Plasma Concentrations of Bupivacaine after Spinal Anesthesia with Single Shot Femoral Nerve Block in Total Knee Arthroplasty

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Background: *Femoral nerve block is commonly established for postoperative analgesia in total knee arthroplasty but no evidence of plasma bupivacaine level has been reported.*
Objective: *Determine the plasma concentrations of bupivacaine in patients who had single-injection of femoral nerve block.*
Material and Method: *A prospective observational study was undertaken with 25 patients scheduled for unilateral total knee arthroplasty under spinal anesthesia and single shot femoral nerve block with 20 mL of 0.5% bupivacaine. Venous blood samples were collected at 0, 5, 10, 15, 30, 60, 90, and 120 minutes after femoral nerve block. Plasma bupivacaine levels were analyzed by high performance liquid chromatography with tandem mass spectrometry.*
Results: *Four males and 21 females, ASA I-II were enrolled in the present study. Mean age, body mass index, and serum albumin level were 69.9±5.95 years, 27±3.67 kg/m^2, and 4.46±0.26 mg/dL, respectively. The median of peak plasma concentration was 538.35 ng/mL (min = 176.30, max = 1,383.99) at 60 minutes after femoral nerve block, while the maximal plasma concentration of bupivacaine was 1,883.39 ng/mL at 10 minutes. None showed signs or symptoms of bupivacaine toxicity.*
Conclusion: *Peak plasma concentrations of bupivacaine were demonstrated at 60 minutes after a single shot femoral nerve block, and no signs or symptoms of bupivacaine toxicity were observed. Therefore, single shot femoral nerve block with 20 mL of 0.5% bupivacaine is safe.*

Keywords: *Plasma bupivacaine level, Femoral nerve block*

J Med Assoc Thai 2013; 96 (3): 312-7
Full text. e-Journal: *http://jmat.mat.or.th*

Femoral nerve block (FNB) is commonly established in patients with total knee arthroplasty for postoperative pain relief. It decreases intravenous morphine use and side effects of intrathecal morphine, provides early ambulation and short hospitalization[1]. Performing a femoral nerve block under nerve stimulator or ultrasound guidance with plain 0.5% bupivacaine in the maximum dose of 2 mg/kg is supposed to be safe from local anesthetic toxicity. However, the rate of absorption of local anesthetic depends on doses and blood flow at the site of injection[2,3]. In FNB, the large amount of plain bupivacaine was administered closed to the femoral artery, so it might be substantially absorbed to the blood stream. So far, no actual toxic level of plasma bupivacaine has been reported and no prior study of the plasma level of bupivacaine after FNB was published. The previous studies determining plasma concentrations of bupivacaine were limited in patients undergone total knee arthroplasty with combined sciatic and femoral 3 in 1 nerve blocks[4,5]. Therefore, the aim of the present study was to assess the plasma concentrations of bupivacaine in patients who had a single shot femoral nerve block with 20 mL of plain 0.5% bupivacaine.

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Material and Method

After the approval from Siriraj Hospital Institutional Review Board and Ethics Committee and written patient informed consent, twenty-five patients, age 30 to 70, ASA physical status I-II scheduled for unilateral total knee arthroplasty under spinal anesthesia and single shot femoral nerve block were

enrolled in the present study. Patients who refused, allergic to bupivacaine, weighed less than 50 kg, with heart or liver disease, coagulopathy, preoperative hematocrit less than 35%, and infection at femoral nerve block puncture site or blood sampling site were excluded. Patients who had more than two attempts of intravenous catheter insertion at any time during blood sampling were also eliminated from the present study.

Anesthetic procedures

All patients were monitored with pulse oximetry, electrocardiogram, and non-invasive blood pressure. Femoral nerve block (FNB) was performed by using a 100 mm-insulated needle (Stimuplex® A, 21Gx4", B. Braun Melsungen AG, Thailand) connected to nerve stimulator (Stimuplex® HNS 12, B. Braun Melsungen AG, Thailand). The needle was inserted laterally to the femoral artery and 1 cm caudal to the inguinal ligament. To localize the femoral nerve, the current was started at 1 mA/0.1 ms (1 Hz) and continuously reduced to achieve twitches of quadriceps muscle at 0.4 mA/0.1 ms (1 Hz). After an aspiration test for blood was negative, 20 mL of plain 0.5% bupivacaine (100 mg) was injected. The time that the insulated needle was withdrawn was counted as time 0. Then, the patients were placed into a lateral position to perform spinal anesthesia. A dural puncture was done with a 26G Quincke spinal needle at L3-L4 or L2-L3 lumbar vertebrae space with hyperbaric 0.5% bupivacaine. The dosage of bupivacaine administered depended on the patients' individual characteristics. The anesthetic level was at least T10 dermatome. Vital signs and adverse events such as tinnitus, seizure, and cardiac arrest were recorded.

Blood sample collections

An 18G IV catheter was inserted into a large vein at the antecubital fossa, contralateral to the intravenous line to prevent IV fluid or drug contamination. The catheter was connected to a 3-way stopcock with a 5 cm extension tube and locked with 3 mL of heparin (1 unit/mL). The first 3 mL of blood sample was discarded prior to the collection of 6 mL of blood at the following times, 0, 5, 10, 15, 30, 60, 90, and 120 min. During blood sample collection in each case, clotted blood tube was put in a refrigerator at 4°C and the tubes were transferred to the laboratory daily. All blood samples were analyzed simultaneously at the end of the present study.

Determination of plasma bupivacaine analysis

Analysis of bupivacaine was performed using a validated high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) in accordance with the USFDA guidelines [US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research 2001]. Sample preparation was performed by liquid-liquid extraction. Briefly, mepivacaine (Internal Standard; IS) solution (50 ng/mL) was added to 100 µL plasma sample or bupivacaine standard spiked plasma and mixed for 10 seconds before adjusting to alkaline pH. After thorough mixing, all samples were added and mixed with extraction solvent and centrifuged at 10,000 rpm for 10 minutes. The organic layer was transferred into a new conical polypropylene tube and evaporated under a nitrogen stream at 30°C until the sample was dried. The residue was reconstituted with 200 µL of a reconstituting solvent and 3 µL was injected into the LC-MS/MS system. Chromatographic separation was carried out on LC-MS/MS with Synergi® Polar-RP column (2.5 µm, 50 mm x 3.0 mm id). A mobile phase consisting of acetonitrile and 0.1% formic acid (Isocratic condition) was delivered with a flow rate of 0.2 mL/minute. Mass spectra were obtained using a Quattro Micro mass spectrometer (Micromass. UK) equipped with positive electrospray ionization (ESI) source. The mass spectrometer was operated in multiple reaction monitoring (MRM) modes. The mass transition ion-pair for bupivacaine [M+H]+ ions was selected as m/z 289.25 >140.11. The mass transition ion-pair for mepivacaine [M+H]+ ions was selected as m/z 247.16 >98.09. The data acquisition was ascertained by Masslynx 4.1 software.

Statistical analysis

The objective of the present study was to estimate the blood concentration of bupivacaine. A previous study reported a mean concentration of 0.7 and SD of 0.4[4]. Based on the estimated 95% CI of the true mean concentration of 0.7±0.16 and SD of 0.4, a sample of 25 subjects was required. Descriptive statistics were used to examine clinical characteristics and perioperative variables. The Friedman test and Wilcoxon signed ranks test were used to compare plasma bupivacaine levels among different time periods. Spearman rank correlations was used to test the relationship between drug concentration and quantitative variables e.g., body mass index (BMI), serum albumin.

Statistical analysis was conducted using IBMSPSS v19 Inc., Chicago, IL, USA. Data were presented as mean±SD, median (Min, Max) and number (percent). A value of $p<0.05$ was considered statistically significant.

Results

Twenty-five patients were enrolled in the present study. All blood samples were collected as described in the protocol except one sample at 5 minutes was missing because of miscommunication. Nobody was terminated during the investigation. All patients had no signs or symptoms of cardiovascular and neurologic toxicity of local anesthetic detected perioperatively. The baseline patient characteristics and demographic data are shown in Table 1.

In the present study, mean plasma bupivacaine level reached its peak at 30 minutes after FNB (657.75 ng/mL). However, the median plasma concentration of bupivacaine was highest at 60 minutes, which was not different from the median plasma concentration of bupivacaine at 30 minutes (538.35 and 524.60 ng/mL respectively; p = 0.24). Three patients had extremely high peak plasma bupivacaine level (Fig. 1). One patient had the highest of plasma bupivacaine at 5 minutes (1,255.76 ng/mL). The others had peak plasma concentration rising at 10 minutes (1,833.39 and 1,580.63 ng/mL). The maximum plasma bupivacaine concentration was 1,833.39 ng/mL at 10 minutes.

The correlation coefficient between plasma bupivacaine concentrations and serum albumin level during study period were very low (r = 0.25 to 0.37; p = 0.07 to 0.23) and were not correlated to spinal bupivacaine dose (r = -0.15 to 0.20; p = 0.34 to 0.91), age (r = -0.34 to -0.06; p = 0.10 to 0.76) and BMI (r = -0.40 to -0.35; p = 0.05 to 0.09).

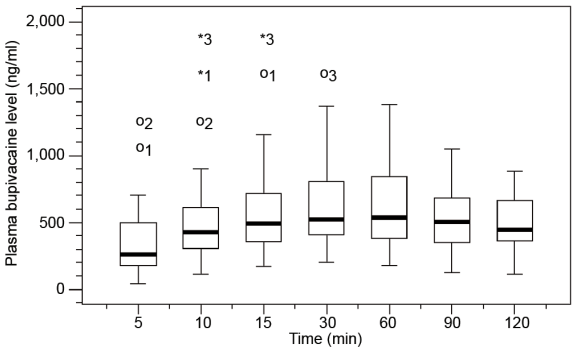

Fig. 1 Plasma bupivacaine concentrations (median and interquartile range) at 5, 10, 15, 30, 60, 90 and 120 minutes after a single-shot femoral nerve block. Three patients had extremely high peak plama concentrations of bupivacaine at 5 and 10 minutes. The third subject had a missing blood sample at 5 minutes.

Table 1. Demographic data of 25 subjects, bupivacaine dose and duration of surgery (M = male, F = female)

Characteristic	Data (n = 25)
Sex (M/F)	4/21
ASA (I/II)	1/24
Age (years)	69.88±5.95
Weight (kg)	63.21±9.05
BMI (kg/m^2)	26.97±3.68
Bupivacaine dose	
Total dose (mg)	113.86±2.10
Dose/weight (mg/kg)	1.84±0.26
Serum albumin (mg/dl)	4.46±0.26
Duration of surgery (min)	108.72±36.41

Data are presented as mean±SD

Discussion

The plasma concentrations of bupivacaine were conducted in four male and 21 female subjects. Most patients had ASA II because of hypertension (80%) and diabetes mellitus (24%). All of them were diagnosed with osteoarthritis and had undergone unilateral total knee arthroplasty. They received 110 to 117.5 mg of bupivacaine (1.84±0.26 mg/kg) for combined spinal anesthesia and a single-injection of FNB. The median of the peak plasma concentration of bupivacaine after FNB alone was observed at 60 minutes. The result was similar to the mean peak plasma bupivacaine level following combined sciatic block and femoral 3 in 1 block reported by Misra et al (60±7 min)[4]. On the contrary, the outcome was slightly different from the conclusion of Moore et al, who found that the mean peak plasma bupivacaine level following sciatic, femoral and lateral femoral cutaneous nerve block occurred at 15 minutes after bupivacaine injection and persisted up to 60 minutes[5]. However, the plasma bupivacaine level during 5 to 10 minutes and 60 to 90 minutes in the present study were significantly different (p = 0.00 and 0.02 respectively). The authors suspected the blood level started rising within 10 minutes and reached its peak at 60 minutes before decreasing.

Three cases had distinctly rapid rising of plasma bupivacaine level within 10 minutes. One of them had a missing blood sample at 5 minutes and

showed the highest plasma concentration, even though the dose of bupivacaine given was only 114 mg. This patient's baseline hematocrit (42.9%), BMI (33.65 kg/m^2) and blood pressure at 5 minutes after FNB (200/100 mmHg) were higher than the other subjects, while two other patients had baseline hematocrit of 35, BMI less than 25 kg/m^2 and normal BP (145/86 and 145/73 mmHg). Thus, the authors suspected that the particular blood levels of those three patients might be affected by incidental vascular puncture during the process of FNB. However, the anesthetic records were presented as uneventful and no intravascular injection was noted.

Bupivacaine dose in the present study was approximately 2 mg/kg (1.84±0.26) as recommended by the manufacturer, and the greatest plasma bupivacaine level presented was 1,833.39 ng/mL. It did not exceed the toxic level of bupivacaine mentioned in previous studies (2,000-4,000 ng/mL)[6-9]. Although Hasselstrom et al reported a plasma concentration of bupivacaine of 1.1 mcg/mL in a 28-year-old healthy woman with convulsive episode after intravenous infusion of bupivacaine[10], the authors did not find any patients who had signs and symptoms of systemic toxicity of bupivacaine. Nevertheless, some patients got intravenous sedation during the operation that could have masked the minor systemic toxicity such as circumoral numbness, light-headed, or tinnitus.

Administrations of doses of bupivacaine were varied in each patient but they had no effect on plasma bupivacaine level as shown by the correlation coefficient. The authors measured the serum albumin level instead of alpha1 acid glycoprotein (AAG), an important plasma protein binding to local anesthetics, due to lack of laboratory equipment. Both variables were found to be affected by age and BMI. Serum albumin level decreased with increasing age, while AAG concentrations increased in obese patients but was not affected by age[11,12]. Furthermore, performing FNB on obese patients might have been technically difficult. These factors may influence plasma concentrations. However, there were low correlations between plasma concentrations of bupivacaine and serum albumin level, as well as age and BMI. One possible explanation is that the plasma concentrations of bupivacaine in the present study were total plasma concentrations, so they would not be affected by serum albumin or AAG levels. In addition, the systemic absorption of local anesthetics is particularly influenced by blood supply at site of injection, volume and dosage, and presence of vasoconstrictors[2,13,14].

In the present study, there were many anesthesiologists involved including staff anesthesiologists and anesthesia residents. Therefore, skills and techniques of blockade used may be different. Multiple insulated needle punctures might have been done during the performance of FNB and might have accidentally punctured the vessels. Therefore, a negative for blood aspiration during bupivacaine injection does not necessarily mean that no absorption of bupivacaine occurred directly into the blood stream. In addition, the effect of FNB postoperatively was not followed so the correlation between its effect and plasma bupivacaine levels was not known.

The plasma bupivacaine level was still high; 446.31 ng/mL (115.13, 883.44) at 120 minutes compared with 538.35 ng/mL (176.30, 1,383.99) at 60 minutes. Sullivan[15] and Liguori[16] reported three cases of bupivacaine toxicity after intraarticular injection even though there were several studies which reported that peak plasma bupivacaine level after intraarticular instillation was less than 650 ng/mL[17,18]. An intraarticular injection of additional bupivacaine for postoperative analgesia, which is routinely done, should be performed with caution.

Finally, all validated results in the present study were found to exhibit good accuracy and reproducibility of new developed LC-MS/MS method that provides a simple assay by liquid-liquid extraction with excellent sensitivity for plasma bupivacaine quantification in the range of 0.1 to 2,000 ng/mL. The best linear fit was achieved with a 1/x weighting factor, showing a mean correlation coefficient (r^2) ≥0.998. The lower limit of quantification (LLOQ) is 0.1 ng/mL and applicable for pharmacokinetic studies. However, the plasma bupivacaine level was not extensively followed long enough to calculate the elimination time or other pharmacokinetic parameters.

Conclusion

The peak plasma concentration of bupivacaine was shown during 30-60 min after combined spinal anesthesia and single shot femoral nerve block with 20 mL of plain 0.5% bupivacaine for unilateral total knee arthroplasty. The plasma concentrations showed no correlation with serum albumin level, spinal bupivacaine dose, age, and BMI. No signs and symptoms of bupivacaine toxicity were observed.

Funding source

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Acknowledgments

The authors wish like to thank all scrub nurses and operative personals at orthopedic theaters in Siriraj Hospital.

Potential conflicts of interest

None.

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การศึกษาระดับความเข้มข้นของยาบิวพิวาเคนในเลือดในผู้ป่วยที่มารับการผ่าตัดเปลี่ยนข้อเข่าภายใต้ การฉีดยาชาเฉพาะที่รอบเส้นประสาทฟีเมอรัล

เสาวภาคย์ ลาภมหาไพศาล, ฐิติมา ชินะโชติ, สุพรชัย กองพัฒนากูล, สมฤดี ฉัตรสิริเจริญกุล, พิสุทธิ์ โตวนิชย์, วินัย ดวงแก้ว, ปิยาภัทร พงศ์นรินทร์, นุชนาถ สกุลพาเจริญ, วรรณกร สมเจริญ

วัตถุประสงค์: *การระงับปวดด้วยการฉีดยาชาเฉพาะที่รอบเส้นประสาทฟีเมอรัลเป็นวิธีที่นิยมในการผ่าตัดเปลี่ยนข้อเข่า แต่ปัจจุบันยังไม่มีการรายงานถึงระดับของยาชาในเลือดด้วยวิธีดังกล่าว การศึกษานี้จึงมีจุดประสงค์เพื่อตรวจหาระดับของยาบิวพิวาเคนในเลือดในผู้ป่วยที่ได้รับการฉีดยาชาเฉพาะที่รอบเส้นประสาทฟีเมอรัล*

วัสดุและวิธีการ: *เป็นการศึกษาไปข้างหน้าในผู้ป่วย 25 ราย ที่มารับการผ่าตัดเปลี่ยนข้อเข่าข้างเดียวด้วยการฉีดยาชาเข้าช่องน้ำไขสันหลังร่วมกับการฉีดยาชา 0.5% บิวพิวาเคน 20 มล. รอบเส้นประสาทฟีเมอรัล โดยจะดูดเลือดผู้ป่วยที่เวลา 0, 5, 10, 15, 30, 60, 90, และ 120 นาที หลังฉีดยาชารอบเส้นประสาทฟีเมอรัล และทำการตรวจวัดระดับยาบิวพิวาเคนด้วยวิธี high performance liquid chromatography ร่วมกับ tandem mass spectrometry*

ผลการศึกษา: *มีผู้ชาย 4 ราย และผู้หญิง 21 ราย ASA I-II เข้าร่วมการศึกษา อายุเฉลี่ย 69.9±5.95 ปี ดัชนีมวลกาย 27±3.67 กก./ตร.ม. และระดับอัลบูมินในเลือด 4.46±0.26 มก./ดล. ค่ามัธยฐานของระดับยาบิวพิวาเคนในเลือดมีค่าสูงสุดที่ 60 นาที หลังฉีดยาชารอบเส้นประสาทฟีเมอรัล และมีค่า 538.35 นก./มล. (ค่าต่ำสุด 176.30 นก./มล. ค่าสูงสุด 1,383.99 นก./มล.) ขณะที่ค่าสูงสุดของระดับยาบิวพิวาเคนในเลือดคือ 1,883.39 นก./มล. ที่ 10 นาที ไม่พบว่ามีผู้เข้าร่วมการศึกษารายใดมีอาการหรืออาการแสดงของพิษจากยาชาเฉพาะที่*

สรุป: *การศึกษานี้พบว่าระดับยาชาบิวพิวาเคนในเลือดขึ้นสูงสุดที่ 60 นาที หลังฉีดยาชารอบเส้นประสาทฟีเมอรัล และไม่มีผู้เข้าร่วมการศึกษารายใดมีอาการหรืออาการแสดงของพิษจากยาชาเฉพาะที่ ดังนั้นการฉีดยาชารอบเส้นประสาทฟีเมอรัลด้วย 0.5% บิวพิวาเคน 20 มล. จึงทำได้อย่างปลอดภัย*