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An Observational Study of the Pharmacokinetics of Adductor Canal Block using Liposomal Bupivacaine in Total Knee Arthroplasty

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Research Article

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ABSTRACT

Background: Periarticular Local Infiltration of Analgesia (LIA) and regional nerve block using Adductor Canal Block (ACB) have been described as effective in managing postoperative pain for Total Knee Arthroplasty (TKA). It has been shown that combining ACB with LIA can significantly reduce pain scores and postoperative consumption of morphine compared with LIA alone. However, this may raise concerns about the potential risk of Local Anesthetic Systemic Toxicity (LAST), especially with the large doses of total local anesthetic used in both LIA and ACB.

Objectives: The purpose of this study was to evaluate the plasma level of bupivacaine over a 72-hour period following ACB using 66.5 mg of Liposomal Bupivacaine (LB) in patients undergoing TKA with LIA using 300 mg ropivacaine. This study aims to provide some pharmacokinetic data of LB in ACB for future dose defining study on LB in ACB together with LIA.

Design: Prospective observational study.

Setting: Ethical approval for this study (Reference Number UW 20 -589) was provided by the Ethical Committee, Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster, Queen Mary Hospital, Hong Kong (Chairman Prof. Brian Liang) on 6 October 2020

Patients: Ten patients underwent primary, unilateral, simple revision TKA were included in the study from December 2020-February 2022.

Main outcome measures: The primary outcomes were the time to peak plasma concentration (Tmax) of bupivacaine and the peak plasma concentration (Cmax) of bupivacaine. The secondary outcome was the presence of LAST.

Results: Tmax of bupivacaine was 48 hours while Cmax of bupivacaine was 88 mcg/L, this value was far below 2000 mcg/L, the defined toxic plasma concentration of bupivacaine.

Conclusion: The report's only validity resides with the dataset describing Tmax and Cmax of LB in a small cohort underwent TKA. Despite there was large variation of Cmax, we did not identify plasma bupivacaine levels within toxic ranges especially with such relatively small dose of LB administered. Therefore, there is still room for increasing the dose of LB used in ACB for TKA patients with LIA using high dose of ropivacaine.

Trial registration: The clinical trial was registered at ClinicalTrials.gov with registration number NCT04916392.

Keywords: Liposomal bupivacaine; Plasma concentration of bupivacaine; Local anesthetic systemic toxicity; Adductor canal block; Total knee arthroplasty

INTRODUCTION

Total Knee Arthroplasty (TKA) is associated with significant tissue damage and postoperative pain problems, which hinder postoperative rehabilitation. Periarticular Local Infiltration of Analgesia (LIA) and Adductor Canal Block (ACB) have been described as effective in managing postoperative pain. Standard Bupivacaine (SB), levobupivacaine, and ropivacaine are used during ACB.

It has become clear that periarticular LIA has better pain control with less opioid consumption than ACB alone [1,2]. Although the duration of single-dose LIA may not be long enough to cover the perioperative period, it has been shown that combining ACB with LIA can significantly reduce pain scores and postoperative consumption of morphine compared with LIA alone [3-5]. However, this may raise concerns about the potential risk of LAST, especially with the large total doses of local anesthetic used in both LIA and ACB.

Liposomal Bupivacaine (LB) is a lipid-encapsulated bupivacaine that allows for depot administration of the medication into the soft tissue [6,7]. Due to the lipid encapsulation of bupivacaine, only 3% of the free bupivacaine is released into the tissue at initial infiltration, with the remainder was released slowly over approximately a 72 hour time frame [8]. This has the proposed advantage of a longer duration of analgesia than standard bupivacaine injections [8-10]. Few studies have investigated the plasma blood level of LB after LIA, and the dosage of LB varies from 133 mg to 532 mg [11-14]. The current literature suggests that plasma levels in the range of 2000-4000 mcg/L can produce neurologic and cardiac toxicity [15,16]. All peak plasma levels of bupivacaine in these studies were below 1200 mcg/L [11-14]. However, Pharmacokinetic (PK) data for LB in ACB alone were not evaluated, especially together with LIA using other local anesthetics. The optimal dosage of LB applied to ACB in these settings has not been defined.

PK data of local anesthetics used in LIA are available. Fenten et al. found that the Tmax (median) of 400 mg ropivacaine used in LIA alone without ACB was 240 minutes (4 hours), with a C max (median) of 1000 mcg/L [16,17].

Affas et al. found that the maximal plasma concentrations in the LIA group using 300 mg ropivacaine were detected at 4 or 6 hours after LIA in TKA patients with a Cmax (mean) of 813 mcg/L [18]. Another PK study of LIA using 270 mg ropivacaine showed that the mean peak concentration of ropivacaine was 530 mcg/L, with a Tmax of 240 minutes [19]. The purpose of this study was to evaluate the plasma level of bupivacaine over a 72-hour period following ACB using 66.5 mg of LB in patients underwent TKA with LIA using 300 mg ropivacaine. This study aims to provide some PK data of LB in ACB for future dose defining study on LB in ACB together with LIA using high dose ropivacaine. The primary outcomes were the time to peak plasma concentration (Tmax) of bupivacaine and the peak plasma concentration (Cmax) of bupivacaine of each individual. The secondary outcome was the presence of any LAST.

MATERIALS AND METHODS

Ethical approval for this study (Reference Number UW 20 -589) was provided by the Ethical Committee, Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster, Queen Mary Hospital, Hong Kong (Chairman Prof. Brian Liang) on 6 October 2020. This prospective observational study was conducted from December 2020–February 2022 at Queen Mary Hospital, Hong Kong, China. Written informed consent was obtained from all subjects included in the study. The clinical trial was registered at ClinicalTrials.gov with registration number NCT04916392.

Patients underwent primary, unilateral, simple revision TKA were included in the study. Patients with bilateral TKA were also included, but only one knee had ACB. Exclusion criteria were refusal to give written informed consent, complicated primary TKA, and known allergy to opioids, local anesthetic drugs, paracetamol, and nonsteroidal anti-inflammatory drugs (NSAIDS), including COX-2 inhibitors. A prospective observational study evaluating the PK data of 66.5 mg LB in ACB in patients underwent TKA with LIA using 300 mg ropivacaine was performed. Ten patients were recruited for this study. Standard monitoring with a pulse oximeter, noninvasive blood pressure and electrocardiogram were applied prior to induction of anesthesia. One 18-gauge intravenous cannula was inserted into one arm for intravenous fluid. Another 14-gauge intravenous cannula was inserted into the antecubital fossa of the other arm for blood sampling. No intravenous fluid or medication was given through this cannula. The designated 14-gauge cannula was used for further blood sampling for plasma bupivacaine levels.

All operations were performed under spinal anesthesia using 2.2 ml - 2.4 ml of 0.5% hyperbaric bupivacaine (AstraZeneca, Australia). ACB was then performed by the listed anesthetist under ultrasound guidance with aseptic techniques. A high-frequency linear array ultrasonic transducer was used to scan the lower part of the thigh so as to identify the adductor canal. The peripheral nerve block needle was directed to the superior-lateral aspect of the femoral artery in the adductor canal and deep to the sartorius muscle under ultrasound guidance. 5 ml 1.33% liposomal bupivacaine with 5 ml 0.9% normal saline was given.

Blood was collected before ACB and 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, 48 hours and 72 hours after the ACB through the designated 14-gauge cannula. During each blood taking, the first 5 ml of blood was discarded, and a second 5 ml blood sample was drawn and added to an appropriate collection tube. In the case of a nonfunctioning intravenous line, venipuncture was performed to collect the blood sample. They were subsequently sent to the laboratory for plasma bupivacaine level measurement using liquid chromatography.

Patients were sedated with a target-controlled infusion of propofol (Fresenius Kabi, Germany) set at a target concentration of 0.3 to 1 mg/ml using the Marsh PK model throughout the whole surgical procedure. Hypotension was managed with intravenous phenylephrine or ephedrine at the discretion of the anesthetist.

The TKAs were performed by the same surgical team with a standardized surgical technique. A pneumatic tourniquet was applied over the thighs of the patients. LIA was administered by the surgeon using the technique described by Kerr and Kohan [20]. The standard regimen used in LIA was a mixture of 40 mL of 0.75% ropivacaine, 0.5 mL of 1:200,000 adrenaline, and 30 mg of ketorolac in 60 mL of 0.9% saline solution.

Patients were transferred to the Postanesthesia Care Unit (PACU) for monitoring. A standardized multimodal oral analgesic regimen was prescribed for 5 days. The regimen included pregabalin 50 mg at night, paracetamol 1 g four times daily and celecoxib 200 mg twice daily. Symptoms and signs of neurotoxicity and cardiac toxicity were monitored every 4 hours until postoperative Day 1.

Blood analysis

Blood samples were centrifuged to obtain the plasma, which was stored at -80°C until assayed. Calibration Standards (CS) and Quality Control (QC) samples were prepared by thoroughly mixing blank plasma (from healthy volunteers who had not been treated with bupivacaine, 90 µl), Milli-Q water (150 µl) and bupivacaine (2 to 8000 ng/ml, in 10 µl of methanol: Milli-Q water (v:v: 1:1)). The internal control, bupivacaine-d9 (500 ng/mL in 50 µl of methanol: Milli-Q water 1:1), was added to all samples, including the CS and QC, except the blank plasma and reconstituted solvent samples. The mixtures were vortexed for 30 s followed by centrifugation for 30 s. Acetonitrile (600 µl) was then added to all samples; the mixtures were then centrifuged at 4°C at 12,000 g for five minutes. The supernatant was collected and filtered through a 0.22 µm membrane before liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis using a C18 LC column (1.6 µm; Luna@ Omega; Phenomenex Inc, Torrance, CA, USA). The chemical source of bupivacaine-d9 was from Toronto Research Chemicals in Canada, and that of bupivacaine hydrochloride was from Santa Cruz Biotechnology Inc. in the USA. The concentration of plasma bupivacaine was in mcg/L.

RESULTS

Twenty-three patients scheduled for primary unilateral/simple revision TKA and bilateral total knee arthroplasty were screened. Thirteen patients declined to participate, and 10 patients were enrolled.

The 10 subjects consisted of 3 men and 7 women with a mean age of 72.6. The PK data and demographic data are summarized in Table 1. The median Tmax of bupivacaine was 48 hours. The median Cmax of bupivacaine was 88 mcg/L (Table 1). There were interindividual variations in the Tmax and Cmax of bupivacaine (Table 2). The total plasma concentration of bupivacaine for all subjects during the 72-hour period is shown in Figure 1.

There were no reported symptoms or signs of LAST for any of the subjects.

Table 1. Demographic and pharmacokinetic data.

Pharmacokinetic data	N=10
Age (y), mean ± SD	72.6 ± 9.6
BMI (kg/m^2), mean ± SD	24.7 ± 4.4
Tourniquet time (min), median (IQR)	70 (16-90)
Sex (male:female)	3:7

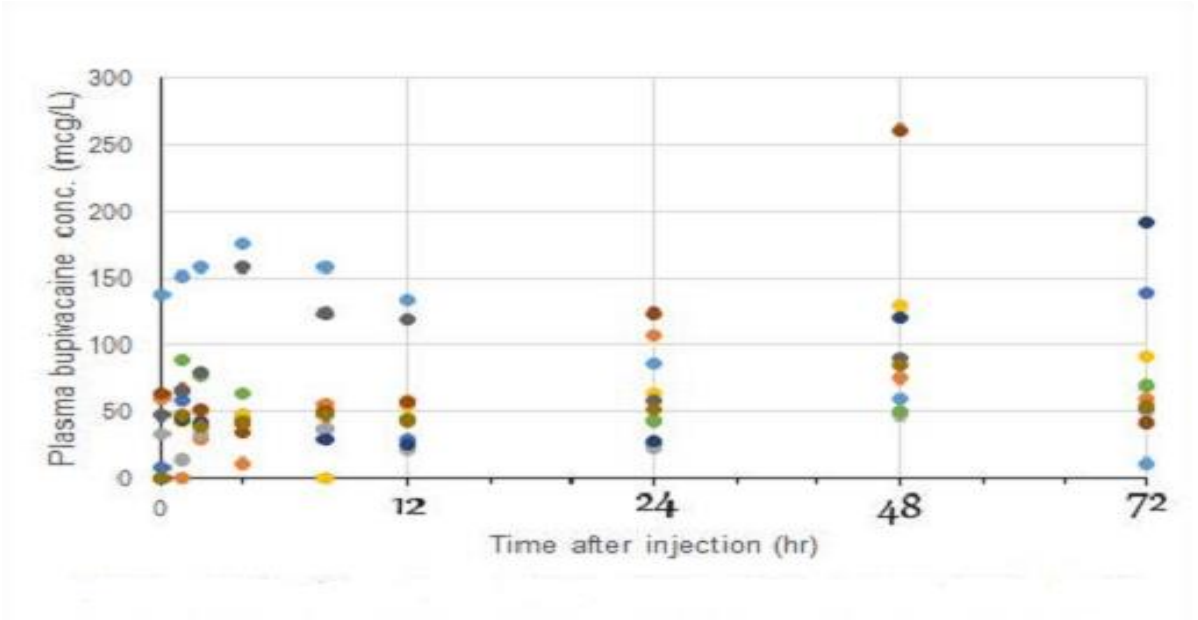
Cmax (mcg/L), median (IQR)	88 (133-180)
Tmax (hr), median (IQR)	48 (4-72)
AUC 0-48 hr (mcg·hr/L), median (IQR)	3164 (2135-445)
AUC 0-72 hr (mcg·hr/L), median(IQR)	5519 (3893-6250)

Table 2. Peak plasma concentration (Cmax) of bupivacaine of each individual subject.

Subject	C max(mcg/L)	T max(hr)
H4492	139.3	72
A665	106.6	24
C094	50	72
K362	129.1	48
MSC	176.1	4
NM	89.4	1
TNW	192.2	72
LYT	261.8	48
NYHJ	157.9	4
SKLA	85.4	48

Figure 1. Total plasma concentrations of bupivacaine in all subjects during the 72 hour period.

Note: (●) Subj 1; (●) Subj 2; (●) Subj 3; (●) Subj 4; (●) Subj 5; (●) Subj 6; (●) Subj 7; (●) Subj 8; (●) Subj 9; (●) Subj 10.



DISCUSSION

There has been only one PK study of LB in peripheral nerve block. It was an observational study measuring the Tmax and Cmax of LB in the posterior multilevel intercostal nerve block of 15 patients underwent posterolateral thoracotomy [21]. A single dose of 266 mg of LB was used for the intercostal nerve block with T max (median) of 24 hours. In present study, we identified a longer Tmax (median), probably because of the much lower dose of LB (66.5 mg) and the lower vascularity of ACB compared with intercostal nerve block. The existing evidence shows that the Tmax (median) in peripheral nerve block is at least 24 hours after injection. This is consistent with the mechanism of action of LB, which has a slower release of bupivacaine into tissue due to its lipid encapsulation.

The optimal dosage of LB used in peripheral nerve block has not yet been clearly defined. In the observational study using LB for the intercostal nerve block, the dosage used was much higher (266 mg), and the median Cmax was 600 mcg/L [21]. In present study, the Cmax (median) for the LB group was 88 mcg/L. This value did not exceed the defined toxic plasma concentration of bupivacaine (2000 mcg/L) and was far below 2000 mcg/L, suggesting that the dosage used in this study (LB of 66.5 mg) was relatively low. Although there was large variation of Cmax (median) in this study, there is little chance that toxic threshold will be reached especially with such low dose of LB. Given the above data, there is still much room for further increasing the dose of LB used in ACB. PK data of ropivocaine used in LIA are available [17-19]. By comparing the PK profile of ropivacaine used in LIA from the above studies *vs*. that of LB used in ACB in present study, we found that the Tmax (median) of LB used in ACB was much

longer than that of ropivacaine used in LIA (48 hours *vs.* 4-6 hours). Although there was such a difference, the Tmax (median) of LB in ACB and LIA using ropivocaine may cross especially there was large variation of Tmax (median) of LB in ACB. This may impose potential LAST.

CONCLUSION

The report's only validity resides with the dataset describing Tmax and Cmax of LB in a small cohort underwent TKA. Despite there was large variation of Cmax, we did not identify plasma bupivacaine levels within toxic ranges especially with such relatively small dose of LB administered. Therefore, there is still room for increasing the dose of LB used in ACB for TKA patients with LIA using high dose of ropivocaine. This study provides some PK data of LB in ACB for future dose defining study of LB in ACB together with LIA.

LIMITATIONS

There were variations in the duration of tourniquet time, timing of ACB and LIA. Sample size was small. All these were accountable for large variation of Cmax (median) and Tmax (median) of LB. The sample size was insufficient to reach the conclusion of safety. This could be increased to make the conclusion more universal. The absence of LAST in a small cohort of patients does not infer safety.

Moreover, the Tmax of LB in ACB and LIA using ropivocaine may cross especially there was large variation of Tmax of LB in ACB, which may impose potential LAST. The PK data of ropivacaine could be evaluated to testify the safety of using LB in this study. PK of LB was studied in a dose (66.5 mg) that was below the usually recommended dose of 133 mg for peripheral nerve block. Therefore, there was a doubt about the clinical relevance of this study for the daily practice.

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ETHICS STATEMENT

Ethical approval for this study (Reference Number UW 20 -589) was provided by the Ethical Committee, Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster, Queen Mary Hospital, Hong Kong (Chairman Prof. Brian Liang) on 6 October 2020. This prospective observational study was conducted from December 2020 – February 2022 at Queen Mary Hospital, Hong Kong, China. Written informed consent was obtained from all subjects included in the study. The clinical trial was registered at ClinicalTrials.gov with registration number NCT04916392.

AUTHOR CONTRIBUTIONS

WSHC, TCWC, and CWC designed the study. WSHC, TCWC, HCYM, MTHC, and CHCC provided clinical care. SWSL and SPYL preformed blood analysis. WSHC, TCWC, SWSL, SPYL, SSCW, and CWC drafted the manuscript. WSHC, TCWC, and CWC reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICTS OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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