Levobupivacaine and Bupivacaine in Spinal Anesthesia for Transurethral Endoscopic Surgery

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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 objective of the present study was to investigate the clinical efficacy and safety of isobaric solution of levobupivacaine compared with hyperbaric solution of racemic bupivacaine in spinal anesthesia.*
Material and Method: *The authors studied 70 patients undergoing elective transurethral endoscopic surgery who received either0.5% isobaric levobupivacaine (n = 35) or 0.5% hyperbaric bupivacaine (n = 35) intrathecally, in a randomized, double blind study.*
Results: *The two groups were similar in terms of time to block suitable for surgery, duration of sensory block, time to two segments regression, time to T12 regression, time to onset and offset of motor block, verbal numeric pain scores at the start of the operation and adverse events.*
Conclusion: *The present study indicated that 2.5 ml of 0.5% isobaric levobupivacaine and 0.5% hyperbaric of racemic bupivacaine show equally effective potencies for spinal anesthesia, regard to both the onset time and duration of sensory blockade.*

Keywords: *Regional anesthesia, Intrathecal, Spinal anesthesia, Local anesthetics, Urologic, Endoscopic, Transurethral*

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Bupivacaine (1-butyl-2',6'-pipercoloxylidine), 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 stereoisomer [i.e., levorotatory (S-) and dextrorotatory (R+) configurations]. However, since its introduction into clinical practice in the early 1960s, bupivacaine has been marketed at 50:50 racemic mixtures of the two enantiomers.

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 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 transurethral endoscopic surgery, spinal anesthesia with racemic bupivacaine is also a preferable choice for anesthesiologists. No study has investigated 0.5% isobaric levobupivacaine compared with 0.5% hyperbaric bupivacaine for spinal

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anesthesia for urological surgery. This prompted the authors to compare hemodynamic effects of isobaric solution of 0.5% levobupivacaine for transurethral endoscopic surgery, with hyperbaric solution 0.5% racemic bupivacaine intrathecally in a prospective, randomized, double-blinded study.

Material and Method

After approval by the Ethical Committee for Research in Human Subjects, Ministry of Public health, urological patients aged between 35-85 yr with ASA physical status I-III who were scheduled for elective transurethral endoscopic surgery under spinal 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 145 cm, or weight of more than 100 kg. The sample size was determined by using the study hospital data for intrathecal 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, 35 patients per group were considered necessary to detect statistical significances (= 0.05) with power (1-) of 80%

The patients were randomly allocated to two groups receiving either 2.5 ml levobupivacaine 0.5% isobaric (Chirocaine ; Abbott Laboratory Ltd. Bangkok, Thailand) or 2.5 ml bupivacaine 0.5% hyperbaric (Marcaine ; Astra Zeneca (Thailand) Limited Bangkok, Thailand) for spinal anesthesia, by random number table, prepared by a nurse anesthetist outside the operating room. None of the patients received premedication, other medications were continued until the operating day. In the operating room, all of the patients had both legs with an elastic bandage wrapped to prevent hypotension, monitoring devices, including non-invasive blood pressure, pulse oximeter (Spo_2), and EKG (Philips IntelliVue MP 20 Junior, Xovic Co.Ltd.) were attached to the patients, and baseline value were recorded. After 2 ml/kg/hr of 0.9% saline was giving intravenously, both drugs were administered intrathecally, under aseptic conditions and with the patients in the lateral decubitus position, through a 27-gauge Quincke needle (BD Medical system, Frankin Lakes, NJ-USA) in the lateral approach at L2-3 slowly at least 10 seconds without Barbotage's technique by an anesthesiologist who did not know the type of local anesthetics. The distal port of the needle was also oriented cranially. Immediately after administration, the patients were turned into a supine position with a pillow under their head. Standard monitoring was continued throughout the operation. Sensory blockade was assessed by using pinprick test on each side of the midclacular line, motor blockade was assessed based on a 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). These tests were performed every 2 min for up to 30 min after spinal anesthesia and every 30 min postoperively until the sensory and motor variables were back to normal. Quality of analgesia defined by pain at the time of endoscopic insertion through the urethra 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 pelvic muscle relaxation (worst, poor, fair, good, excellent) was graded by the urologist and overall assessment (fail, fair, very satisfied) was graded by the attending anesthetist.

The surgical procedure was started 20 min after initiation of spinal anesthesia, or analgesic level at T10. If the level of analgesia was inadequate, 50 g of fentanyl was administered intravenously, if its level was still inadequate the regimen was switched to general anesthesia. Intraoperatively, the patients received 2 ml/kg/hr 0.9% saline solution.

The hemodynamic variables and Spo_2 were recorded before spinal anesthesia and thereafter every 1 min for 20 min, every 5 min until the end of the procedure. Postoperatively, the recordings were repeated every 30 min for 4 h or until the patient was transferred to the ward. A decrease > 25% from baseline, or to < 90 mmHg, in systolic blood pressure, was defined as hypotension and treated with ephedrine bolus 6 mg; a heart rate < 50 bpm was defined as bradycardia and treated with 0.3 atropine; and a decrease in Spo_2 to < 93% was defined as hypoxia and treated with supplemental oxygen via face mask. Nausea-vomiting, shivering 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). Metoclopamide 10 mg, pethidine 20 mg intravenously was administered for treatment of vomiting, shivering respectively. In such cases, only the pretherapeutic data were included in the statistical analysis.

In the post anesthesia care unit (PACU), hemodynamic variables and Spo_2 were recorded every 30 min for 4 h or until recovery of S1 sensory and motor blockade were back to normal or until recovery of dorsiflexion of the great toe. The nausea-vomiting,

shivering were also recorded. The patients were discharged from the PACU when S1 sensation recovery and recovery of dorsiflexion of the great toe. After discharge, routine post-operative care was performed as usual. After 24 hours the post dural puncture headache (PDPH) and transient neurolytic syndrome (TNS) were also recorded.

Statistical analysis of the results was performed by using SPSS version 12.0 (SPSS Inc., Chicago, IL). The unpair t test was used for continuous data, chi-square test or Fisher Exact for categorical data and Mann-Whitney U test for ordinal data. The priori level of significance was set at $p < 0.05$.

Results

Seventy patients were enrolled in the present study and randomized into the levobupivacaine group (n = 35) and the bupivacaine group (n = 35). There were no significant differences between the levobupivacaine and bupivacaine groups for demographic data, baseline hemodynamic parameters, ASA classification or operation duration (Table 1) and operation types (p = 0.77). There were no significant differences between the two groups in the quality of sensory and motor block as shown in Table 2.The peak block height of the levobupi-vacaine group was T4, in the bupivacaine group was T6 and average in both groups were T9. No statistically significant difference was seen in the onset of sensory, motor blockade and the duration of complete motor blockade. Complete motor blockade was eventually achieved in 35 of 35 patients in the levobupi-vacaine group (100%) and 34 of 35 patients in the bupivacaine group (97.1%).

Only highest level of sensory block showed slightly statistical difference.

No patient had anesthesia rated as failure or unsatisfactory by the urologist or nurse anesthetist. In terms of pelvic muscle relaxation, 94.3% of patients in the levobupivacaine group and 97.2% of patients in the bupivacaine group were rated as “best”. In terms

Table 1. Demographic and baseline characteristics

	Levobupivacaine (n = 35)	Bupivacaine (n = 35)	p-value
Sex (Male/Female)	27/8 (77.1%/22.9%)	25/10 (71.4%/28.6%)	0.28
Age (yr)	56.4 (12.3)	56.9 (14.2)	0.41
Weight (kg)	57.8 (8.4)	55.1 (11.1)	0.31
Height (cm)	159.3 (6)	159.1 (6.6)	0.58
Operative duration (min)	26.8 (18.5)	36.9 (22.5)	0.26
ASA (1/2&3)	13/22 (37.1%/62.9%)	9/26 (25.7%/74.3%)	0.44
Systolic blood pressure (mmHg)	132.7 (18.6)	135.7 (18.7)	0.67
Diastolic blood pressure (mmHg)	74.3 (11.1)	75.0 (10.5)	0.77
Heart rate (beats per minute)	72.5 (12.9)	78.6 (13.8)	0.91

Value shown as mean (SD) and frequency (percentage). No significant differences between groups

Table 2. Sensory and motor blockade

	Levobupivacaine (n = 35)	Bupivacaine (n = 35)	p-value
Time to onset of sensory block (T10) (min)	10.0 (4.3)	7.3 (3.6)	0.22
Time to onset of motor block (Bromage > 0) (min)	3.9 (1.7)	3.0 (1.3)	0.52
Time to onset of complete motor block (Bromage = 3) (min)	7.5 (3.2)	4.9 (2.7)	0.34
Highest level of sensory block	T9 (T4-T10)	T9 (T6-T10)	0.05
Time to two segment regression of sensory block (min)	101.0 (54.3)	111.7 (44.2)	0.12
Time to T12 regression of sensory block (min)	139.5 (46.9)	133.3 (43.9)	0.27
Time to offset of motor block (Bromage < 3) (min)	192.1 (51.6)	154.1 (45.2)	0.49
Time to recovery of dorsiflexion of great toe (min)	232.1 (51.8)	192.9 (50.9)	0.84
Time to S1 sensation recovery (min)	256.2 (48.1)	215.1 (50.8)	0.83

Value shown as mean (SD). No significant differences between groups

of the overall quality of sensory and motor block, 82.9% of the patients in the levobupivacaine group and 97.1% of patients in the bupivacaine group were rated as "very satisfied".

For assessment of pain with VNPS at the start of the operation when 0 is no pain and 10 is the worst imaginable pain. There were rated VPNS score, with 0 at the time the operation started in both groups. None of the seventy patients required supplement analgesics during the operative procedure.

There was neither significant difference in recovery of sensory and motor, time to S1 sensation recovery or PACU duration time in both groups. No evidence of postural hypotension after recovery of dorsiflexion of the great toe in all seventy patients.

With regard to intraoperative adverse events, hypotension was reported in 2 of 35 cases (5.7%) in the levobupivacaine group compared to 4 of 35 cases (11.4%) in the bupivacaine group; p = 0.39. Ephedrine was administered to 1 of 35 patients (2.9%) in the levobupivacaine group and 3 of 35 patients (8.6%) in the bupivacaine group. The doses of ephedrine were 12 mg and 18 mg respectively. Shivering was statistically significant in the levobupivacaine group, others adverse events were no significant differences between the groups as shown in Table 3. Bradycardia was a significant difference in the levobupivacaine group as PACU adverse events. The doses of paracetamol as analgesic supplemented in PACU showed no significant differences between the groups as shown in Table 4. Adverse events at different times were also no significant differences between the groups (Table 5).

None of seventy patients were reported as PDPH or TNS after 24 hrs. All of these patients were put in the supine position with a pillow under their head through the beginning of the spinal block and in the ward. They could sit after recovery of dorsiflexion of the great toe without symptoms and signs of postural hypotension. The recovery time of dorsiflexion of the great toe in the levobupivacaine group was 232.1 min and 192.9 min in the bupivacaine group.

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

Table 3. Intraoperative adverse events

	Levobupivacaine (n = 35)	Bupivacaine (n = 35)	p-value
Intraoperative complications	13 (37.1%)	6 (17.1%)	0.06*
Hypotension	2 (5.7%)	4 (11.4%)	0.39
Shivering	9 (25.7%)	1 (2.9%)	0.01*
Nausea and vomiting	2 (5.7%)	0 (0%)	0.15
Bradycardia	2 (5.7%)	1 (2.9%)	0.56
Abnormal EKG	1 (2.9%)	0 (0%)	0.31
Penile erection	1 (2.9%)	0 (0%)	0.31

Value shown in frequency (percentage). * Significant differences between groups

Table 4. Postoperative adverse events

	Levobupivacaine (n = 35)	Bupivacaine (n = 35)	p-value
PACU complications	15 (37.1%)	4 (11.4%)	0.003*
Hypotension	2 (5.7%)	0 (0%)	0.15
Shivering	3 (8.6%)	1 (2.9%)	0.30
Nausea and vomiting	1 (2.9%)	0 (0%)	0.31
Bradycardia	9 (25.7%)	2 (5.7%)	0.02*
Abnormal EKG	1 (2.9%)	0 (0%)	0.31
Paracetamol (500 mg)	7 (20.0%)	10 (28.6%)	0.10

Value shown in frequency (percentage). * Significant differences between groups

Table 5. Adverse events at difference time

	Levobupivacaine (n = 35)	Bupivacaine (n = 35)	p-value
PACU complications	4 (11.4%)	4 (11.4%)	1.00
Hypotension	0 (0%)	0 (0%)	na
Shivering	7 (20%)	1 (2.9%)	0.02
Nausea and vomiting	3 (8.6%)	1 (2.9%)	0.30
Bradycardia	2 (5.7%)	0 (0%)	0.15
Abnormal EKG	1 (2.9%)	0 (0%)	0.31

Value shown in frequency (percentage). No significant differences between groups

dose for levobupivacaine was significantly smaller than for bupivacaine[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]. Due to its long duration of action, racemic bupivacaine is one of the commonest local anesthetics used. However, profound myocardial depression and even cardiac arrest can occur after accidental intravascular injection. Resuscitation from bupivacaine induced cardiovascular collapse has been found to be difficult and may be unsuccessful[9,10]. Levobupivacaine administered via epidural has the advantage of less cardiotoxicity should accidental intravascular injection occur. Since the dose of bupivacaine used in spinal anesthesia is small, the issue of cardiotoxicity is less important. Nevertheless, investigation of the clinical effects of intrathecal levobupivacaine is important; because there is the possibility of accidental intrathecal injection during epidural anesthesia and the event of sudden cardiovascular collapse, cardiac arrest during spinal anesthesia with racemic bupivacaine were also reported rate as 1:1000[15,16]. In Thailand during the year 2003-2004, there were 14 cases reported cardiac arrest during the 24 cases of spinal anesthesia[17]. Multiple factors and mechanisms are proposed. Precipitating factors of sudden bradycardia and asystole are the activation of vagovagal reflex or Bezold-Jarisch reflex by reduction of venous return and increase in vagal tone. Spinal or epidural anesthesia is the causative factor in blocking sympathetic nerves leading to unopposed parasympathetic activities, increased vagal tone, bradycardia, vasodilatation and decreased venous return.

The currently available data on levobupivacaine and racemic bupivacaine for epidural anesthesia, brachial plexus blocks and local infiltration show a similar analgesic potency whereas levobupivacaine tends to induce more sustained sensory and motor blocks.

In a previous study that measured the effects of levobupivacaine in urological surgery patients compared the efficacy of 2.6 ml of an isobaric solution of 0.5% levobupivacaine with 0.5% racemic bupivacaine[11]. There were no significant differences in potency and side effects. Glaser et al performed a study comparing an isobaric solution of 0.5% levobupivacaine and 0.5% racemic bupivacaine 3.5 ml for spinal anaesthesia for elective hip replacement[12]. They found similar clinical effects, including sensory and motor block. Alley et al conducted a randomized, double-blind, cross-over study in healthy volunteers to compare 0.25% hyperbaric levobupivacaine and racemic bupivacaine for spinal anaesthesia[13]. Veracauteren et al used 2ml of 0.125% levobupivacaine or racemic bupivacaine as the initial subarachnoid injection for combined spinal-epidural analgesia in labour[14]. They found similar clinical effects except that levobupivacaine produced no motor block, compared with 34% of patients in the bupivacaine group having motor block equivalent to grade 1 Bromage score. Levobupivacaine and racemic bupivacaine showed equivalent efficacy in terms of sensory and motor block.

The present study demonstrated that 0.5% isobaric levobupivacaine, the pure S (-) enantiomer of racemic bupivacaine, is as effective as 0.5% hyperbaric bupivacaine for spinal anesthesia in transurethral endoscopic urological surgery that requires a sensory block of at least T10. Onset time and duration of the sensory and motor blocks, peak block height, and recovery time of the sensory and motor and hemodynamics are similar to those obtained with racemic bupivacaine. Because 12.5 mg (2.5 ml) is too high a dose and cause a high level of sensory block (T4-T8), especially in the levobupivacaine group, and caused adverse events such as bradycardia, abnormal EKG, or shivering, Lee et al studied 50 patients undergoing urological surgery under spinal anesthesia with 2.6 ml

of isobaric solution of levobupivacaine and racemic bupivacaine. They found that the peak level of sensory block ranged T3-T10[11].

To summarize, the results of the present study indicate that 2.5 ml of 0.5% isobaric levobupivacaine and 0.5% hyperbaric of racemic bupivacaine show equally effective potencies for spinal anesthesia, both regards to the onset time and duration of sensory blockade. Indeed, levobupivacaine generally showed a more sustained sensory and motor blockade. Intrathecal administration resulted in similar hemodynamic changes and adverse events regardless of whether isobaric levobupivacaine or hyperbaric of racemic bupivacaine was used. Based on these data, levobupivacaine is an interesting alternative to bupivacaine for spinal anesthesia.

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การระงับความรู้สึกด้วยเลโวบูพิวาเคนและบูพิวาเคนทางช่องน้ำไขสันหลังเพื่อการผ่าตัดผ่านท่อปัสสาวะโดยกล้อง

โอภาส หว่านนา, ละไม ชุมแสง, ศรินรา ทองมี

***วัตถุประสงค์**: บูพิวาเคนเป็นยาชาซึ่งเป็นส่วนผสมของเด็กโตรบูพิวาเคน และเลโวบูพิวาเคน ซึ่งมีการศึกษาพบว่าเด็กโตรบูพิวาเคนมีผลเป็นพิษต่อระบบประสาทส่วนกลาง และระบบไหลเวียนเลือดมากกว่าเลโวบูพิวาเคน การศึกษานี้มีวัตถุประสงค์เพื่อดูประสิทธิภาพทางคลินิก และความปลอดภัยของเลโวบูพิวาเคนเทียบกับบูพิวาเคนที่ฉีดเข้าช่องน้ำไขสันหลัง*

***วัสดุและวิธีการ**: สุ่มตัวอย่างแบ่งผู้ป่วยซึ่งเข้ารับการผ่าตัดผ่านทางท่อทางเดินปัสสาวะด้วยกล้อง ที่ต้องการระดับการชา T10 โดยใช้เทคนิคฉีดยาชาเข้าทางช่องน้ำไขสันหลัง 70 ราย โดยกลุ่มที่ 1 จำนวน 35 ราย ได้รับ 0.5% ไอโซแบริคเลโวบูพิวาเคน 2.5 มล. กลุ่มที่ 2 จำนวน 35 ราย ได้รับ0.5% ไฮเปอร์แบริค บูพิวาเคน 2.5 มล.โดยการสุ่มตัวอย่างและปกปิดทั้ง 2 กลุ่ม*

***ผลการศึกษา**: ทั้ง 2 กลุ่มที่ทำการศึกษาไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในแง่ของระยะเวลา ตั้งแต่ฉีดยาจนยาชาเริ่มออกฤทธิ์ระงับปวด ระยะเวลาระงับปวด ระยะเวลาที่เริ่มชาลดลง 2 ระดับ ระดับชาลดลงถึง T12 ระยะเวลาตั้งแต่ฉีดยาชาจนกล้ามเนื้อเริ่มหย่อนตัว ระยะเวลาที่กล้ามเนื้อหย่อนตัว ระดับความเจ็บปวดขณะเริ่มผ่าตัด ผลไม่พึงประสงค์*

***สรุป**: การศึกษานี้แสดงให้ทราบว่า 0.5% ไอโซแบริค เลโวบูพิวาเคน และ 0.5% ไฮเปอร์แบริค เรซมิคบูพิวาเคน ขนาด 2.5 มล.สำหรับการฉีดเข้าทางช่องน้ำไขสันหลัง มีประสิทธิภาพในการระงับความรู้สึกที่ไม่แตกต่างกันทั้งระยะเวลายาชาเริ่มออกฤทธิ์ระงับปวด ระยะเวลาระงับปวด และผลข้างเคียง*