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Paediatrics

Pharmacokinetics of levobupivacaine with epinephrine in transversus abdominis plane block for postoperative analgesia after Caesarean section

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Abstract

Background: Transversus abdominis plane block is increasingly used for post-Caesarean section analgesia. Cases of toxicity and the limited pharmacokinetic information during pregnancy motivated this study. The objective of the study was to characterise and compare the pharmacokinetics of levobupivacaine with epinephrine in tranversus abdominis plane block, in post-Caesarean section patients and healthy volunteers.

Methods: After approval by the Ethics Committee, we collected data from 12 healthy parturients after elective Caesarean section (Study 1) and data from 11 healthy male volunteers from a previous study (Study 2). Transversus abdominus plane block was performed under ultrasound guidance. The following injectates were used: levobupivacaine 0.25%, 20 ml with epinephrine 5 μg ml^{-1} (Study 1) per side; 20 ml of the same solution (unilateral block) (study 2). The plasma venous concentration of levobupivacaine was measured serially for 90 min. Pharmacokinetic parameters (volume of distribution, clearance, and absorption half-life) were estimated using a non-linear mixed effects model (NONMEM). Simulation in 1000 patients estimated the maximum concentration and the time to reach it after bilateral transversus abdominis plane block.

Results: Venous concentrations were below toxic levels (2.62 mg L^{-1}). Levobupivacaine volume of distribution after Caesarean section was higher than in healthy volunteers [172 L (70 kg)$^{-1}$ (95% confidence interval: 137–207) *vs* 94.3 L (70 kg)$^{-1}$ (95% CI: 62–128); $P<0.01$]. Clearance and absorption half-life were similar. The simulation showed that maximum levobupivacaine concentration is lower and occurs later in postpartum patients ($P<0.01$). Postoperative analgesia was effective.

Conclusions: Postpartum women reached relatively low plasma concentrations of levobupivacaine after transversus abdominal plane block given a volume of distribution 80% higher than volunteers, which could confer a greater margin of safety.

Clinical trial registration: NCT02852720.

Keywords: analgesia; Caesarean section; levobupivacaine; pharmacokinetics; transversus abdominis

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Editor's key points

- Transversus abdominis plane (TAP) block with levobupivicaine is commonly used for analgesia after Caesarean section.
- The aim of the current study was to investigate the influence of pregnancy on levobupivacaine pharmacokinetics.
- Administration of 100 mg levobupivacaine with epinephrine for TAP block resulted in plasma concentrations well below toxic levels.
- Volume of distribution and time to maximum concentration were significantly higher in pregnant females than in healthy male volunteers.

Caesarean section is among the 10 most painful surgeries performed on a regular basis.[1] Multiple strategies have been proposed for pain control after this surgery, including neuraxial analgesia, systemic opioids, non-opioid drugs, and peripheral nerve blocks, among others. In recent years, transversus abdominis plane (TAP) block has become a popular technique to provide post-Caesarean section analgesia and a reasonable alternative for patients who are unable to receive neuraxial morphine.[2]

Several studies have shown that this technique is highly effective and safe when used as part of a multimodal analgesic regime after abdominal surgery.[3,4] However, TAP block requires a relatively large volume (40 ml) of local anaesthetic solution injected in the muscular plane, between the internal oblique and transversus abdominis muscles, to optimise the spread within a fascial plane.[5] This fact has raised concerns about the safety of this technique in the obstetric population,[6,7] as most of local anaesthetic toxicity cases have occurred in this population.[8]

A previous study of our group in healthy volunteers showed that the addition of epinephrine in TAP block was highly effective to reduce levobupivacaine peak plasma concentrations.[9] Currently, there is scarce information on levobupivacaine pharmacokinetics (PK) after TAP block in pregnant patients. Dose schemes routinely used for pain control after Caesarean section have been extrapolated from studies in non-obstetric patients without considering possible differences in drug disposition because of pregnancy. A formal PK analysis, including data from healthy volunteers and pregnant patients, should allow a more comprehensive approach to guide dosing schemes in this population.

We hypothesised that levobupivacaine PK after TAP block is altered in post-Caesarean section patients because of body composition and cardiovascular changes associated with late pregnancy. Our objective was to generate a PK model derived with data from pregnant patients after Caesarean section and in healthy volunteers, to characterise and compare levobupivacaine with epinephrine disposition after TAP block in both populations.

Methods

Data from two sources were used in the analysis.

Study 1

After institutional Ethics Committee approval (School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile) and written informed consent, 12 term non-obese pregnant patients, ASA Physical status 1 or 2, scheduled for elective Caesarean section, were recruited in this prospective, single-blind PK study (ClinicalTrials.gov identifier: NCT02852720). Patients were excluded if they had any allergy/sensitivity to the local anaesthetic, significant renal or liver dysfunction, or a BMI greater than 35 kg m^{-2}.

An i.v. catheter (18-gauge) was placed under local anaesthesia for co-hydration. After the initiation of standard monitoring (continuous electrocardiogram, non-invasive arterial blood pressure, and pulse oximetry), all patients received spinal anaesthesia with a 25G Whitacre needle (B. Braun Melsungen AG, Melsungen, Germany) at L3–L4 or L4–L5 interspace with hyperbaric bupivacaine 0.75%, 1.4 ml and fentanyl 20 μg to achieve bilateral anaesthetic level of at least T6, determined by pinprick. All surgeries were performed with a Pfannenstiel incision.

After surgery, a second i.v. catheter contralateral to the i.v. infusion was inserted for venous sample extraction. An ultrasound-guided TAP block was performed with levobupivacaine 0.25%, 20 ml with epinephrine 1:200 000 (5 μg ml^{-1}) on each side. One anaesthesiologist experienced in the technique performed all TAP blocks using a SonoSite M-Turbo ultrasound machine (SonoSite, Inc., Bothell, WA, USA) with a L38 × 10^{-5} MHz, 38 mm broadband linear array probe. Blocks were performed with a 21G, 110 mm spinal Quincke needle (Nipro Medical Industries, Ltd., Tatebayashi, Japan) using an in-plane approach.

The extent of bilateral sensory blockade of TAP blocks to temperature, light touch, and sharp touch was determined using ice, cotton wool, and pinprick, respectively, at 1, 2, 6, and 12 h post-block, and the metameric extent of the blockade was recorded. Venous blood samples (2 ml) were obtained at 2, 5, 10, 30, 45, 60, and 90 min after TAP block. The duration of blockade expressed as first dose of rescue pain medications (i.v. morphine 3 mg) was also recorded and symptoms of local anaesthetic systemic toxicity (LAST) were assessed on every control.

Levobupivacaine assay

Levobupivacaine was extracted from plasma using liquid–liquid extraction according to the methods described by Adams and colleagues.[10] The internal standard solution (mepivacaine 30 μg ml^{-1}, 10 ml) was added to 0.2 ml of plasma, sodium hydroxide 100 μl (2 M solution), and diethyl ether 0.6 ml. The mixture was stirred for 1 min and centrifuged for 5 min at 3000 revolutions min^{-1}. Subsequently, the organic phase was transferred to another tube to which 0.05 N sulphuric acid 0.25 ml was added. The mixture was stirred again for another minute and centrifuged for 5 min at 3000 revolutions min^{-1}. The aqueous phase was transferred to another tube for subsequent injection. An aliquot of 100 μl was injected into the high-performance liquid chromatography system. The linearity of the method was evaluated in the range of 0.125–10 μg ml^{-1}, and three concentrations (0.75, 3, and 7.5 μg ml^{-1}) were extracted during each protocol as controls.

Study 2

Data from 11 healthy volunteers were obtained from a study by our group.[9] Briefly, we characterised levobupivacaine PK after TAP block (levobupivacaine 50 mg) with and without epinephrine in healthy male volunteers. Each patient