Levobupivacaine versus Racemic Bupivacaine for Extradural Anesthesia for Cesarean Delivery

Pornswan Ngamprasertwong MD, FRCAT*, Danai Udomtecha MD, FRCAT*,
Somrat Charuluxananan MD, MSc, FRCAT**, Oraluxana Rodanant MD*,
Chaiwat Srihatajati MD*, Sintichai Baogham MD*

** Department of Anesthesiology and Clinical Epidemiology Unit, Faculty of Medicine, Chulalongkorn University*
*** Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University*

Background and Objectives: *Bupivacaine is available as a racemic mixture of dextrobupivacaine and levobupivacaine. Many studies show that dextrobupivacaine has a greater inherent central nervous system and cardiovascular toxicity than levobupivacaine. The aim of the present study was to investigate the clinical efficacy and safety of levobupivacaine compared with racemic bupivacaine for extradural anesthesia.*
Meterial and Method: *The authors studied 61 patients undergoing elective cesarean delivery who received either 0.5% levobupivacaine (n = 31) or 0.5% bupivacaine (n = 30) extradurally, in a randomized, double blind study.*
Results: *The 2 groups were similar in terms of time to block suitable for surgery, duration of sensory block, time to T10 regression, time to onset and offset of motor block, verbal numeric pain scores at abdominal opening and at child birth. Mean (SD) dose of 0.5% levobupivacaine and 0.5% bupivacaine were 19.3 (4.6) ml and 17.3 (3.8) ml respectively, p = 0.069.*
Conclusion: *Levobupivacaine produces an extradural block that is similar to bupivacaine, and is an alternative to bupivacaine for cesarean delivery patients.*

Keywords: *Regional anesthesia, Extradural, Local anesthetics, Levobupivacaine, Obstetrics, Cesarean delivery*

J Med Assoc Thai 2005; 88 (11): 1563-8
Full text. e-Journal: *http://www.medassocthai.org/journal*

Bupivacaine (1-butyl-2',6' -pipecoloxylidide), an aminoamide local anesthetic, was first synthesized in the laboratories of Bofors Nebel-Pharma, Sweden and first described by Af Ekenstam et al in 1957[1]. The molecular structure of this highly lipid-soluble and protein-bound compound contains a chiral center on the piperidine ring, resulting in two optically active stereoisomers [i.e., levorotatory (S-) and dextrorotatory (R+) configurations]. However, since its introduction into clinical practice in the early 1960s, bupivacaine has been marketed as a 50:50 racemic mixture of the two enantiomers.

Correspondence to : Charuluxananan S, Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Rama IV Rd., Pathumwan, Bangkok 10330, Thailand. Phone: 0-2256-4295, 0-2252-1699, Fax: 0-2256-4294, E-mail: somratcu@hotmail.com

In the 1980s, concerns regarding this compound's adverse cardiac effects motivated researchers to investigate the mechanisms underlying local anesthetic-induced toxicity and to develop new, safer compounds. As a result of these efforts, (S-) bupivacaine (levobupivacaine) has been recognized as the lesser toxic of this compound's two enantiomers[2,3]. More recently, the toxicity of levobupivacaine has been reassessed to determine its potential benefits for clinical use[4]. Its decrease of cardiovascular and central nervous system toxicity makes levobupivacaine a less toxic substitute for bupivacaine[5,6]. A higher dose of levobupivacaine was required to induce convulsion, QRS widening and ventricular arrhythmia[4]. Bupivacaine has been used in Thailand for decades. For cesarean section, epidural anesthesia with racemic bupivacaine is also a preferable choice for anesthesi-

ologists. This prompted the authors to compare the appropriate dose and hemodynamic effects of epidural levobupivacaine for cesarean section, with epidural racemic bupivacaine in a prospective, randomized, double-blinded study.

Material and Method

After approval by the institutional ethical committee, full term normal parturients aged between 18-40 yr with ASA physical status I or II who were scheduled for elective cesarean section under extradural anesthesia were enrolled in the present prospective, randomized, double-blind study. Written informed consent was obtained from all patients. Exclusion criteria were known hypersensitivity to amide local anesthetics, coagulopathy, height of less than 150 cm, or weight of more than 110 kg. Sample size was determined by using our institutional data for extradural bupivacaine and by assuming a difference in proportion of hypotension between the two groups was greater than 20% from 100% in the bupivacaine group as clinically significant, thirty patients per group were considered necessary to detect statistical significance ($\alpha = 0.05$) with power ($1-\beta$) of 80%.

None of the patients received premedication. In the operating room, monitoring devices, including non-invasive blood pressure, pulse oxymeter, and EKG were attached to the patient, and baseline values were recorded. After 500 ml of 0.9% saline was given intravenously, the L2-3 or L3-4 epidural space was identified with patients in the lateral decubitus position, using an 18-gauge Tuohy needle and the loss-of-resistance to air technique. A 20-gauge multi-orifice catheter was advanced 3-4 cm into the epidural space. After negative aspiration, 3 ml of 2% lidocaine with 15 mcg of epinephrine was administered as a test dose. If there was no evidence of intravascular or subarachnoid injection, the patient was allocated to either the levobupivaciane group, or the bupivacaine group, in a randomized fashion with random number table. Fifteen milliliters of study drug prepared by a nurse anesthetist was incrementally injected through the catheter in the supine position by an anesthesiologist who did not know the type of local anesthetics. Standard monitoring was continued throughout the operation. Level of analgesia to pinprick was assessed bilaterally every 5 min. After 15 min, if the sensory block was inadequate (below T6), an additional 5 ml of study drug was given. The analgesic level was then reassessed every 5 min and incremental 5 ml of the study drug was given until adequate analgesia was achieved. A dilute solution of 4 mg of preservative-free morphine was given epidurally once the baby was delivered.

Motor blockade was assessed according to modified Bromage scale (0 = no motor block, 1 = inability to raise extended legs, 2 = inability to flex knees, and 3 = inability to flex ankle joints) at 5, 15, 30, and 60 min after the injection. Quality of analgesia as defined by pain at the time of skin incision, the time of abdominal opening and the time of child birth was recorded as a 0-10 verbal numeric pain score (VNPS) when 0 is no pain and 10 is the worst imaginable pain. Quality of overall abdominal muscle relaxation (worst, poor, fair, good, excellent) was graded by the obstetrician and overall assessment (fail, fair, very satisfy) was graded by the anesthesiologist. Hypotension was defined as a 30% decrease of systolic blood pressure (SBP) compared to the baseline value. Ephedrine was given intravenously as needed if the SBP decreased for > 30% of baseline or if it was lower than 90 mmHg. Nausea-vomiting, pruritus, shivering and sedation were recorded on a four point scale (0 = no symptom, 1 = mild, did not require any treatment, 2 = moderate, responded to treatment, 3 = severe, persisted after treatment). Nalbuphine 3 mg, metoclopramide 10 mg and pethidine 20 mg intravenously was given for treatment of pruritus, vomiting and shivering respectively. The total amount of study drug, other intraoperative medication, birth weight and APGAR score at 1 and 5 min were also recorded.

In the Post Anesthesia Care Unit (PACU), vital signs were recorded every 15 min for 4 h according to the institutional monitoring protocol. The nausea-vomiting, pruritus, shivering, sedation and pain as VNPS scores were recorded every hour until the bromage score was less than 3 and the sensory block tested by pinprick was regressed to T10. Then the patients were discharged from the PACU. After discharge, routine post-operative care was performed as usual.

Statistical analysis of the results was performed by using SPSS version 10 (SPSS Inc., Chicago, IL). The unpair t test was used for continuous data, chi-square test or Fisher Exact test for categorical data and the Mann-Whitney U test for ordinal data. The priori level of significance was set at $p < 0.05$.

Results

Sixty one parturients were enrolled in the present study and randomized into the Levobupivacaine group (n = 31) and the Bupivacaine group (n = 30). There was accidental dural puncture at L2-3 interspace in one patient in the levobupivacaine group, therefore

the epidural catheter was inserted in L3-4 interspace. This case was proceeded as allocated and the data was included in the present study. There was neither postdural puncture headache nor other serious adverse events in this case.

Maternal demographics and baseline characteristics are shown in Table 1. There was no difference between the groups in terms of age, weight, height, operation time, primigravida, neonatal birth weight and APGAR score. None of the neonates had an APGAR scores less than 7 at 1-min time point or less than 9 at 5-min time point.

Amount of study drug required for adequate analgesia (T6) varied from 15-30 ml. The mean (SD) drug dose was 19.3 (4.6) ml in the levobupivacaine group and 17.3 (3.8) in the bupivacaine group (p = 0.069).

There was no statistically significant difference between groups in time to onset of adequate anesthesia for surgery (T6) (p = 0.224), and time to T10 regression (p = 0.064) as shown in Table 2. The peak block height varied between T2 and T6 in both groups with mode of T4. No statistically significant difference was seen in the onset of motor blockade (p = 0.890) and the duration of complete motor blockade (p = 0.886). By 30 min after completion of epidural injection, Bromage scores varied from 0 to 3. Complete motor blockade was eventually achieved in 20 of 31 patients in the levobupivacaine group (64.52%) and 13 of 30 patients in the bupivacaine group (43.33%).

There was neither significant difference in muscle relaxation scores rated by the obstetrician (p = 0.587) nor difference in overall assessment by the anesthesiologist (p = 0.707). No patient had anesthesia rated as a failure or unsatisfactory by the obstetrician or anesthesiologist. In terms of muscle relaxation, 67.7% of patients in the the levobupivacaine group and 73.3% of patients in the bupivacaine group were rated as "best". In terms of the overall quality of sen-

Table 1. Demographic and baseline characteristics

	Levobupivacaine (n = 31)	Bupivacaine (n = 30)
Age (yr)	31.2 (5.0)	30.8 (5.5)
Weight (kg)	67.8 (8.7)	67.0 (7.6)
Height (cm)	157.4 (5.1)	156.6 (3.9)
Operative duration (min)	51.1 (10.2)	53.4 (19.2)
Primigravida/Multiparous (%)	13/18 [41.9%, 58.1%]	14/16 [46.6%, 53.4%]
Birth weight (g)	3,246.20 (429.9)	3,136.3 (286.3)
APGAR at 1 min	8.90 (0.8)	9.0 (0.0)
APGAR at 5 min	9.94 (0.3)	10.0 (0.0)

Values shown as mean (SD) and frequency [precentage]

Table 2. Drug amount, sensory and motor blockade, and verbal numeric pain score (VNPS)

	Levobupivacaine		Bupivacaine		p value
	Mean (SD)	95%CI	Mean (SD)	95%CI	
Total amount of drug for adequate analgesia (ml)	19.3 (4.6)	17.6-21.0	17.3 (3.8)	15.8-18.7	0.069
Time to onset of sensory block (T6) (min)	16.7 (5.7)	14.6-18.8	15.0 (5.5)	12.92-17.08	0.224
Time to T10 regression of sensory block (min)	244.4 (65.9)	220.2-268.6	281.4 (85.8)	249.3-313.5	0.064
Time to offset of motor block (Bromage > 0) (min)	12.3 (1.5)	9.1-15.5	12.0 (1.1)	9.8-14.3	0.890
Time to starting offset of motor block (Bromage < 3) (min)	126.2 (58.6)	98.7-153.6	129.9 (89.3)	75.9-183.9	0.886
VNPS at skin incision	0.3 (0.9)	0.0-0.7	0.0 (0)	0.0	0.046
VNPS at abdominal opening	1.0 (1.8)	0.3-1.6	0.5 (1.3)	0.1-1.1	0.262
VNPS at child birth	2.1 (2.2)	1.2-2.9	1.6 (2.2)	0.7-2.4	0.387

Values shown as mean (SD) and 95% confidence interval (CI)

sory and motor block, 83.9% of the patients in the levobupivacaine group and 90% of the patients in the bupivacaine group were rated as "very satisfied".

For assessment of pain with verbal numeric pain score (VNPS) when 0 is no pain and 10 the worst imaginable pain, there was no statistical difference in pain intensity between the groups at the time measured except VNPS at the time of skin incision as shown in Table 2. Despite no patient having a VNPS score higher than 3, three cases in the levobupivacaine group and one case in bupivacaine group required fentanyl for relief of discomfort from visceral pain.

With regard to adverse events, intraoperative hypotension was the most common side effect attributed to both study drugs; 12 of 31 cases (38.7%) in levobupivacaine group compared to 20 of 30 cases (66.7%) in the bupivacaine group; p = 0.054). Ephedrine was administered to 16 of 31 patients (51.9%) in the levobupivacaine group and 22 of 30 patients (73.3%) in the bupivacaine group. The mean (SD) dose of ephedrine was 12.6 (8.4) mg in the levobupivacaine group and 13.6 (6.1) in the bupivacaine group (p = 0.366). Intraoperative adverse events are shown in Table 3. These adverse events such as shivering, pruritus, nausea-vomiting and sedation were mild to moderate and treatable. One case in the levobupivacaine group had moderate shivering and required pethidine for treatment. Three cases in the levobupivacaine group and one case in the bupivacaine group had vomiting and were treated successfully with metoclopramide. There were no significant differences between the groups in these side effects. Intraoperative electrocardiogram did not show any clinically significant abnormalities. There were no statistically significant differences in PACU adverse events as shown in Table 4.

Discussion

Levobupivacaine is increasingly popular in replacement of bupivacaine because of its equipotency with lower cardiovascular and central nervous system side effects. It has very similar pharmacokinetic properties to those of racemic bupivacaine, several studies supported the notion that its faster protein binding rate reflects a decreased degree of toxicity[7]. The lethal dose for bupivacaine was significantly smaller than for levobupivacaine[6]. Accidental intravenous injection of bupivacaine during attempted epidural anesthesia in pregnant women caused cardiac arrest. The same event of levobupivacaine caused only transient agitation and the patient recovered fully[8].

The present study demonstrated that 0.5% levobupivacaine is as effective as 0.5% bupivacaine for epidural anesthesia in cesarean section. The present results are in concordance with previous studies. Burk et al compared 0.25% levobupivacaine with 0.25% bupivacaine in laboring women and found no difference in the onset, spread and duration of analgesia[9]. Cox et al studied 96 patients undergoing lower limb surgery

Table 3. Intraoperative adverse events

	Levobupivacaine (n = 31)	Bupivacaine (n = 30)	p value
Hypotension	12 (38.7%)	20 (66.7%)	0.054
Abnormal EKG	0 (0%)	0 (0%)	
Shivering	3 (9.7%)	2 (6.7%)	0.611
Pruritus	1 (3.2%)	0 (0%)	1.000
Nausea/vomiting	6 (19.4%)	4 (13.3%)	0.605
Sedation	9 (29.0%)	8 (26.7%)	1.000

Table 4. Postoperative adverse events

	Levobupivacaine (n = 31)	Bupivacaine (n = 30)	p value
Hypotension	2 (6.5%)	0 (0%)	0.492
Shivering	11 (35.5%)	7 (23.3%)	0.410
Pruritus	11 (35.5%)	15 (50.0%)	0.490
Nausea/vomiting	5 (16.1%)	7 (23.3%)	0.258
Sedation	12 (40.0%)	20 (66.7%)	0.07

under epidural anesthesia and found no significant difference in the nature and quality of blockade produced by 0.5% levobupivacaine compared with 0.5% racemic bupivacaine[10]. That study showed a trend toward less motor blockade in levobupivacaine group but in the present study, there was no statistical and clinically significant difference between the groups.

In a previous study that measured the effects of levobupivacaine in obstetric patients compared the efficacy of 30 ml of epidural 0.5% levobupivacaine with 0.5% racemic bupivacaine[11]. There were no significant differences in potency and side effects. In the present study, the authors found that 19.3 (4.6) ml of levobupivacaine and 17.3 (3.8) ml of racemic bupivacaine were the average effective doses for cesarean section. No significant difference in time of onset and offset of sensory and motor block were found between both groups. Glaser, et al also demonstrated that 25 ml of epidural 0.5% levobupivacaine or 0.5% bupivacaine were similar in terms of time to block suitable for surgery and duration of sensory block. However, lower-limb motor block was significantly longer in the levobupivacaine group but of significantly less intensity[12]. In summary, the present study shows that levobupivacaine produces extradural block that is similar to bupivacaine, and is an alternative to bupivacaine for cesarean section patients.

References

1. Af Ekenstam B, Egner B, Pettersson G. N-alkyl pyrrolidine and N-alkyl piperidine carboxylic acid amides. Acta Chem Scand 1957; 11: 1183-90.
2. Aberg G. Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. Acta Pharmacol Toxicol 1972; 31: 273-86.
3. Luduena FP, Bogado EF, Tullar BF. Optical isomers of mepivacaine and bupivacaine. Arch Int Pharmacodyn 1972; 200: 359-69.
4. Huang YF, Pryor ME, Mather LE, Veering BT. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. Anesth Analg 1998; 86: 797-804.
5. Gristwood O, Bardsley H, Baker H, Dickens J. Reduced cardiotoxicity of levobupivacaine compared with racemic bupivacaine (marcaine): new clinical evidence. Exp Opin Invest Drugs 1994; 3: 1209-12.
6. Morrison SG, Dominguez JJ, Frascarolo P, Reiz S. A comparison of the electrocardio graphic cardiotoxic effects of racemic bupivacaine, levobupivacaine, and ropivacaine in anesthetized swine. Anesth Analg 2000; 90: 1308-14.
7. Burm AGL, Van der Meer AD, Van Kleef JW, Zeiman PWM, Groen K. Pharmacokinetics of the enantiomers of bupivacaine following intravenous administration of the racemate. Br J Clin Pharmacol 1994; 38: 125-9.
8. Kopacz DJ, Allen HW. Accidental intravenous levobupivacaine. Anesth Analg 1999; 89: 1027-9.
9. Burke D, Henderson DJ, Simpson A, Faccenda KA, Morrison LMM, Bannister J, et al. A comparison of 0.25% S(-)-bupivacaine with 0.25% racemic bupivacaine for extradural analgesia in labour. Br J Anaesth 1999; 83: 750-9.
10. Cox CR, Faccenda KA, Gilhooly C, Bannister J, Scoth NB, Morrison LMM. Extradural S(-)-bupivacaine: a comparison with racemic RS-bupivacaine. Br J Anaesth 1998; 80: 289-93.
11. Bader AM, Lawrence CT, Camann WR, Nephew E, Datta S. Clinical effects and maternal and fetal plasma concentrations of 0.5% epidural levobupivacaine versus bupivacaine for cesarean delivery. Anesthesiology 1999; 90: 1596-601.
12. Faccenda KA, Simpson AM, Henderson DJ, Smith D, McGrady EM, Morrison LMM. A comparison of levobupivacaine 0.5% and racemic bupivacaine 0.5% for extradural anesthesia for cesarean section. Reg Anesth Pain Med 2003; 28: 394-400.

การศึกษาเปรียบเทียบการใช้เลโวบูพิวาเคนและบูพิวาเคนฉีดเข้าชั้นนอกดูราสำหรับการระงับความรู้สึกในการผ่าตัดคลอดเด็กทางหน้าท้อง

พรสวรรค์ งามประเสริฐวงศ์, ดนัย อุดมเตชะ, สมรัตน์ จารุลักษณานันท์, อรลักษณ์ รอดอนันต์, ชัยวัฒน์ ศรีหัตถจาติ, สินธิชัย บัวงาม

วัตถุประสงค์: *บูพิวาเคนเป็นยาชาซึ่งเป็นส่วนผสมของเด็กซโตรบูพิวาเคน และเลโวบูพิวาเคน ซึ่งมีการศึกษาพบว่าเด็กซโตรบูพิวาเคนมีผลเป็นพิษต่อระบบประสาทส่วนกลาง และระบบไหลเวียนเลือดมากกว่าเลโวบูพิวาเคน การศึกษานี้มีวัตถุประสงค์เพื่อดูประสิทธิภาพทางคลินิก และความปลอดภัยของเลโวบูพิวาเคนเทียบกับบูพิวาเคนที่ฉีดเข้าชั้นนอกดูรา*

วัสดุและวิธีการ: *สุ่มตัวอย่างแบ่งหญิงตั้งครรภ์ซึ่งเข้ารับการผ่าตัดคลอดเด็กทางหน้าท้องแบบไม่ฉุกเฉิน 61 ราย โดยกลุ่มที่ 1 จำนวน 31 รายได้รับการฉีดยา 0.5% เลโวบูพิวาเคนเข้าชั้นนอกดูรา ขณะที่ กลุ่มที่ 2 จำนวน 30 ราย ได้รับการฉีดยา 0.5% บูพิวาเคนเข้าชั้นนอกดูรา โดยการสุ่มตัวอย่าง และปกปิดทั้ง 2 กลุ่ม*

ผลการศึกษา: *ทั้ง 2 กลุ่มที่ทำการศึกษาไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในแง่ของระยะเวลาตั้งแต่ฉีดยาจนยาชาเริ่มออกฤทธิ์ระงับปวด ระยะเวลาระงับปวด ระยะเวลาที่เริ่มชาลดลง ระยะเวลาตั้งแต่ฉีดยาชาจนกล้ามเนื้อเริ่มหย่อนตัว ระยะเวลาที่กล้ามเนื้อหย่อนตัว ระดับความเจ็บปวดขณะเปิดหน้าท้อง และขณะเด็กคลอด โดยค่าเฉลี่ย (เบี่ยงเบนมาตรฐาน) ของปริมาณ 0.5% เลโวบูพิวาเคน และ 0.5% บูพิวาเคนเท่ากับ 19.3 (4.6) มล. และ 17.3 (3.8) มล. ตามลำดับ ซึ่งไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ $p = 0.069$*

สรุป: *การฉีดยาชาเลโวบูพิวาเคนเข้าชั้นนอกดูรา สามารถให้การระงับความรู้สึกได้เช่นเดียวกับการฉีดบูพิวาเคน และเป็นอีกทางเลือกหนึ่งสำหรับผู้ป่วยผ่าตัดคลอดเด็กทางหน้าท้อง*