# Research Paper: Pharmacokinetic Profile of Plasma Levobupivacaine Following Fascia Iliaca Compartment Block for Proximal Femoral Fracture in Older Patients

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## ABSTRACT

**Background:** Fascia Iliaca Compartment Block (FICB) is commonly used in older patients to provide effective analgesia following hip fracture.

**Objectives:** However, only limited Pharmacokinetic (PK) data about levobupivacaine are available to help clinical practice and establish safe volumes and amounts of local anesthetics.

**Methods:** Ten patients aged between 53 and 87 years, who underwent hemiarthroplasty following femoral neck fracture were recruited into this study. A fixed volume (40 mL) of 0.25% levobupivacaine was injected before the induction of anesthesia using ultrasound guidance. Venous blood samples were obtained at 0, 10, 20, 30, 45, 60, 75, 90, and 120 min time points and analyzed using mass spectrometry.

**Results:** The median (interquartile range) maximum observed plasma concentration (Cmax) of levobupivacaine was 0.48 (0.45-0.61) µg/mL, with the time to reach Cmax (tmax) of 38 minutes (30–105) after administration, a half-life of 2.8 h (1.65–5.8), and clearance rate of 0.72 L/min (0.36–1.26). The fixed volume (40 mL) of 0.25% levobupivacaine FICB did not exceed the recognized toxic threshold in adults (2.6 µg/mL).

**Conclusion:** The data described here indicate a similar levobupivacaine PK profile for older patients undergoing FICB for hip arthroplasty compared with the levobupivacaine PK profile for the general population.

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## Introduction

Fascia iliaca compartment block (FICB) is commonly used in older patients to provide effective analgesia following a hip fracture [1]. The fascia iliaca compartment is a potential space, which contains femoral nerve, lateral cutaneous nerve of the thigh, and obturator nerve. The local anesthetic, levobupivacaine, has several favorable features, including low cardio- and neuro-toxicity, high protein binding, and long duration of clinical effect [2]. The proximity of the femoral artery and vein in the fascia iliaca compartment increases the rapid systemic absorption of local anesthetic, and also increases the risk of toxicity.

Older patients and those with pre-existing cardiac, renal, or hepatic conditions have a higher risk of Local Anesthetic Systemic Toxicity (LAST), which can lead to cardiac arrest and death. The Pharmacokinetic (PK) profile of plasma levobupivacaine in these patients is poorly described. This study describes the PK profile of levobupivacaine following FICB in patients undergoing hip arthroplasty.

## Materials and Methods

This study was registered with Research Registry, Identifier 229. Following written and informed consent, 10 patients were recruited to receive FICB before the induction of anesthesia. The inclusion criteria were adult patients with a confirmed fractured neck of femur who were scheduled to receive FICB as part of their anesthetic care. The patients with contraindications to regional anesthesia (The International Normalized Ratio [INR] >3, platelets <50000/μL, localized infections), with a plasma creatinine >300 μM/L, and or those unable or unwilling to give consent were excluded.

An ultrasound-guided FICB with 40 mL of 0.25% levobupivacaine was performed using an in-plane approach. A 22G 50–80 mm insulated long bevel needle (StimuplexR) was used to perform the FICB. Subsequent anesthetic management was at the discretion of the attending anesthetist, with routine care provided as per local departmental guidelines for perioperative management of these patients. Venous blood samples were taken from a dedicated peripheral cannula at 0, 10, 20, 30, 45, 60, 75, 90, and 120 minutes post FICB. The anonymized samples were processed in the laboratory of Scotia Biologics Ltd. The samples were centrifuged (3000 g for 10 min at 4ºC), and aliquots from the upper layer of the resulting plasma fraction were prepared for storage at -80°C. The concentration of levobupivacaine from these samples was quantified by mass spectrometry. The analyzed pharmacokinetic parameters included maximum observed plasma concentration, time to reach maximal concentration, clearance, and half-life.

### Patient plasma analysis

Sample preparation and LC-MS/MS (liquid chromatography with tandem mass spectrometry) analysis were performed in the Rowett Institute, University of Aberdeen. The stock solutions of racemic bupivacaine were prepared daily at 3 mg/mL in methanol, with separate bupivacaine stock solutions used for the preparation of calibration standards and QC (quality control) samples. Calibration standards and QC samples were prepared using human plasma obtained from individuals not given levobupivacaine and spiking them with known concentrations of bupivacaine in the range 3-3000 ng/mL for the calibrants and at 3 ng/mL (low), 90 ng/mL (middle) and 2300 ng/mL (high) for the QC samples. The patients' samples, calibration standards and QC samples (50 μL) were extracted by the addition of 200 μL of acetonitrile containing 0.1% formic acid and 500 ng/mL D9-bupivacaine (internal standard). After vortex mixing and placing on ice for 30 minutes, an equal volume (250 μL) of 0.1% formic acid was added, and the samples were centrifuged. All standard and QC samples were analyzed in duplicate. Five microliters of the supernatant were injected on to the chromatograph.

Chromatography was performed on an ACE 3μ C18 (150 x 2.1 mm) column (Hichrom, Reading, UK) maintained at 50°C with gradient elution using a mobile phase consisting of water (A) and acetonitrile (B) containing 0.1% formic acid. The gradient started at 30% B, increasing to 100% B over a 3-minute period. This process was held for 2 minutes at 100% B before returning to 30% B for 4 minutes for re-equilibration, giving a total run time of 9 minutes. Bupivacaine and the internal standard were eluted with a retention time of 5.1 minutes. MS/MS analysis was performed using a Thermo Surveyor–TSQ Quantum (Thermo Scientific, Hemel Hempstead, UK) system with electrospray ionization in positive ion mode. Flow injection analysis determined the parent and product ions (Figure 1) for single reaction monitoring utilizing the following SRM transitions; bupivacaine, m/z 289.2–140.1 (qualifier), 98.1 (qualifier 1), 84.1 (qualifier 2), and D9-bupivacaine, m/z 298.2–149.2. Calibration curves of concentration versus peak area ratio were plotted and analyzed using weighted least squares or linear regression with a weighting of $1/X^2$ (Figure 2). The lower

limit of quantification was 3 ng/mL, and the method was fully validated following EMA guidelines [3].

### Data analysis

The number of patient volunteers included in the study was based on previous pharmacokinetic studies on local anesthetics [4].

Quantification of levobupivacaine in patients' samples was analyzed using the descriptive statistics of the median (interquartile range) and mean (standard deviation). The calculated PK parameters were maximum observed bupivacaine plasma concentration (Cmax), time taken to reach Cmax (tmax), half-life, and clearance. The median concentration of bupivacaine in the patients' plasma at 10, 20, 30, 45, 60, 75, 90, and 120 min time points was used to determine Cmax and tmax. The equation of the exponential line of best fit for each patient data set was used to calculate the median concentration at time zero (C0) and median elimination rate constant (kel). C0 and kel values were used to calculate the median half-life (0.693/kel) and clearance ([Dose/C0] x kel).

## Results

Ten patients with the median (interquartile range) age of 71 (64 - 75) years and weight of 63.5 (57 - 64) kg were recruited between August 2017 and February 2018 (Table 1). Their concentration of levobupivacaine was used to calculate the mean levobupivacaine concentration at each time point (Figure 3). The maximum observed plasma concentration of levobupivacaine (Cmax) was calculated for 10, 20, 30, 45, 60, 75, 90, and 120 min samples for all 10 patients. The PK parameters were calculated for each patient, and the median values for the cohort are presented in Table 2.

## Discussion

This study describes the pharmacokinetics of levobupivacaine to increase our understanding of the PK profile of levobupivacaine in patients undergoing hip arthroplasty and FICB under ultrasound control. The data described here are consistent with previously reported PK studies using different regional anesthetic techniques. All analyzed blood samples demonstrated that the plasma levobupivacaine concentrations were below the recognized toxic concentration of 2.6 µg/mL. No symptoms of LAST were reported.

This study used mass spectrometry, an established, robust technique for post-operative quantification of the local anesthetic in plasma [5]. As demonstrated by the product ion spectra for bupivacaine and the deuterated internal control D9-bupivacaine (Figure 1), although lo-

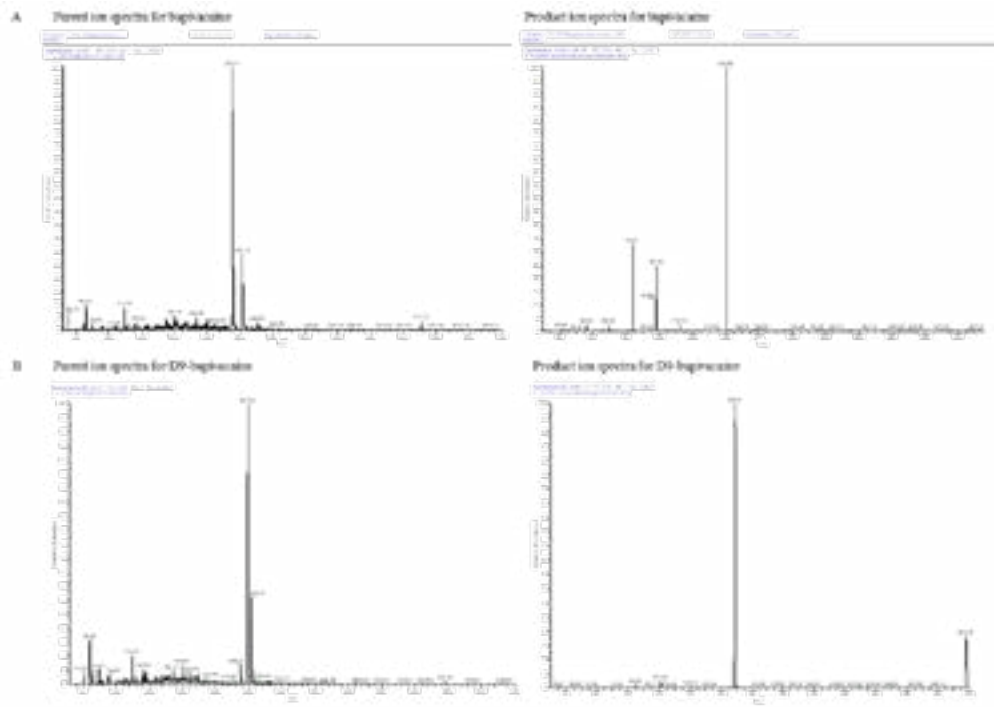

**Figure 1.** Parent and product ion spectra for bupivacaine
A. D9-bupivacaine; B. Obtained using electrospray ionization in positive ion mode

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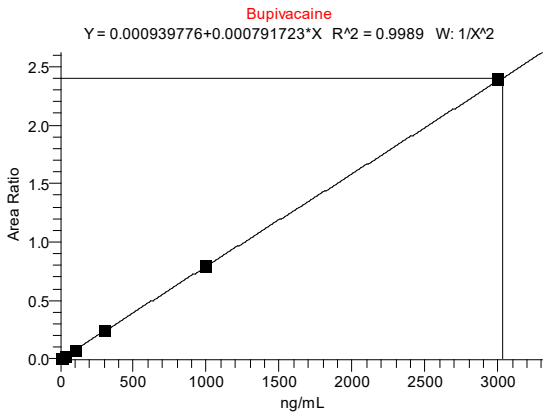


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**Figure 2.** Typical calibration curve for the determination of bupivacaine in human plasma using weighted least squares linear regression with a weighting of $1/X^2$ (All data points represent duplicate analyses.)

cal anesthetics can be very close in size and chemistry, they can be distinguished from one another by chromatography [6]. The data in this study are in general agreement with the gas chromatography-mass spectrometry data described by Odor et al. [7]. Although LC-MS/MS is an accurate analytical method, it cannot be used for

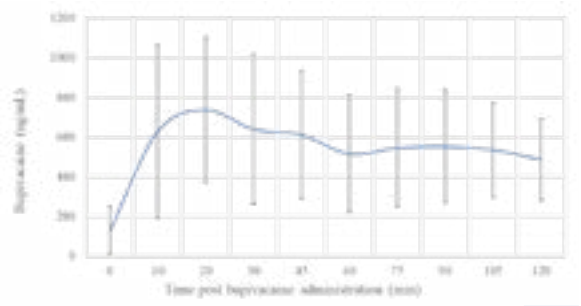

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**Figure 3.** Patient plasma bupivacaine concentration over time following FICB, Mean±SD; n = 10) patient plasma bupivacaine concentration over 120 min post bupivacaine administration (duplicate samples per patient)

real-time detection of toxic plasma levels of levobupivacaine, as blood sample preparation and running of the LC-MS/MS method takes over 8 hours.

This study's experimental findings for levobupivacaine half-life and clearance in older patients are within the range of the recognized parameters for the general population [8]. It is expected that the older population has a lower hepatic clearance and prolonged half-life of

**Table 1.** Demographic profile of study participants

| Patient | Weight, kg | Sex | Age, y |
|---|---|---|---|
| 1 | Not recorded | Male | 75 |
| 2 | 78 | Female | 53 |
| 3 | 69.8 | Female | 79 |
| 4 | 57 | Male | 58 |
| 5 | 63.5 | Female | 68 |
| 6 | 53 | Male | 75 |
| 7 | 58 | Female | 87 |
| 8 | 52.6 | Female | 64 |
| 9 | 64 | Female | 74 |
| 10 | 63.5 | Female | 68 |
| Median (IQR) | 63.5 (57–64) | | 71 (64–75) |

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**Table 2.** Pharmacokinetic profile of study group (Data are given as median [interquartile range])

| Pharmacokinetic Parameter | Finding |
|---|---|
| Maximum plasma concentration Cmax | 0.483 µg/mL (0.454–0.609) |
| Time taken to reach Cmax | 38 min (30–105) |
| Half-life | 2.8 h (1.65–5.8) |
| Total plasma clearance | 0.72 L/min (0.36–1.26) |

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lipid-soluble drugs [9]. Surprisingly, this study found a little discrepancy between the recognized PK profiles of the general population and the older patient group. This finding underlines the need for a greater body of plasma levobupivacaine pharmacokinetic data for older patients.

The main limitation of this current study is the small sample size. Still, the present data may be pooled in combined PK analyses to provide robust evidence of the safety of ultrasound-guided FICB in patients undergoing hip arthroplasty.

This study has found FICB a successful and safe technique for the administration of levobupivacaine to older patients. The data from this study have added to the pharmacokinetic profile of plasma levobupivacaine of older patients following FICB for hip fracture surgery. This local anesthetic technique was demonstrated to be safe for use in older patients supporting previous results [7]. The data collected can be used to help local anesthetic dosing in older patients and improve local anesthetic safety.

## Ethical Considerations

### Compliance with ethical guidelines

The research was given a favourable ethics opinion by the North of Scotland Research Ethics Committee.

### Funding

This article was extracted from the PhD. thesis of Rebecca Parr in Scotia Biologics Ltd. LC-MS/MS.

### Authors' contributions

Conceptualization: Thomas Engelhardt, Keith Charlton and Gillian Broadbent; Methodology: Thomas Engelhardt, Keith Charlton, Hal Robinson, Gillian Broadbent, Gary Cameron, Rebecca Parr; Investigation: Thomas Engelhardt, Keith Charlton, Hal Robinson, Gillian Broadbent, Gary Cameron, Rebecca Parr; Writing-original draft and Writing–review & editing: All authors; Funding acquisition: Keith Charlton, Gillian Broadbent, Rebecca Parr, Thomas Engelhardt; Resources: Thomas Engelhardt, Keith Charlton, Hal Robinson, Gillian Broadbent, Gary Cameron; Supervision: Thomas Engelhardt, Heather Wallace, Keith Charlton and Gillian Broadbent.

### Conflict of interest

The authors declared no conflict of interest.

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