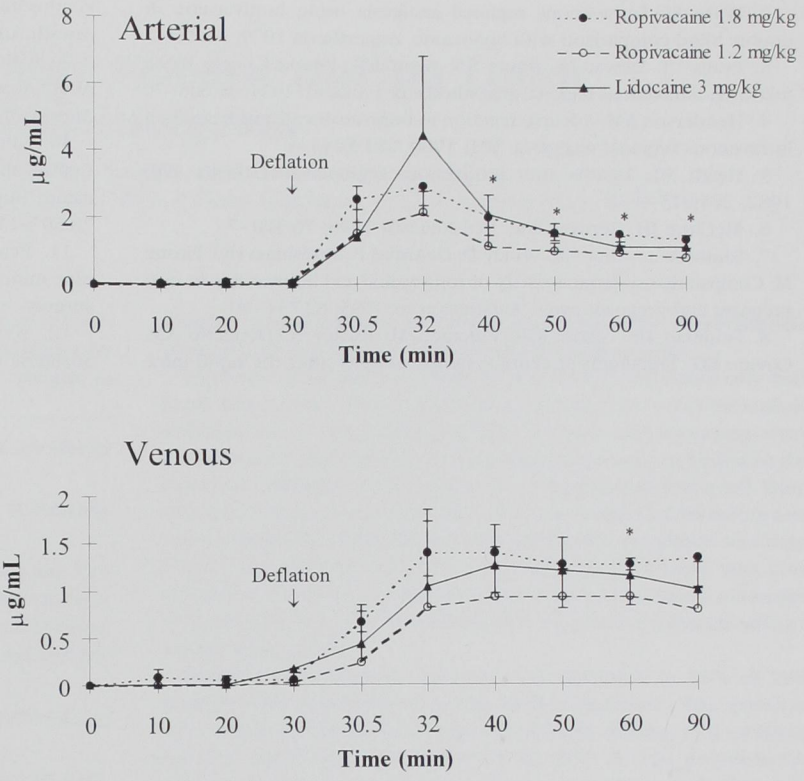


Fig. 2. Arterial and venous plasma concentrations of ropivacaine and lidocaine increase after tourniquet release at 30 min (first) and 31.5 min (final). Peak arterial concentrations occur at 32 min and decrease rapidly thereafter compared with a slower increase but more sustained venous plasma concentrations in all three treatment groups.

* P<0.05, Ropivacaine 1.8 mg/kg vs. Ropivacaine 1.2 mg/kg

when plasma venous ropivacaine concentration was between 1 and 2 μg/ml. Knudsen *et al.*[10] reported a similar degree of tolerance in volunteers; that is, slow administration of 115 ± 29 mg ropivacaine before the onset of muscle twitching and dysarthria when arterial and venous ropivacaine concentrations were 4.3 ± 0.6 μg/ml and 2.2 ± 0.8 μg/ml, respectively. Although the administered ropivacaine dose in the high-dose group was greater than that in the study by Knudsen *et al.*,[10] the resultant arterial and venous plasma ropivacaine levels, 3 ± 0.6 μg/ml and 1.7 ± 0.5 μg/ml, respectively, were lower. The difference in peak plasma levels likely reflects ropivacaine tissue binding during the 30-min period of tourniquet inflation and release of less drug into the systemic circulation when the tourniquet is deflated.

Study Limitations

First, the lack of difference in anesthetic effects between low-dose ropivacaine (1.2 mg/kg) and lidocaine can be the result of a small sample size (five volunteers in each group). Second, the safety of ropivacaine IVRA cannot be determined from the current study. Third, we measured the duration of sensory and motor block by the response to two painful stimuli, pinprick and TES nerve stimulation, in the absence of a surgical incision. The time to complete recovery of sensation to both forms of stimuli was measured as the time to recovery of sensation at all four nerve sites. Because the speed of recovery for each sensation in each nerve distribution is variable and the site of residual anesthesia may not correspond to the site of surgery, the recovery times reported here may overestimate the duration of clinical analgesia after surgery.

Our preliminary study in volunteers has shown that 1.8 mg/kg ropivacaine appears to provide equally effective anesthesia and longer-lasting analgesia compared with lidocaine.

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