# A Comparison of the Pharmacodynamics and Pharmacokinetics of Bupivacaine, Ropivacaine (with Epinephrine) and Their Equal Volume Mixtures with Lidocaine Used for Femoral and Sciatic Nerve Blocks: A Double-Blind Randomized Study

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**BACKGROUND:** Mixtures of lidocaine with a long-acting local anesthetic are commonly used for peripheral nerve block. Few data are available regarding the safety, efficacy, or pharmacokinetics of mixtures of local anesthetics. In the current study, we compared the effects of bupivacaine 0.5% or ropivacaine 0.75% alone or in a mixed solution of equal volumes of bupivacaine 0.5% and lidocaine 2% or ropivacaine 0.75% and lidocaine 2% for surgery after femoral-sciatic peripheral nerve block. The primary end point was onset time.
**METHODS:** In a double-blind, randomized study, 82 adults scheduled for lower limb surgery received a sciatic (20 mL) and femoral (20 mL) peripheral nerve block with 0.5% bupivacaine (200 mg), a mixture of 0.5% bupivacaine 20 mL (100 mg) with 2% lidocaine (400 mg), 0.75% ropivacaine (300 mg) or a mixture of 0.75% ropivacaine 20 mL (150 mg) with 2% lidocaine (400 mg). Each solution contained epinephrine 1:200,000. Times to perform blocks, onset times (end of injection to complete sensory and motor block), duration of sensory and motor block, and morphine consumption via IV patient-controlled analgesia were compared. Venous blood samples of 5 mL were collected for determination of drug concentration at 0, 5, 15, 30, 45, 60, and 90 min after placement of the block.
**RESULTS:** Patient demographics and surgical times were similar for all four groups. Sciatic onset times (sensory and motor block) were reduced by combining lidocaine with the long-acting local anesthetic. The onset of bupivacaine-lidocaine was 16 ± 9 min versus 28 ± 12 min for bupivacaine alone. The onset of ropivacaine-lidocaine was 16 ± 12 min versus 23 ± 12 for ropivacaine alone. Sensory blocks were complete for all patients within 40 min for those receiving bupivacaine–lidocaine versus 60 min for those receiving bupivacaine alone and 30 min for those receiving ropivacaine–lidocaine versus 40 min for those receiving ropivacaine alone ($P < 0.05$). Duration of sensory and motor block was significantly shorter in mixture groups. There was no difference among groups for visual analog scale pain scores and morphine consumption during the 48 h postoperative period, except for bupivacaine alone (median: 9 mg) versus bupivacaine–lidocaine mixture (15 mg), $P < 0.01$. There was no difference in the incidence of adverse events among groups. Plasma concentrations of bupivacaine and ropivacaine were higher, and remained elevated longer, in patients who received only the long-acting local anesthetic compared to patients who received the mixture of long-acting local anesthetic with lidocaine ($P < 0.01$).
**CONCLUSION:** Mixtures of long-acting local anesthetics with lidocaine induced faster onset blocks of decreased duration. Whether there is a safety benefit is unclear, as the benefit of a decreased concentration of long-acting local anesthetic may be offset by the presence of a significant plasma concentration of lidocaine.
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Bupivacaine has been the most widely used long-acting local anesthetic for several decades. However, after the report of several cases of almost simultaneous seizure and cardiac arrest, with prolonged resuscitation and a disproportionally high number of deaths after unintended intravascular injection of bupivacaine, it became evident that bupivacaine differs from

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other local anesthetics in that it has a narrower margin between the dose or plasma concentrations required to produce seizures and those resulting in cardiovascular collapse.[1–4] For this reason, there has been a search for alternative local anesthetics with duration of action of bupivacaine but a greater margin of safety. Ropivacaine has been proposed as an alternative drug with fewer cardiovascular and central nervous system toxic effects compared with bupivacaine.[3,4] However, several cases of systemic toxicity after peripheral nerve blocks have been reported.[5–7]

For epidural anesthesia, lidocaine-bupivacaine mixtures have been used to combine the faster onset of sensory blockade of lidocaine and the more profound and longer duration of sensitive blockade of bupivacaine.[8] The action duration of the mixture tends to be similar or shorter than that obtained with bupivacaine alone.[8–10] Despite the fact that such combinations have been applied clinically for more than 40 yr, little has been published about the properties of mixtures of lidocaine and long-acting local anesthetics for peripheral nerve blocks.

The aim of this controlled, randomized, double-blind study was to investigate the onset time (sensory block induced by mixture: primary end point) and efficacy (failed block and duration of postoperative analgesia: secondary end points) of bupivacaine compared with bupivacaine-lidocaine, and ropivacaine compared with ropivacaine-lidocaine in patients undergoing elective orthopedic surgery under femoral and sciatic nerve blocks. We also measured plasma concentrations of local anesthetics to understand how the mixtures affected the time course of drug concentration.

## METHODS

### Patients

After approval by the institutional ethics committee (Comite Protection Personne, Faculté de Médecine Nîmes, France) and written informed consent from each patient had been obtained, patients scheduled to undergo lower limb surgery under combined femoral-sciatic nerve block were prospectively and randomly enrolled into 4 parallel groups with a planned enrollment of 82 patients. Patients were randomized (random number generator) preoperatively using sealed envelopes to receive one of four treatments: bupivacaine alone, ropivacaine alone, bupivacaine-lidocaine or ropivacaine-lidocaine. Exclusion criteria were patient refusal, age <18 yr, weight <50 kg, ASA physical status >3, anticoagulant treatment, allergy to local anesthetics, neurologic or neuromuscular disease, severe liver or renal insufficiency, women of childbearing age or patients unlikely to be fully cooperative during the study, such as those with neurological or psychiatric disorders.

### Preparation of the Solution

Administered solutions were prepared by an independent anesthesiologist not involved in the study:

- Bupivacaine: 40 mL of bupivacaine-HCl 0.5% (Qualimed, Lyon, France), (200 mg of bupivacaine)
- Ropivacaine: 40 mL ropivacaine-HCl 0.75% (AstraZeneca, Rueil Malmaison, France), (300 mg of ropivacaine)
- Bupivacaine-lidocaine: 20 mL of bupivacaine-HCl 0.5% (Qualimed, Lyon, France) added with 20 mL lidocaine 2% (AstraZeneca, Rueil Malmaison, France), (100 mg of bupivacaine and 400 mg of lidocaine)
- Ropivacaine-lidocaine: 20 mL of ropivacaine 0.75% (AstraZeneca, Rueil Malmaison, France) added with 20 mL lidocaine 2% (AstraZeneca, Rueil Malmaison, France), (150 mg of ropivacaine and 400 mg of lidocaine).

Because the bupivacaine and ropivacaine doses were at the upper limit of the dose range (200 mg and 300 mg, respectively), all four local anesthetic solutions were prepared with epinephrine 1:200,000 to reduce absorption. Solutions were distributed in two 20 mL syringes (1 syringe for femoral nerve block and 1 for sciatic nerve block).

### Procedures

Patients were given hydroxyzine (100 mg) orally 1 h before surgery. In the preoperative area, patients were monitored ($Spo_2$, electrocardiogram, noninvasive arterial blood pressure) and venous access was secured. Small doses of IV alfentanil (3–5 $\mu$g/kg) were administered as necessary while the block was administered to avoid any anxiety or major discomfort. All patients were given a femoral-sciatic nerve block performed before surgery. All blocks were performed using a 100-mm insulated needle (Stimuplex®, B Braun, Melsungen Germany) connected to a nerve stimulator (HNS 11, B Braun, Melsungen Germany). The stimulating current was set initially between 2.0 and 2.5 mA (frequency, 1 Hz; pulse duration, 100 $\mu$s). The needle was considered to be close enough to the nerve when the stimulating current was ≤0.5 mA.

The femoral nerve block was performed following the paravascular inguinal "3-in 1" approach.[11] The localization of the nerve was considered successful when output <0.5 mA elicited a typical quadriceps motor response ("dancing patella"). At this point, patients received 20 mL of study solution.

The sciatic nerve block (single injection) was performed via the posterior parasacral approach.[12] The localization of the nerve was considered successful when either component of the sciatic nerve (tibial or peroneal) was identified: output <0.5 mA elicited a dorsiflexion or plantar flexion of the foot. At this point, 20 mL of the study drug was injected. The end of injection for sciatic nerve block was defined as Time 0.

## Efficacy Measurements and Variables

### Primary End Point

The primary end point was sensory onset time for sciatic and femoral nerve blocks. Sensory onset time was defined as the time elapsed between Time 0 (end of injection for sciatic nerve block) to complete sensory block (absence of sensation using a pinprick test). For femoral nerve block (performed before sciatic nerve block), onset time was calculated at the end of femoral nerve injection. Sensation was assessed every 5 min for a 50 min period by an anesthesiologist unaware of the study solution used. Blocks were assessed in the peripheral sensory distribution of the femoral and sciatic nerve: femoral nerve (distal anterior femoral and patella area), tibial nerve (plantar side of the foot), peroneal common nerve (lateral cutaneous side of the calf) and superficial peroneal nerve (dorsal aspect of the foot). Sensory block was determined using a 3 point rating scale: 0 = normal sensation, 1 = blunted sensation, 2 = absence of sensation (anesthesia).

### Secondary End Points

The onset of motor block was evaluated by asking the patient to move: leg extension (femoral nerve), adduction of the femur (obturator nerve), plantar flexion of foot (tibial nerve) and dorsiflexion of foot (peroneal nerve). Movement was rated on a 3 point scale: 0 = normal contraction, 1 = reduced contraction (paresis), 2 = no contraction (paralysis). Onset time of motor block was time elapsed between Time 0 (end of block placement) to paralysis. Resolution of sensory and motor block for the knee and the foot of the operated leg was tested every hour after surgery.

The intensity of nerve stimulation and time required to perform the blocks were recorded. The time required to perform the block was defined as the time elapsed from the beginning of the procedure (insertion of the needle through the skin) to the end of local anesthetic injection. Paresthesia was noted at the end of the study (at 48 h).

A thigh tourniquet was used in all patients during surgery. Pain at surgical incision or from the tourniquet was noted. When necessary (pain during surgery or tourniquet pain >3/10), general anesthesia was induced with propofol and sufentanil (0.3 $\mu$g/kg). Anesthesia was maintained with sevoflurane, supplemented with intraoperative administration of sufentanil (bolus 10 $\mu$g). Other intraoperative analgesics were not permitted.

Postoperative pain was evaluated at rest by a nurse blinded to the study drug using a visual analog scale (VAS) ranging from 0 mm (no pain) to 10 mm (worst imaginable pain). During the first 48 h after surgery, all patients received 2 g propacetamol by a 15 min IV infusion at 6-h intervals and 100 mg IV ketoprofen at 8-h intervals. The first dose of both drugs was given 30 min before the end of the surgery. In the postoperative care unit, all patients with VAS >30 mm received an initial manual titration of 2 mg IV morphine at 5-min intervals until VAS scores <30 mm were obtained. At this time, an IV patient-controlled analgesia (PCA) pump with morphine was connected, delivering 1.5-mg doses with a 6-min lockout period. Pain scores were determined on arrival in the postanesthesia care unit, as well as 6, 12, 18, 24, 30, 36, 42, and 48 h after surgery.

Postoperative respiratory rate was measured in all patients. Respiratory depression was defined as a respiratory rate <10 breaths/min. Sedation was assessed with a 4-point scale as follows: 0 = awake, 1 = sleepy but awakened by voice, 2 = sleepy but awakened by nociceptive stimulation, and 3 = not awakened. Nausea and vomiting were assessed by the absolute presence or absence of the symptom.

Analgesic efficacy was recorded as need for rescue morphine (total morphine consumption in mg, number of morphine boluses via PCA, number of morphine requests via PCA).

## Plasma Pharmacokinetics

A second separate randomization scheme was used to select patients for pharmacokinetic analysis. Pharmacokinetic assessments were performed by the independent anesthesiologist who only knew this randomization. Pharmacokinetic assessments were performed on only five patients in each group via an in-dwelling large-bore IV catheter with a stopcock connected. After drawing and discarding 5-mL of blood, an additional 5 mL of venous blood was collected for determination of drug concentration at the following times: 0, 5, 15, 30, 45, 60, and 90 min. Plasma blood samples were centrifuged and stored at −70°C until the assays were performed. The total plasma concentrations of local anesthetic were determined by using liquid chromatography-mass spectrometry (Laboratoire Biochimie, Groupe Hospitalo-Universitaire, CHU Carémeau, Nimes, France). The assay was shown to be sensitive for as little as 5 ng/mL (defined by a signal-to-noise ratio of 3:1) and showed average recoveries >90% for the 3 drugs. The lower limit of quantitation was defined as the concentration at which the coefficient of variation exceeded 10%. The lower limit of quantitation was 25 ng/mL for all 3 local anesthetics. The linear regression showed linearity in the range of at least 25 to 2000 ng/mL for the 3 compounds ($r > 0.998$). The within-day reproducibility of the method was evaluated at a plasma concentration of 100 ng/mL ($n = 6$) and was respectively 6.2% for bupivacaine, 4.5% for ropivacaine and 3.7% for lidocaine. The between-day reproducibility was evaluated at a plasma concentration of 128 ng/mL in 13 sets of independently prepared samples. The results were 13.1% for bupivacaine, 10.33% for ropivacaine, and 8.6% for lidocaine.

## Statistical Analysis

Statistical analysis was conducted using SAS (release 8.0; SAS institute, Cary). The primary end point

**Table 1.** Anthropometric Characteristics and Surgical Duration

| | Bupivacaine ($n = 20$) | Bupivacaine-Lidocaine ($n = 21$) | Ropivacaine ($n = 20$) | Ropivacaine-Lidocaine ($n = 21$) |
|---|---|---|---|---|
| Age (yr) | 55 ± 16 | 46 ± 18 | 51 ± 17 | 45 ± 16 |
| Height (cm) | 167 ± 9 | 170 ± 7 | 162 ± 24 | 166 ± 7 |
| Weight (kg) | 72 ± 12 | 71 ± 14 | 75 ± 12 | 68 ± 13 |
| Sex (M/F) | 11/9 | 15/6 | 12/8 | 13/8 |
| Limb: right/left | 9/11 | 11/10 | 9/11 | 11/10 |
| Duration of surgery (min) | 64 (34–123) | 50 (30–100) | 62 (34–125) | 51 (34–75) |
| Surgical procedures | | | | |
| Knee arthroplasty | 5 | 8 | 5 | 8 |
| Tibial osteotomy | 7 | 4 | 4 | 7 |
| Ankle fracture | 5 | 6 | 9 | 6 |
| Foot surgery (Hallux) | 3 | 3 | 2 | 0 |

Values are mean (SD) and medians (5th–95th percentiles), except for sex, side and surgical procedures (count).

There were no significant differences among the groups.

was the onset time of sensory blocks in mixture groups compared with ropivacaine and bupivacaine groups. The number of patients required for this study was estimated based on a pilot study of 20 patients per group, in which a combination of bupivacaine and lidocaine decreased the sciatic block onset time from 30 ± 10 min to 10 ± 5 min compared with bupivacaine alone. In this pilot study, complete sensory recovery for duration of analgesia (h) was $18^{10-21}$ for bupivacaine and $12^{9-14}$ for the mixture of bupivacaine and lidocaine. We calculated that we would need to study 20 patients/group to detect a statistically significant difference among the groups ($P = 0.05$, power = 80%). An intention-to-treat analysis was performed. Comparisons of continuous variables among the groups were performed using unpaired Student's *t*-test or the Mann–Whitney *U*-test. Categorical variables were analyzed using a contingency table analysis with Fisher's exact test. Continuous variables are presented as mean (SD), 95% confidence interval, or both or median (range). Categorical variables are presented as number (percent). Onset times were compared using log rank test (Kaplan-Meier diagram). Pain scores were compared by the Wilcoxon two sample confidence interval with Bonferroni correction for multiple comparisons.

All comparisons were two-tailed, and a $P$ value of $<0.05$ was required to exclude the null hypothesis.

## RESULTS

Eighty-two patients were enrolled in the study. No differences in age, sex, weight, height, ASA classification and duration or type of surgery were observed among the groups (Table 1).

All nerves (femoral and sciatic) for all patients were localized. For sciatic nerve block, the common peroneal nerve was elicited in 16 patients (19%), whereas the tibial nerve was elicited in 66 patients (80%), with no difference among the 4 groups. Intensity of current stimulation is listed in Table 2. Times to perform femoral block (median: 3 min) and sciatic nerve block (median: 3 min) were similar among groups (Table 2). No changes in arterial blood pressure, heart rate or hemoglobin oxygen saturation were observed during the observation period, and no adverse hemodynamic events were reported among groups (data not provided).

Primary outcomes: for bupivacaine, onset times of complete sensory block were significantly reduced in the bupivacaine-lidocaine group compared with the bupivacaine group (Fig. 1) for femoral, tibial, and peroneal nerves. For ropivacaine (Fig. 2), no difference was observed for the peroneal nerve. Onset times of surgical block (time 0 to complete sensory and motor block) for femoral and sciatic nerves are listed in Table 2. Sensory and motor recovery times were shorter for femoral and sciatic nerves in mixture groups compared with pure solutions (Table 2).

Table 3 shows the incidence of tourniquet pain and inadequate surgical anesthesia (general anesthesia). During the first 24 h after surgery, 7 patients in the bupivacaine group, 6 patients in the ropivacaine group, 8 patients in the bupivacaine-lidocaine group, and 7 patients in ropivacaine-lidocaine group did not require any titration or bolus of morphine ($P > 0.05$). VAS pain score were similar among all four groups. Postoperative nausea and vomiting were similar in all four groups (Table 3). No patient reported pruritus, sedation or respiratory depression. No paresthesia was identified on the operated limb.

The total plasma concentrations of bupivacaine and ropivacaine were larger in patients receiving bupivacaine or ropivacaine alone than in patients receiving the mixtures with lidocaine ($P < 0.05$) (Figs. 3 and 4). Mixing lidocaine with bupivacaine reduced the Cmax for bupivacaine from 1095 ± 520 ng/mL to 450 ± 80 ng/mL. Mixing lidocaine with ropivacaine reduced the $C_{max}$ for ropivacaine from 1840 ± 590 ng/mL to 460 ± 270 ng/mL. The $T_{max}$ for the groups did not differ and was 30–45 min for all subjects. $C_{max}$ for lidocaine in both solutions groups was 2625 ± 610 ng/mL (Fig. 5). No sign of neurologic or cardiac toxicity occurred in any patient.

**Table 2.** Time to Perform Block, Intensity of Stimulation, Onset Time, Recovery Time

| | Bupivacaine ($n$ = 20) | Bupivacaine-Lidocaine ($n$ = 21) | Ropivacaine ($n$ = 20) | Ropivacaine-Lidocaine ($n$ = 21) |
|---|---|---|---|---|
| Time to perform femoral block (min) | 3 (2–4) | 3 (2–3) | 3 (2–3) | 3 (2–3) |
| Minimal intensity (femoral block) (mA) | 0.45 (0.35–0.53) | 0.45 (0.35–0.50) | 0.45 (0.35–0.50) | 0.45 (0.35–0.50) |
| Time to perform sciatic block (min) | 3 (2–5) | 3 (2–4) | 3 (2–5) | 3 (2–4) |
| Minimal intensity (sciatic block) (mA) | 0.46 (0.40–0.55) | 0.46(0.40–0.56) | 0.46 (0.40–0.56) | 0.46 (0.40–0.56) |
| Tibial nerve response | 6 (30%) | 3 (21%) | 3 (15%) | 4 (20%) |
| Common peroneal nerve response | 14 (70%) | 18 (79%) | 17 (85%) | 16 (80%) |
| Total onset time for surgical surgery (sensory and motor block) | | | | |
| Femoral nerve (min) | 30 (15–45) | 15 (15–20)* | 15 (10–25) | 10 (5–15) |
| Sciatic nerve (min) | 30 (15–45) | 15 (5–25)* | 25 (15–40) | 15 (5–25)† |
| Recovery sensory time | | | | |
| Femoral nerve (h) | 22 (15–32) | 13 (5–24)* | 18 (10–22) | 12 (8–16)† |
| Sciatic nerve (h) | 19 (12–28) | 12 (4–20)* | 14 (8–20) | 10 (8–13)† |
| Recovery motor time | | | | |
| Femoral nerve (h) | 18 (13–28) | 12 (4–20)* | 15 (9–24) | 11 (6–14)† |
| Sciatic nerve (h) | 18 (12–23) | 12 (4–18)* | 13 (8–20) | 10 (7–12)† |

Values are mean (SD), medians (5th–95th percentiles) and number (percentage).

Total Onset time of sensory block and motor block for surgery was defined as the interval between time 0 (end of injection) and a complete sensory and motor block.

* $P < 0.05$ vs bupivacaine alone.

† $P < 0.05$ vs ropivacaine alone.

## DISCUSSION

Mixtures of bupivacaine or ropivacaine with lidocaine have a significantly faster onset than bupivacaine or ropivacaine alone when used for combined sciatic-femoral nerve block. Postoperatively, ropivacaine and bupivacaine alone provided longer duration of effect, but did not significantly decrease postoperative analgesic requirements.

### Pharmacodynamics

The choice of local anesthetic reflects a balance between the need for rapid onset time and desire for a prolonged duration of postoperative analgesia.[13,14] Because orthopedic procedures produce significant postoperative pain, long-acting local anesthetics are advocated to improve the quality of postoperative analgesia.[13]

Our study demonstrated that bupivacaine, when used for combined sciatic-femoral nerve blocks, may require up to 50 min (Fig. 1) to produce complete sensory anesthesia. The addition of lidocaine (400 mg) and the corresponding reduction in bupivacaine dose (200–100 mg) significantly reduced local anesthetic onset times for combined block (Table 2 and Fig. 1). These results agree with those reported by Fanelli et al.[15] who found a sensory onset time of 51 ± 32 min with bupivacaine (0.5%) used for femoral (10 mL) and sciatic (15 mL) blocks. With 20 mL of bupivacaine 0.5% for femoral nerve block, Marhofer et al.[14] found a shorter onset time (30 ± 11 min) compared with our results. A possible explanation for the faster sensory onset time could be the different level of intensity of stimulation: <0.3 mA for Marhofer et al.[14] <0.5 mA for Fanelli et al.[15] and our study (Table 2). In our study, similar intensities of nerve stimulation were required in both the bupivacaine and the bupivacaine-lidocaine groups.

Mixture solutions have the disadvantage of a short duration of analgesia compared with using a long-acting local anesthetic alone. In our study, time to first morphine request was less in patients receiving the bupivacaine-lidocaine mixture than those receiving bupivacaine alone.

Fanelli et al.[15] suggested that ropivacaine may be the most suitable choice of local anesthetic for rapid onset. In our study, the onset time of ropivacaine alone was similar to that reported by Marhofer et al.[14] (30 ± 11 min with 20 mL of ropivacaine 0.5%) or with Casati et al.[13] (15 ± 30 min, with 12 mL ropivacaine 0.75%). We found that the addition of lidocaine to ropivacaine produced the most rapid onset of the four groups, but also the shortest duration (Table 3).

All solutions were prepared with epinephrine (1:200,000) to reduce the peak concentration of bupivacaine and ropivacaine. For the bupivacaine group, the dose was 200 mg for all patients, which is not recommended without epinephrine.[16] In this manner, we were able to safely study combined femoral-sciatic nerve blocks using large volumes (40 mL) of the most concentrated commercially available solutions of bupivacaine (0.5%) and ropivacaine (0.75%). The use of these large volumes and highest concentrations has been shown to provide faster onset of nerve block and slightly delayed first request for pain medication.[13]

For epidurals, such combinations of mixtures have been used clinically for more than 40 yr with varied

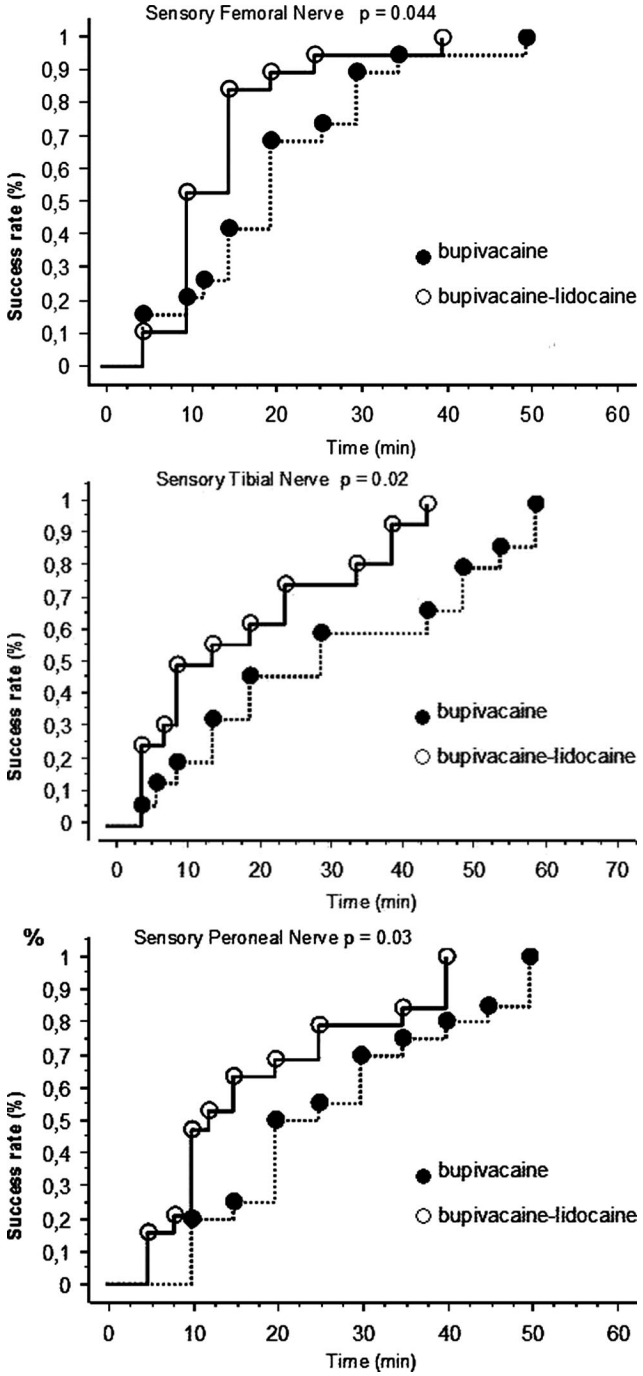


**Figure 1.** Kaplan-Meier plot of the onset of complete sensory block with bupivacaine 200 mg versus bupivacaine 100 mg mixed with lidocaine 400 mg (bupivacaine-lidocaine). Time 0 was defined as the time corresponding to the end of the local anesthetic solution injection. Success was defined as absence of sensation using a pinprick test.

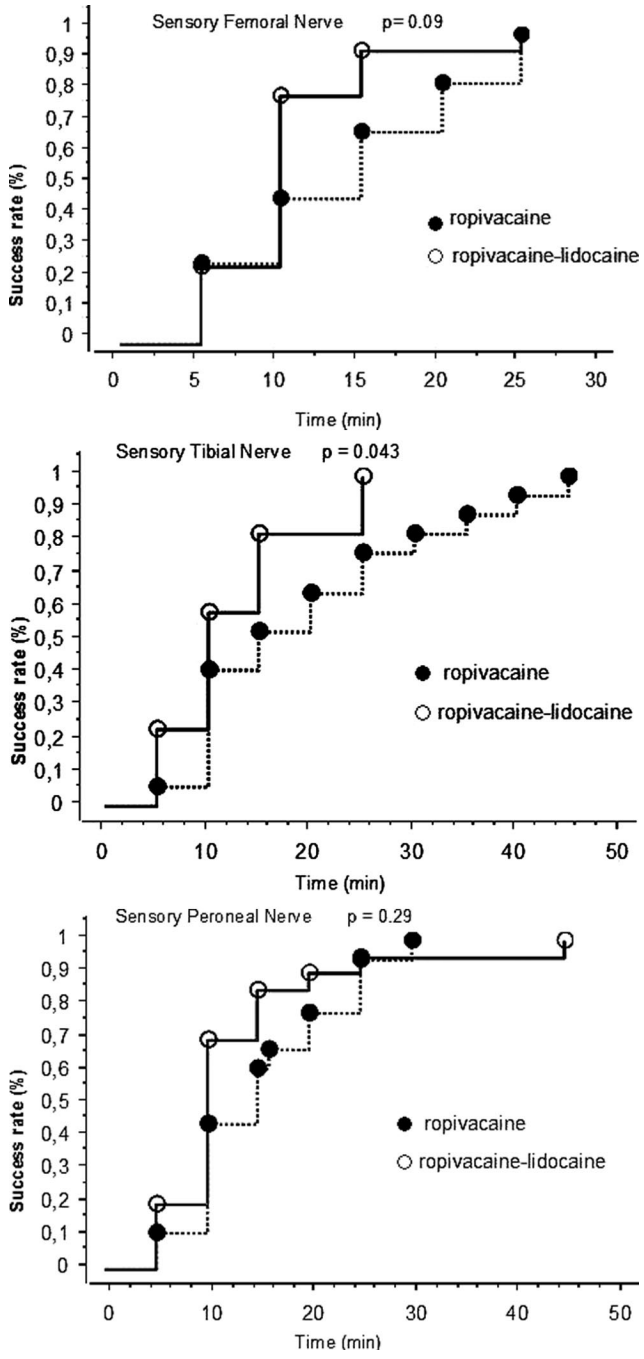


**Figure 2.** Kaplan-Meier plot of the onset of complete sensory block with ropivacaine 300 mg versus ropivacaine 150 mg mixed with lidocaine 400 mg (ropivacaine-lidocaine). Time 0 was defined as the time corresponding to the end of the local anesthetic solution injection. Success was defined as absence of sensation using a pinprick test.

results[8–10,17,18] and the rationale for combining the drugs remains unclear.[17] Results with bupivacaine indicate a limited clinical advantage in speed of onset without significant shortening of duration of action for mixtures[8,9]: no difference among the groups in the time taken for bilateral loss of cold sensation to reach T4. A mixture of etidocaine(1%)-lidocaine (1%) does not offer any advantages as compared to etidocaine alone,[18] because the sensory block produced by the mixture tended to begin more slowly and had a distinctly shorter duration as compared to the block caused by etidocaine alone. For ropivacaine or levobupivacaine, no studies have been conducted to demonstrate any shorter onset sensory time.

### Pharmacokinetics

Recently, Vanterpool et al.[20] analyzed plasma concentrations of a pure solution of ropivacaine after a

**Table 3.** Frequency of Principal Side Effects in the Four Groups

| | Bupivacaine ($n = 20$) | Bupivacaine-Lidocaine ($n = 21$) | Ropivacaine ($n = 20$) | Ropivacaine-Lidocaine ($n = 21$) |
|---|---|---|---|---|
| Tourniquet pain | 1 (5) | 1 (5) | 0 (0) | 0 (0) |
| Conversion (general anesthesia) | 3 (15) | 4 (19) | 1 (5) | 2 (9.5) |
| Total intraoperative IV sufentanil ($\mu$g) | 25 (20–30) | 30 (20–35) | 25 | 30 |
| Number (%) of patients requiring | | | | |
| No morphine during the first 24 h | 7 (35) | 8 (38) | 6 (30) | 7 (33) |
| Total morphine consumption (mg/48 h) | 9 (0–48) | 15 (0–55)* | 13 (0–63) | 10 (0–44) |
| Time to first morphine request (h) | 16 (5–23) | 12 (1–15)* | 10 (0–17) | 10 (1–13) |
| Postoperative VAS pain at rest | | | | |
| 0 h | 0 (0–1) | 0 (0–0) | 0 (0–0) | 0 (0–0) |
| 6 h | 0 (0–1) | 0 (0–1) | 0 (0–0) | 0 (0–0) |
| 12 h | 0 (0–1) | 0 (0–4) | 0 (0–4) | 2 (1–4) |
| 18 h | 0 (0–0) | 0 (0–3) | 1 (0–5) | 3 (1–4) |
| 24 h | 0 (0–5) | 0 (0–3) | 1 (0–4) | 3 (1–4) |
| 30 h | 3 (0–6) | 1 (0–4) | 1 (0–5) | 3 (1–5) |
| 36 h | 2 (0–6) | 0 (0–1) | 0 (0–3) | 1 (1–3) |
| 42 h | 0 (0–3) | 0 (0–1) | 0 (0–3) | 1 (1–3) |
| 48 h | 0 (0–2) | 0 (0–1) | 0 (0–1) | 1 (1–3) |
| PONV | 3 (15%) | 2 (10%) | 3 (15%) | 1 (5%) |

Values are medians (5th–95th percentiles) and number (percentage).

For total intraoperative IV sufentanil ($\mu$g), data are presented only with median for ropivacaine (1 patient received 25 $\mu$g) and for lidocaine-ropivacaine (the 2 patients received 30 $\mu$g).

VAS = visual analog scale; PONV = postoperative nausea and vomiting.

* $P < 0.05$ vs bupivacaine.

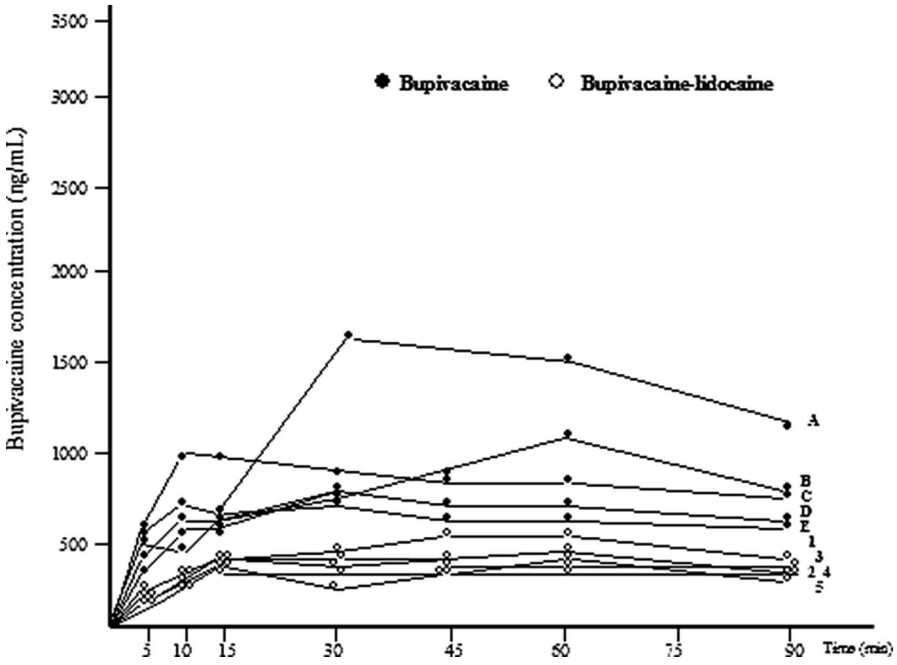


**Figure 3.** Plasma concentrations of bupivacaine after femoral and sciatic nerve injection with 200 mg of bupivacaine alone ($n = 5$) or with 100 mg of bupivacaine mixed with lidocaine (400 mg) (1:200,000 epinephrine for both solutions). Venous blood samples were obtained at 5, 10, 15, 30, 45, 60, and 90 min after the final injection. Each curve of patient was identified with a letter A, B, C, D, E (for bupivacaine alone) and a number 1, 2, 3, 4, 5 (for bupivacaine mixed with lidocaine). Bupivacaine versus bupivacaine-lidocaine: $P = 0.01$.

combined sciatic-femoral block. With 300 mg ropivacaine, $C_{max}$ was 1560 ± 351 ng/mL, with a range of 1118 to 2346 ng/mL, similar to our study (Fig. 4). Several studies have shown that the blood level of local anesthetics is influenced by the site, concurrent use of epinephrine and conditions under which blood samples are obtained.[19,21] When combined blocks are performed at the lower limb, Kaloul et al.[21] and Vanterpool et al.[20] demonstrated that the peak plasma concentration appeared within the first 60 min.

The time course of local anesthetic mixtures has not been published. However, there are several cases of reported toxicity associated with modest doses local anesthetic combinations. Reinikainen et al.[6] reported a cardiac arrest after an interscalene block with ropivacaine 150 mg combined with lidocaine 360 mg. The plasma concentration after 110 min was 1243 ng/mL for ropivacaine and 1500 ng/mL for lidocaine. These concentrations were less than the threshold measured after similar complications with pure solution.[19] However, the toxicity of local anesthetics seems to be additive.

If the toxicities of local anesthetics are additive, then the apparent safety of reducing the concentration of bupivacaine or ropivacaine may be offset by the

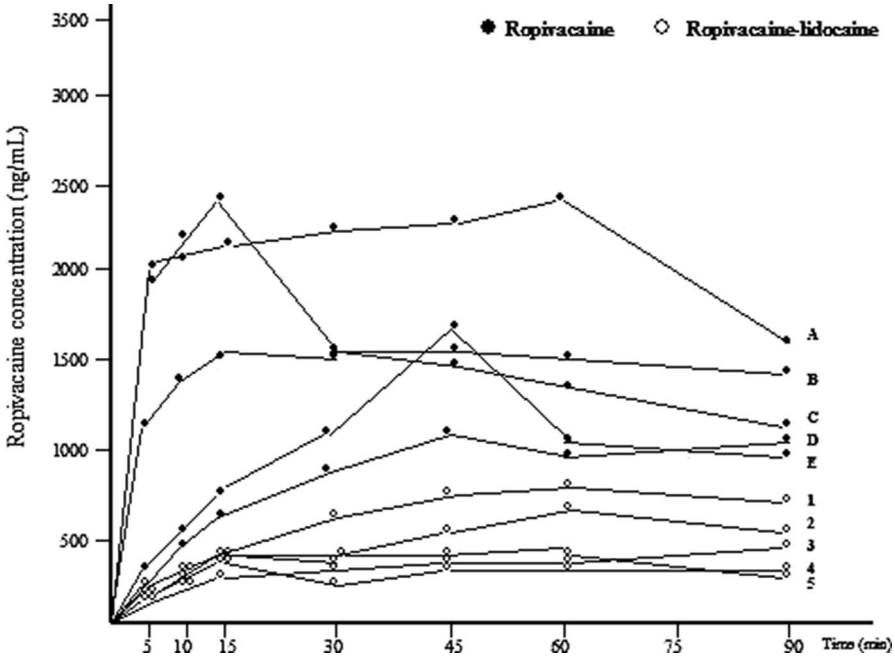


**Figure 4.** Plasma concentrations of ropivacaine after femoral and sciatic nerve injection with 300 mg of ropivacaine alone ($n = 5$) or with 150 mg of ropivacaine mixed with lidocaine (400 mg) (1:200,000 epinephrine for both solutions). Venous blood samples were obtained at 5, 10, 15, 30, 45, 60, and 90 min after the final injection. Each curve of patient was identified with a letter A, B, C, D, E (for ropivacaine alone) and a number 1, 2, 3, 4, 5 (for ropivacaine mixed with lidocaine). Ropivacaine versus ropivacaine-lidocaine: $P = 0.009$.

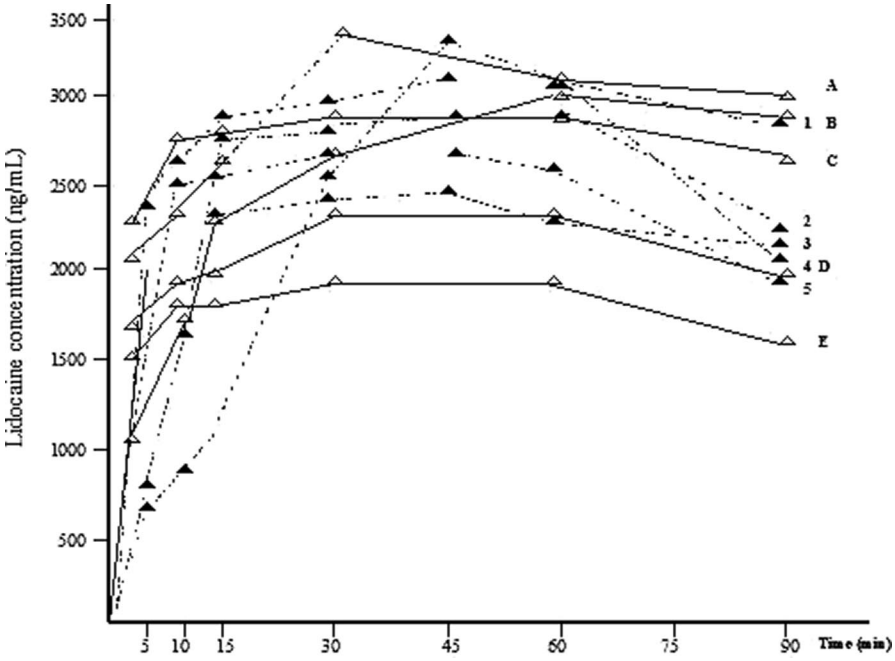


**Figure 5.** Plasma concentrations of lidocaine after femoral and sciatic nerve injection with 400 mg of lidocaine mixed with 100 mg of bupivacaine ($n = 5$) or 150 mg of ropivacaine ($n = 5$) (1:200,000 epinephrine). Venous blood samples were obtained at 5, 10, 15, 30, 45, 60, and 90 min after the final injection. Each curve of patient was identified with a letter A, B, C, D, E (for lidocaine mixed with bupivacaine) and a number 1, 2, 3, 4, 5 (for lidocaine mixed with ropivacaine).

additional toxicity from the lidocaine. For example, one patient in the ropivacaine–lidocaine group had a peak concentration of lidocaine >3500 ng/mL. Although this was not a toxic concentration *per se*, it might produce toxicity in combination with the additional 500 ng/mL ropivacaine in that individual.[2,6] Because of this consideration, we recommend that clinicians use lower doses than we used in this study to preclude possible toxicity from the additive toxicities of lidocaine and the long-acting local anesthetics.

### Study Limitations

The number of patients in this study was inadequate to assess the safety of the combination of lidocaine with long-acting local anesthetics. As mentioned above, lower concentrations of ropivacaine or bupivacaine may not be safer in the presence of significant concentrations of lidocaine. A substantially larger study is required to demonstrate whether the combination provides a safety benefit.

In conclusion, we have demonstrated that adding 20 mL of 2% lidocaine to an equal volume of 0.5% bupivacaine or 0.75% ropivacaine produces a faster onset of a femoral-sciatic block, but reduces block duration. There is still the potential for toxicity from accidental vascular injection or the additive toxicity of lidocaine. Thus, slow injections and vigilant postoperative monitoring are recommended.

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