

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

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Objective: To determine the plasma concentrations of bupivacaine and toxicity after periarticular injection (PAI) combined with spinal anesthesia and femoral nerve block (FNB).

Material and Method: Forty-three patients scheduled for unilateral total knee arthroplasty (TKA) were enrolled in the prospective observational study. The dose of bupivacaine for spinal anesthesia was adjusted by the attending anesthesiologist. The single-shot femoral nerve block (FNB) and periarticular injection (PAI) were performed with 20 ml of 0.5% bupivacaine and 20 ml of 0.25% bupivacaine respectively. Venous blood samples from antecubital vein were collected at 60 minutes after femoral nerve block and at the time before periarticular injection, then at 15, 30, 45, and 60 minutes afterwards. Plasma bupivacaine concentrations were analyzed, using a high performance liquid chromatography with tandem mass spectrometry.

Results: Ten males and 32 females, ASA I-II were included. The highest median plasma concentration was 586.22 ng/ml (min = 245.39, max = 1,614.36) at 45 minutes after periarticular injection. The maximum plasma bupivacaine concentration was 1,709.71 ng/ml at 60 minutes after periarticular injection. No clinical toxicity was encountered.

Conclusion: The plasma concentration of bupivacaine in patients performed periarticular injection with 20 ml of 0.25% bupivacaine after spinal anesthesia and single-shot femoral nerve block with 20 ml of 0.5% bupivacaine is below the plasma toxic level.

Keywords: Plasma bupivacaine level, Femoral nerve block, Periarticular block

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Large dose of local anesthetics; especially bupivacaine, is needed for combined regional anesthesia which may induce neurological or cardiovascular toxicities. Nevertheless, the recommendations regarding the maximum doses for bupivacaine are debatable. The responsible pharmaceutical companies recommend the dose of 2 mg/kg; however, larger doses of bupivacaine were sometimes used by anesthesiologists. Several studies had evaluated toxicities of bupivacaine using dosage ranged from 2.5 to 4 mg/kg, there were no clinical adverse events found⁽¹⁻³⁾. Even though there are no reports of toxic reactions, the possibilities of such events are of concern.

Periarticular injection (PAI), additional to spinal block and femoral nerve block (FNB), is commonly performed in patients undergoing total knee arthroplasty to provide postoperative analgesia, facilitate early ambulation, and shorten hospital stay. In a current practice, the authors usually use 20 ml of 0.5% bupivacaine for FNB, 20 ml of 0.25% bupivacaine for PAI and 0.5% bupivacaine, either heavy or isobaric, 2.5 to 3.5 ml for spinal anesthesia depending on patients' characteristics. The cumulative amount of bupivacaine used is possibly up to 165 mg, which is definitely exceeding 2 mg/kg in patients weighed between 50 to 80 kg.

None of previous studies had demonstrated plasma bupivacaine concentration after combined FNB, spinal block and PAI, neither the safety of bupivacaine administration after a repeated dose at a certain time interval. The purpose of the present study is to determine plasma bupivacaine concentration after FNB, spinal block, and PAI. It is also to evaluate

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the side effect of bupivacaine and whether it is correlated to plasma concentration.

Material and Method

This prospective descriptive study was approved by Siriraj Hospital's Institutional Review Board (IRB). Written informed consents were obtained from 43 patients who were 30 to 70 years old, ASA I-II and scheduled to undergo elective unilateral total knee arthroplasty. Patients who were allergic to bupivacaine, body weight less than 50 kg, had preexisting cardiovascular or liver disease, coagulation disorder, preoperative hematocrit less than 35%, and had contraindication for regional anesthesia or patients' refusal were excluded. In addition, patients who had infection around FNB area or antecubital fossa were rejected. Patients who required more than two attempts of intravenous catheter insertion for blood sampling were also discarded.

The patients were monitored with standard ASA monitoring; pulse oximetry, electrocardiogram and noninvasive blood pressure. An 18G intravenous catheter was inserted in a large vein at antecubital fossa, contralateral to intravenous fluid administration side to prevent contamination of fluid or drugs, which might affect bupivacaine concentration analyses. Supplemental intravenous midazolam and/or fentanyl could also be used upon patients' requests or at discretion of an anesthesiologist.

FNB was performed under nerve-stimulator or ultrasound-guided technique. A twitch of quadriceps muscle at a current of 0.4 mA/0.1 msec (1 Hz) was accepted as a proper position if a nerve stimulator was used. Twenty ml of plain 0.5% bupivacaine (100 mg) was injected after an aspiration to preclude intravascular injection. The time once the needle withdrawn was counted as time zero of FNB. Then, the patient was performed spinal block with 0.5% heavy or isobaric bupivacaine, dosages were adjustable according to the attending anesthesiologists. PAI using 20 ml of 0.25% plain bupivacaine (50 mg) was done by the surgeons at the end of the operations.

Blood samples were obtained at 60 minutes after FNB, at the time before PAI (control; c) then 15, 30, 45, and 60 minutes afterwards. Six milliliters of venous blood was collected in an unheparinized tube and kept in refrigerator at 4°C until the process of blood collection was completed. The samples were delivered daily to Siriraj Bioequivalence Center and simultaneously analyzed when the study was finished. Analysis of bupivacaine was performed using a

validated high performance liquid chromatography with tandem mass spectrometry as mentioned in the author's previous study⁽⁴⁾. Vital signs and adverse events such as tinnitus, peri-oral numbness, seizure, arrhythmias, or cardiac arrest were recorded.

Statistical analysis

The sample size was calculated based on the average level of serum bupivacaine of the Kaeding's study⁽⁵⁾ which was 480±200 ng/ml and the peak level was 43 minutes after administration. Forty-three subjects were calculated with the formula of $n = (Z_{\alpha/2})^2 (SD)^2/d^2$ and sufficient to demonstrate these results with an allowable error of 0.06.

Data were collected on the standard forms and entered into a private computer database. Categorical variables were presented with number and percentage. Continuous variables are presented as mean and standard variation or median and interquartile range when data were not normally distributed. The data were compared between groups using a Student paired t test, the Mann-Whitney U test, or analysis of variance as appropriate. All statistical tests were 2-tailed at a significant level of 0.05. Statistical analysis was performed using IBM SPSS v19 Inc., Chicago, IL, USA.

Results

Forty-three subjects, aged 46 to 70 years were recruited to the present study. Most of them had ASA II due to either hypertension or diabetes mellitus. All patients were diagnosed osteoarthritis. One patient was excluded due to technical error rendered the plasma bupivacaine level unmeasurable. As a result, the number of patients analyzed was 42. The patients' characteristic information is presented in Table 1.

After the first dose of bupivacaine administered via FNB, a relevant plasma bupivacaine concentration was shown at 60 minutes later, which was quite similar to the level at 60 minutes after PAI (425.93 vs. 566.52 ng/ml). There were no statistically significant between plasma level at 60 minutes after a single-short FNB and at the time before PAI then 15, 30, 45, and 60 minutes afterwards. All *p*-value were higher than 0.05 by Mann-Whitney U test. The highest median concentration among the whole group of patients was 586.22 ng/ml at 45 minutes after PAI. Six patients had notable high level of bupivacaine concentrations. One of them had the level of 1,709.71 ng/ml at 60 minutes after PAI, which was found to be the single maximum value in the study

Table 1. Demographic data of 42 patients, bupivacaine dose, time interval and duration of surgery

Characteristics	Total (n = 42)
Sex (M/F, %)	23.8:76.2
ASA (I/II, %)	11.9:88.1
Age (year)	63.76±6.27
Weight (kg)	63.27±11.81
BMI (kg/m ²)	26.45±4.04
Hct (%)	39.82±2.89
Alb (g/dL)	4.2±0.39
Bupivacaine dose	
Total dose (mg)	163.48±1.72
Dose/weight (mg/kg)	2.66±0.46
Duration of surgery (min)	96.19±24.36
Interval from FNB to PAI (min)	97.43±29.95
Tourniquet time (min)	84.76±23.29
Interval from PAI to tourniquet deflation (min)	22.38±18.00

Data are presented as mean ± SD, number (%)
M/F = male/female; ASA = American Society of Anesthesiology Classification; BMI = body mass index; Hct = hematocrit; Alb = albumin, FNB = femoral nerve block, PAI = periarticular injection

(Fig. 1). No neurotoxicity or cardiac toxicity was observed.

Thirty-five patients received PAI before tourniquet was deflated (group 1) while seven patients were injected after the time of deflation (group 2). The patients in group 1 had the highest median plasma bupivacaine level at 60 minutes after PAI, but group 2 was shown at 45 minutes (606.20 ng/ml vs. 557.38 ng/ml). The maximum plasma concentration was 1,709.71 ng/ml at 60 minutes in group 1, compared with 802.93 ng/ml at 45 minutes in group 2 (Fig. 2). All patients who had extremely high plasma bupivacaine level after PAI were in group 1. Nevertheless, plasma concentration between two groups was not different.

Discussion

Bupivacaine is more popular than other local anesthetics due to long duration of action. The major disadvantage of bupivacaine is the cardiovascular adverse effects that are more pronounced than ropivacaine and lidocaine^(6,7). Bupivacaine had been reported to cause at least 10 fatal cardiac arrests in obstetrical epidural anesthesia⁽⁸⁾. The potential toxicity of local anesthetics is known to correlate with an absorption rate which is determined by several factors

including site of injection^(9,10) and vascularity of the area injected^(9,11). Absorption from richly vascularized regions leads to high peak plasma concentration. Several studies had shown that the blood level depended on total dose but not concentration of local anesthetics⁽¹²⁾.

According to the previous studies of single intraarticular injection with bupivacaine after knee arthroscopy, the peak plasma concentration occurred at 20 to 60 minutes^(5,7,13), so the authors designed to investigate plasma bupivacaine concentration until 60 minutes after PAI. As peak plasma concentration of bupivacaine was found at 60 minutes after FNB⁽⁴⁾, the plasma level was measured at that time as a reference level before another dosage of bupivacaine was

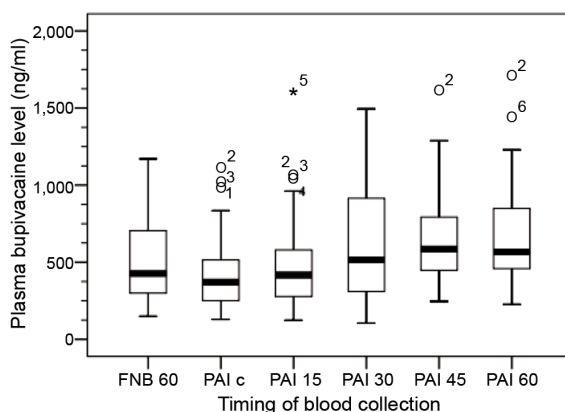


Fig. 1 Plasma bupivacaine concentrations (median and interquartile range) at 60 min after a single-shot FNB and at the time before PAI then 15, 30, 45 and 60 min afterwards. Six patients had distinctly high plasma concentrations.

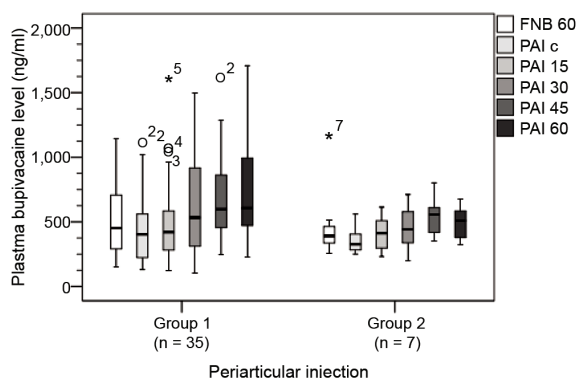


Fig. 2 Plasma bupivacaine levels divided to two groups: group 1 = periarticular injection before tourniquet was deflated, group 2 = periarticular injection after tourniquet was deflated.

administered by PAI. The median plasma bupivacaine concentration was supposed to decrease from its peak after the first dose of FNB until the top up dose of PAI was given. The present study demonstrated that the plasma bupivacaine level was slightly increased after PAI was done. From the author's previous study, the median plasma bupivacaine level was increased up to 490.96 ng/ml after 15 minutes of FNB⁽⁴⁾ whereas the PAI's went up to 44.98 ng/ml in 15 minutes compared to the controlled level (PAIc). As a result, the plasma bupivacaine level given periarticularly increased only 9.16% of FNB. The author assumed that the increment of plasma bupivacaine level from PAI on top of FNB was not as tremendous as from single shot FNB. It might be explained by the proximity of femoral nerve to great vessels compared with poor vascularity of soft tissue around knee joint, which resulted in higher systemic absorption of local anesthetics.

The mean interval from FNB to PAI was 97.43±29.95 minutes. The shortest time interval was 55 minutes. Two patients had PAI after FNB within one hour; however, their plasma levels were in range and had their peak levels at 45 minutes (245.39 and 507.25 ng/ml) before decreasing.

The patients received a total dose of 2.66±0.46 mg/kg of bupivacaine; the maximum dose was 166 mg, which exceeded the recommended dose of 2 mg/kg by the manufacturer. However, the median peak plasma concentration was 586.22 ng/ml at 45 minutes after PAI, which was far below the toxic level of bupivacaine (2,000 to 4,000 ng/ml)^(6,12,14-17). While the maximum value of bupivacaine level observed was 1,709.71 ng/ml at 60 minutes after PAI which was the last blood sampling taken, the authors could not establish a definite conclusion that plasma bupivacaine concentration will not reach the previously described critical level after combined regional blocks. Furthermore, there was no clinically manifested adverse event encountered within 24 hours postoperative. The margin of safety of bupivacaine is possibly much wider than the current standards⁽¹⁸⁾. Anyway, the recommended dose of bupivacaine was based on the use as a single bolus in a highly vascularized area, the higher dose of bupivacaine might be used safely in the present study because it was an additional dose of FNB and injected into a poorly vascularized periarticular region.

Six patients had higher level of bupivacaine concentration compared to the remainders. None of them had significant difference in patient's individual characteristics, anesthesia, and surgical techniques.

This incidence was similar to de Leeuw et al's study⁽¹⁸⁾. They reported that one patient had an extremely high bupivacaine level after combine psoas compartment-sciatic nerve block with the value of 3,240 ng/ml but neither patient-related factors (age, weight, height) nor procedural related factors (blood aspiration prior injection, difficult procedure) were correlated with this relatively large amount of plasma concentration⁽¹⁸⁾. Therefore, the authors suspected that it might be an accidental vascular puncture during attempts of FNB or absorption of bupivacaine into disruption of blood vessels at periarticular sites.

A higher peak plasma level was also related to longer tourniquet time according to Kaeding and Solanki et al^(5,7). This could be explained by the hyperemia from a postischemic reperfusion, as a result of the increased blood flow, the rate of absorption would supposedly be more excessive. In addition, shorter time interval between bupivacaine injection and tourniquet release decreased systemic absorption of bupivacaine by local tissue binding of local anesthetics⁽⁵⁾. However, the sample size of PAI after tourniquet deflation was small (n = 7) compared with the sample size of PAI before tourniquet deflation (n = 35), so the present study could not determine the correlation between plasma bupivacaine concentration and tourniquet time nor interval from PAI to tourniquet deflation.

The present study was limited by the variety of duration from the last dose of bupivacaine in FNB to the PAI, which would affect the plasma bupivacaine level after PAI. Furthermore, the blood sampling collected was restricted to 60 minutes after PAI, which the plasma level of bupivacaine was not clearly decreased. The level might be sustained or unlikely climbed up, so the authors could not certainly conclude that the plasma bupivacaine level reached its peak at 45 minutes after PAI.

Conclusion

The plasma concentration of bupivacaine in patients performed PAI with 20 ml of 0.25% bupivacaine after spinal block and single-shot FNB with 20 ml of 0.5% bupivacaine was below the critical plasma level suggested by existing literatures. Even large dose of bupivacaine used during combined regional blocks did not result in adverse side effects.

What is already known on this topic?

There are a number of studies about bupivacaine after an intraarticular injection^(2,5,7),

combined sciatic and femoral nerve blocks⁽³⁾ or combined spinal anesthesia with femoral nerve block⁽⁴⁾ in terms of plasma concentrations and toxicities. None of existing literatures has any information of plasma concentrations of bupivacaine nor its toxicity after spinal anesthesia combined with single-shot femoral nerve block and periarticular injection, which is usually performed in patients undergoing total knee arthroplasty.

What this study adds?

Plasma bupivacaine concentrations after combined spinal anesthesia with single-shot femoral nerve block and periarticular injection are within safety limit according to the current evidence and can be performed without adverse effect of bupivacaine toxicity

The incremental plasma concentration of bupivacaine after periarticular injection is minimal compared to single-shot femoral nerve block alone, therefore, it can be used safely in addition to spinal anesthesia and single-shot femoral nerve block to provide further postoperative analgesia and facilitate early ambulation.

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Potential conflicts of interest

None.

References

1. Wasudev G, Smith BE, Limbird TJ. Blood levels of bupivacaine after arthroscopy of the knee joint. *Arthroscopy* 1990; 6: 40-2.
2. Meinig RP, Holtgrewe JL, Wiedel JD, Christie DB, Kestin KJ. Plasma bupivacaine levels

following single dose intraarticular instillation for arthroscopy. *Am J Sports Med* 1988; 16: 295-300.

3. Misra U, Pridie AK, McClymont C, Bower S. Plasma concentrations of bupivacaine following combined sciatic and femoral 3 in 1 nerve blocks in open knee surgery. *Br J Anaesth* 1991; 66: 310-3.
4. Lapmahapaisan S, Chinachoti T, Kongpatanakul S, Chatsiricharoenkul S, Tovnich B, Duangkaew W, et al. Plasma concentrations of bupivacaine after spinal anesthesia with single shot femoral nerve block in total knee arthroplasty. *J Med Assoc Thai* 2013; 96: 312-7.
5. Kaeding CC, Hill JA, Katz J, Benson L. Bupivacaine use after knee arthroscopy: pharmacokinetics and pain control study. *Arthroscopy* 1990; 6: 33-9.
6. Knudsen K, Beckman SM, Blomberg S, Sjoval J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; 78: 507-14.
7. Solanki DR, Enneking FK, Ivey FM, Scarborough M, Johnston RV. Serum bupivacaine concentrations after intraarticular injection for pain relief after knee arthroscopy. *Arthroscopy* 1992; 8: 44-7.
8. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; 51: 285-7.
9. Neill RS, Watson R. Plasma bupivacaine concentrations during combined regional and general anaesthesia for resection and reconstruction of head and neck carcinomata. *Br J Anaesth* 1984; 56: 485-92.
10. Thorburn J, Moir DD. Bupivacaine toxicity in association with extradural analgesia for caesarean section. *Br J Anaesth* 1984; 56: 551-3.
11. Steen PA, Michenfelder JD. Neurotoxicity of anesthetics. *Anesthesiology* 1979; 50: 437-53.
12. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* 1989; 69: 563-9.
13. Gerber H, Censier K, Gachter A, Arstufli A, Romppainen J. Intra-articular absorption of bupivacaine during arthroscopy. *Anesthesiology* 1985; 64: A217.
14. Jorfeldt L, Lofstrom B, Pernow B, Persson B, Wahren J, Widman B. The effect of local anaesthetics on the central circulation and

- respiration in man and dog. *Acta Anaesthesiol Scand* 1968; 12: 153-69.
15. Moore DC, Balfour RI, Fitzgibbons D. Convulsive arterial plasma levels of bupivacaine and the response to diazepam therapy. *Anesthesiology* 1979; 50: 454-6.
 16. Santos AC, DeArmas PI. Systemic toxicity of levobupivacaine, bupivacaine, and ropivacaine during continuous intravenous infusion to nonpregnant and pregnant ewes. *Anesthesiology* 2001; 95: 1256-64.
 17. Moore DC, Mather LE, Bridenbaugh LD, Thompson GE, Balfour RI, Lysons DF, et al. Bupivacaine (Marcaine): an evaluation of its tissue and systemic toxicity in humans. *Acta Anaesthesiol Scand* 1977; 21: 109-21.
 18. de Leeuw MA, Bet PM, Wilhelm AJ, Vos RM, Hoeksema M, de Lange JJ, et al. Total plasma concentrations of bupivacaine, levobupivacaine and ropivacaine after combined psoas compartment-sciatic nerve block. *Eur J Anaesthesiol* 2009; 26: 1083-5.

การศึกษาระดับความเข้มข้นของยาบิวพิวาเคนในเลือดในผู้ป่วยที่ได้รับการผ่าตัดเปลี่ยนข้อเข่า ภายใต้การฉีดยาชาเข้าช่องน้ำไขสันหลัง ร่วมกับการฉีดยาชารอบเส้นประสาทฟิเอร์ลด์บริเวณขาหนีบ และการฉีดยาชารอบข้อเข่า

เสาวภาคย์ ลาภมหาไพศาล, ฐิติมา ชินะโชติ, วิริยา ไหมสาสน์, ณัฐวรรณ กลีบจันทร์, สมฤดี ฉัตรสิริเจริญกุล, กิรติ เจริญชลาพานิช, ปวีณัส รุ่งวัฒนกิจ, นุชนาถ สกฤพาเจริญ, จุรีพร ศรีอินทร์

วัตถุประสงค์: เพื่อหาระดับความเข้มข้นของยาบิวพิวาเคนในเลือดในผู้ป่วยที่ได้รับการฉีดยาชาเข้าช่องน้ำไขสันหลังร่วมกับการฉีดยาชารอบเส้นประสาทฟิเอร์ลด์และฉีดยาชารอบข้อเข่า และศึกษาความสัมพันธ์ของอาการเป็นพิษจากยาชากับระดับความเข้มข้นของยาบิวพิวาเคนในเลือด

วัสดุและวิธีการ: เป็นการศึกษาไปข้างหน้าในผู้ป่วย 43 ราย ที่ได้รับการผ่าตัดเปลี่ยนข้อเข่าข้างเดียวด้วยการฉีดยาชาเข้าช่องไขสันหลังร่วมกับการฉีดยาชา 0.5% บิวพิวาเคน 20 มล. รอบเส้นประสาทฟิเอร์ลด์ และฉีดยาชา 0.25% บิวพิวาเคน 20 มล. รอบข้อเข่า โดยจะดูดเลือดผู้ป่วยที่เวลา 60 นาที หลังจากฉีดยาชารอบเส้นประสาทฟิเอร์ลด์ และเวลา 0, 15, 30, 45 และ 60 นาที หลังฉีดยาชารอบข้อเข่า การตรวจวัดระดับยาบิวพิวาเคนในเลือดใช้วิธี *high performance liquid chromatography* ร่วมกับ *tandem mass spectrometry*

ผลการศึกษา: ประชากรศึกษาทั้งหมด 42 ราย เป็นผู้ชาย 10 ราย และผู้หญิง 32 ราย อยู่ใน ASA I และ II ค่ามัธยฐานของระดับยาบิวพิวาเคนในเลือดมีค่าสูงสุดที่ 45 นาที หลังจากฉีดยาชารอบข้อเข่า และมีค่า 586.22 นก./มล. (ค่าต่ำสุด 245.39 นก./มล. ค่าสูงสุด 1,614.36 นก./มล.) ขณะที่ค่าสูงสุดของระดับยาบิวพิวาเคนในเลือด คือ 1,709.71 นก./มล. ที่ 60 นาที หลังฉีดยาชารอบข้อเข่า ไม่พบอาการหรืออาการแสดงของพิษจากยาชาเฉพาะที่ในผู้ป่วยที่เข้าร่วมการศึกษา

สรุป: ความเข้มข้นของยาบิวพิวาเคนในเลือดในผู้ป่วยที่ได้รับการฉีดยาชาเข้าช่องน้ำไขสันหลัง ร่วมกับฉีดยาชา 0.5% บิวพิวาเคน 20 มล. รอบเส้นประสาทฟิเอร์ลด์ และ 0.25% บิวพิวาเคน 20 มล. รอบข้อเข่า มีค่าต่ำกว่าระดับความเป็นพิษของยาบิวพิวาเคนในเลือด