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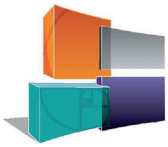

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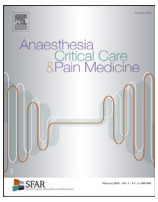

Original Article

Plasma concentrations of ropivacaine following ultrasound-guided or nerve-stimulator-guided femoral nerve block: A prospective randomised study☆

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ABSTRACT

Objective: Our aim was to establish a plasma concentration curve for ropivacaine following femoral nerve blockade and to ascertain whether the resulting plasma concentrations differ significantly depending on whether neurostimulation (NS) or ultrasound (US) guidance was used.
Methods: Sixteen male and female subjects aged 18 to 80 who were scheduled to undergo unilateral total knee replacement or anterior cruciate ligament reconstruction under general or spinal anaesthesia, and for whom a femoral nerve block was indicated for postoperative analgesia, were enrolled in this prospective, randomised study. Patients were randomised to undergo either US or NS-guidance femoral nerve blocks. All blocks were performed with 20 mL of 5 mg/mL ropivacaine. Blood samples were drawn before the nerve block and 20, 30, 40, 50, 60, 70, and 80 minutes after the block. Plasma levels of ropivacaine were analysed by high performance liquid chromatography (HPLC).
Results: All blocks were successful and no patient showed signs or symptoms of local anaesthetic toxicity. The plasma concentration of ropivacaine peaked at 30 minutes in both arms. There was no significant difference in peak levels between US and NS-guidance (0.325 ± 0.186 versus 0.356 ± 0.106 μg/mL). Cmax and tmax were very similar between groups (0.364 ± 0.177 versus 0.344 ± 0.127 μg/mL, 33.75 ± 15.06 versus 31.25 ± 13.56 min for US and NS, respectively).
Conclusion: Plasma concentrations of ropivacaine peak around 30 minutes after a femoral nerve block regardless of the technique used. No significant difference was found between US- and NS-guidance.

1. Introduction

Regional anaesthesia (RA) is a very effective anaesthesia and analgesia technique. Although the incidence of local anaesthetic systemic toxicity (LAST) is very low [1], it remains a concern. It usually results from a large overdose or an accidental intravascular injection. Data on the maximum admissible dose of local anaesthetic using different techniques are rather old [2–5] and are not specific to the site of injection. In 2007, Rettig et al. [6] corroborated previous thinking that maximal doses of local anaesthetic should be block- and approach-specific by demonstrating that the peak arterial plasma concentration of ropivacaine was higher after a supraclavicular approach than after an infraclavicular one. More recently, a study by Lapmahapaisan et al. [7] demonstrated that mean plasma concentrations of bupivacaine peaked 30 minutes after a single-injection femoral nerve block. Affas et al. [8] compared plasma concentrations of ropivacaine after periarticular infiltration analgesia and femoral block for primary total knee arthroplasties. They found that the plasma concentration of ropivacaine after repeated femoral blocks tended to accumulate during the first 24 hours after surgery, likely peaking more than 24 hours later. However, their data did not cover the early peak plasma concentration time points.

There are currently limited data on how plasma levels of local anaesthetics vary according to the nerve block technique used.

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Practitioners typically inject the entire dose of local anaesthetic in one location with neurostimulation (NS) guidance, while they tend to perform multiple intermittent injections after needle repositioning to optimize local anaesthetic spread with ultrasound (US) guidance. Thus, this might lead to different absorption rates. A study by Barrington et al. suggests that US-guidance is associated with a reduced incidence of local anaesthesia systemic toxicity [9].

The aim of this study was to establish a plasma concentration curve for ropivacaine following femoral nerve blockade and to ascertain whether the resulting plasma concentrations differ significantly depending on the nerve localization technique used (US vs. NS). We determined Cmax and tmax. However, no attempt was made to establish an area under the curve (AUC).

2. Methods

The Institutional Review Board and Ethics Committee of the Hospital for Joint Diseases at the NYU Langone Medical Center approved the study protocol (11-01266). Male and female subjects aged 18 to 80 who were scheduled to undergo unilateral total knee replacement or anterior cruciate ligament reconstruction under general or spinal anaesthesia, and for whom a femoral nerve block was indicated for postoperative analgesia, were asked to participate in this prospective, randomised study. Patients younger than 18 or older than 80; patients with an allergy or a contra-indication to any of the medications used in the study, or with a contra-indication to any of the procedures; and patients with any diagnosed or reported cognitive dysfunction were excluded from participation. Written, informed consent was obtained from all participants.

In order to establish the minimum number of blood samples needed to accurately determine the peak plasma level of ropivacaine, an initial (unpublished) pilot study including 5 patients using 7 time points for blood sampling was performed, demonstrating a peak level between 30 and 40 minutes following block performance and suggesting higher plasma levels in the ultrasound-guided group. Based on previous literature data and our pilot data, we estimated that in order to detect a difference of 0.2 μg/mL between the means of the groups, assuming a standard deviation of 0.10 μg/mL in both groups, with an alpha of 0.05 and a power of 80%, we would need 8 patients per group. Sixteen patients were subsequently enrolled and randomly assigned, using a computer-generated permutation table with blocks of four, to receive the femoral nerve block under either nerve-stimulation or ultrasound guidance. One of the authors (AA) generated the random allocation sequence. Sequentially numbered opaque envelopes were used to conceal group assignment until enrolment. Three of the authors (AA, LM and GC) enrolled patients and assigned participants to the specific nerve block technique.

After applying standard ASA monitors and administering oxygen via nasal cannula, patients were sedated with a combination of fentanyl and midazolam. The site of injection was prepped with chlorhexidine and standard sterile technique was utilized. All nerve blocks were performed with a 50-mm 22G stimulating needle (Stimuplex®, B-Braun, Bethlehem, PA) and all patients received 20 mL of 5 mg/mL ropivacaine. This volume of local anaesthetic has been shown to provide a high quality femoral nerve blockade [10]. For ultrasound-guided blocks, the femoral nerve was visualized lateral to the artery using a high frequency 13–16 MHz probe and the local anaesthetic was injected with negative intermittent aspiration and deposited perineurally. For the nerve-stimulation guided nerve blocks, the femoral artery was palpated and the needle was inserted 1 cm lateral to the artery and 1 cm caudal to the inguinal ligament. The ropivacaine was injected when a sustained quadriceps twitch was elicited at $\leq$ 0.4 mA with a nerve-stimulator (Stimuplex®, B-Braun, Bethlehem, PA). The patients then received either a standard general or spinal anaesthetic for the case. Whereas the patients allocated to the intervention group and their physicians were aware of the allocated study arm, outcome assessors, i.e., the authors performing the HPLC measurements (OA, EL and EC), were kept blinded to the allocation.

Blood samples were drawn before the femoral nerve block, usually upon insertion of the intravenous catheter, and at 20, 30, 40, 50, 60, 70 and 80 minutes after the injection, from an intravenous catheter inserted on the upper limb contralateral to the intravenous line used to administer fluids. Each 3 mL blood sample was collected in a tube containing EDTA for anticoagulation and immediately placed on ice. Centrifugation was used to separate the plasma.

Plasma ropivacaine levels were measured using High-Pressure Liquid Chromatography (HPLC) following extraction according to a method described by Reif et al. [11]. However, a number of alterations were made to this method. A different column (C18 rather than C8) was used and the composition of the mobile phase was optimized. The previously published method conditions were not suitable as the retention times of ropivacaine and the internal standard (bupivacaine) were very similar, resulting in overlapping peaks. A decrease in polarity of the mobile phase to 10 mM potassium dihydrogen-phosphate and acetonitrile 73:27 (v/v) gave reasonable retention times for both the analyte and the internal standard. In addition, the *n*-heptane ethyl acetate mixture used for extraction was replaced with ethyl ether, which was considerably easier to completely remove under argon because of its high volatility.

In brief, samples were centrifuged at 3000 RPM for 10 minutes (centrifuge model 614, The Drucker Company, Philipsburg, PA) and then 100 μL of internal standard (bupivacaine) at a concentration of 10 μg/mL was added to each tube, except for blank (control) samples. The samples were then alkalinized with 50 μL of 1 M NaOH and 3 mL of ethyl ether was also added to each tube. The tubes were shaken and centrifuged and the organic phase (ethyl ether) was transferred to a clean tube to which 50 μL of 0.1 M H_2SO_4 was added. The tubes were again shaken (3 min) and after centrifugation (5 min at 3500 rpm), the organic phase was discarded. The aqueous phase containing the analyte was transferred to a HPLC vial. The aqueous phase was then buffered with approximately 200 μL of 0.2 M sodium acetate and each sample was injected into the chromatographic system. Aliquots of 40 μL were injected in the HPLC apparatus. A mobile phase of acetonitrile-potassium dihydrogen-phosphate (10 mM, pH 2.1) (73:27, v/v) was delivered with a flow rate of 1 mL/min. The detector was set at 205 nm and the column temperature was maintained at 30 °C. Ropivacaine was detected at tR = 5–6 min and bupivacaine at tR = 9–10 min.

A calibration curve was established using known concentrations of authentic standards. Plasma samples with a concentration of 5, 2.5,1, 0.25, 0.1, and 0.05 μg/mL were made up (n = 6 for each concentration). The drug was extracted from the plasma. Samples of drug free plasma were also extracted for control experiments. The curve was obtained by plotting the ratio of the peak area of the drug (ropivacaine) to the peak area of the internal standard (bupivacaine) versus the concentration of ropivacaine.

3. Statistical analysis

We examined the time progression of the primary variable between 20 and 80 minutes, comparing values between the two groups. Repeated measures Anova were abandoned (due to poor goodness-of-fit statistics) in favour of multivariate analysis. As a control, we compared groups pairwise at each time point using rank analysis. Analysis was repeated after normalizing to body