CASE REPORT

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Isobaric levobupivacaine for intrathecal anesthesia as an effective and safe option in transurethral resection of the prostate surgery

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Abstract

The search for safer anesthetic solutions has always been one of the primary needs in anesthesiology practice. Levobupivacaine, the pure S (-) enantiomer of bupivacaine, emerged as a safer alternative for intrathecal anesthesia than its racemic parent (bupivacaine). Levobupivacaine shows a lower risk of the central nervous system and cardiovascular toxicity. However, in many countries, levobupivacaine is only available in isobaric solution, where the isobaric solution for intrathecal anesthesia is still often be questioned its effectiveness because of the fear that the block spreading is unpredictable. In this case series, we describe sensory and motor block characteristics, hemodynamics profile and adverse effects of isobaric levobupivacaine in intrathecal anesthesia for six patients with American Society of Anesthesiology physical status II-III whose undergo transurethral endoscopic surgery.

Keywords: levobupivacaine, isobaric, intrathecal anesthesia
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INTRODUCTION

Intrathecal anesthesia is an easy and preferable technique for transurethral endoscopic surgery, as it provides effective sensory and motor block with rapid onset, reduces hospital length of stay, and postoperative pain.[1,2] Hyperbaric bupivacaine is a commonly used local anesthetic solution for intrathecal anesthesia. The hyperbaric solution is expected to provide more predictable block because it tends to spread according to gravity. Bupivacaine is a racemic mixture of S (-) and R (+) enantiomers.[1,3] The two enantiomers have exactly similar in physicochemical properties but can have different affinity for the side of action or the side effects. The differential affinity of each enantiomer for sodium, potassium, and calcium channels results in a significant reduction of neurological dan cardiac toxicity of the S-enantiomer in comparison to the R-enantiomer.[4]

Levobupivacaine is the S (-) or Levo enantiomers of bupivacaine.[1,3,4] In many countries, levobupivacaine is only available in isobaric solution. Isobaric solution for intrathecal anesthesia is less popular because of the fear that the block spreading is unpredictable. Therefore, we report this case series to prove that isobaric levobupivacaine is effective clinically (it can become a better alternative to hyperbaric bupivacaine in intrathecal anesthesia) with better safety profile because it has lower toxic effects on the central nervous system and cardiovascular.

CASE SERIES

Six patients with the aged ranged from 40 to 78 years old with American Society of Anesthesiology (ASA) physical status II-III, were scheduled for elective transurethral endoscopic surgery under intrathecal anesthesia. From their physical examination revealed no vertebra anomaly. Laboratory and radiology examination finding no coagulopathy nor spinal metastases.

Peripheral IV lines (18G) were secured. All of the patients received premedication with 1 mg of intravenous midazolam, 10 mg dexamethasone, and 10 mg diphenhydramine. 5 ml/kg of ringer lactate was commenced to preload the patient before intrathecal anesthesia. In the operating theatre, standard monitoring was applied to the patient. Baseline vitals were recorded. Oxygen 2 L/min was administered via nasal cannula. The patient was placed in a left lateral position and then took all aseptic precautions, a 27 G Quincke's spinal needle was introduced via a midline approach in L2-L3 interspace. Correct needle placement was identified by free-flowing cerebrospinal fluid (CSF), and 12.5 mg isobaric levobupivacaine was injected in subarachnoid space. After the injection, the patient was placed into a supine position with a small pillow under the head. Sensory and motor block characteristics can be seen in table 1. After achieving complete sensory (as high as minimal thoracic 10) and motor block (Bromage score of 3),

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Table 1 Profile of sensory and motoric block for each patient in this study

During Surgery	Patient I	Patient II	Patient III	Patient IV	Patient V	Patient VI
Time to onset of sensory block (T10) (min)	8	4	4	5	5	4
Time to onset of motor block (Bromage>0) (min)	4	5	2	4	3	3
Time to onset of complete motor block (Bromage=3) (min)	7	7	6	9	8	6
Highest level of sensory block	T8	T6	T6	T6	T6	T6
Time to T12 regression of sensory block (min)	130	120	132	150	158	159
Time to recovery of motor block (Bromage=0) (min)	210	220	212	194	218	199

Table 2 Intraoperative hemodynamics for each subject

Hemodynamics during surgery	Patient I	Patient II	Patient III	Patient IV	Patient V	Patient VI
Sistole (mmHg)	135-150	105-115	95-107	108-138	95-114	126-165
Diastole (mmHg)	75-89	69-75	56-63	67-91	53-65	72-81
Heart rate (beats/min)	68-81	55-78	52-71	79-105	54-68	56-72
Respiratory rate (breaths/min)	12-15	12-14	12-15	14-16	12-15	12-14
SpO2 (%)	98-99	98-100	98-100	97-99	97-99	97-99

Table 3 Intraoperative adverse events for each subject

Intraoperative adverse events	Patient I	Patient II	Patient III	Patient IV	Patient V	Patient VI
Nausea	no	no	no	no	no	no
Vomiting	no	no	no	no	no	no
Bradycardia	no	no	no	no	no	no
Hypotension	no	no	no	no	no	no
Shivering	no	yes	no	yes	yes	no

the patient is positioned into a lithotomy position. During surgery, the patient remained hemodynamically stable (table 2). No additional vasopressor was given. Side effects such as nausea, vomiting, bradycardia (heart rate less than 50x/min), hypotension (fall in basal blood pressure more than 25%), or shivering were recorded during surgery. The surgery lasted for 40-70 minutes. Postoperative analgesia was maintained with paracetamol tablet 500 mg every 6 hours and tramadol 50 mg for additional systemic analgesia if needed.

DISCUSSION

Levobupivacaine was developed following concerns of the serious central nervous system (CNS) and cardiovascular adverse reactions after inadvertent systemic spreading of bupivacaine.[1,4,5] The uptake of bupivacaine by the central nervous cells is enantio-selective. Thus both levobupivacaine and ropivacaine are much safer compared to bupivacaine. Their convulsive threshold is found to be higher in various animal models, leading to fewer CNS symptoms after intravenous administration in human volunteers and fewer excitatory changes in the electroencephalogram than bupivacaine.[6] In human studies, the mean dose of intravenous levobupivacaine and bupivacaine associated with CNS symptoms was similar, 56-68 mg and 48-65 mg, respectively. At this similar dose, levobupivacaine shows less myocardial contractility and atrioventricular conduction depressant effect than bupivacaine significantly.[7,8]

The cardiotoxic effects of local anesthetics follow a two-stage pathway: an initial activation of the sympathetic nervous system during the CNS excitatory phase leads to tachycardia and hypertension that can mask direct myocardial depression followed by arrhythmias and profound contractile dysfunction.[9] There seems a dose-dependent prolongation of cardiac conduction with the use of local anesthetics leading to an increase in the PR interval and QRS duration on the electrocardiogram. This is due to the persistent blockade of sodium channels into diastole, predisposing to re-entrant arrhythmias depending on the drugs dissociation. As bupivacaine takes ten times more time to dissociate than that of lidocaine, its blockade can accumulate, resulting in a more marked cardiac depression.[4] The pure enantiomers (ropivacaine and levobupivacaine) have less myocardial depressant profile than racemic bupivacaine. The levorotatory isomer

is sevenfold less potent in blocking the potassium channel and hence, decreases the propensity to prolong QTc interval.[4]

Levobupivacaine (like other local anesthetic agents) exerts its effects on neuronal membranes by binding sodium ion channels reversibly at the nodes of Ranvier in myelinated nerves, leading to faster onset as compared to unmyelinated nerves, therefore preventing voltage-dependent increases in sodium-ion conductance, ultimately inhibiting the initiation and propagation of action potentials in neuronal cells. Levobupivacaine blocks small diameter neuronal fibers more readily than large fibers, explaining the blocking of nociception before other sensory modalities.[3,4] It is > 97% plasma protein-bound (mainly to α1-acid glycoprotein), compares to 95% racemic bupivacaine. Less than 3% of the drug circulates free in plasma so that it can cause an action on the other tissues causing unexpected side effects and toxic manifestations.[1] Its high plasma protein binding and high lipid solubility seem to explain its prolonged duration of action, while its pKa (higher than that of lignocaine) explains its slower onset of action, as less of the drug will be unionised at physiological pH.[3]

Levobupivacaine is extensively metabolized in the liver by hepatic cytochrome (CYP) CYP3A4 isoform and CYPP1A2 isoform to inactive metabolites, desbutyl levobupivacaine and 3-hydroxy levobupivacaine. 3-hydroxy levobupivacaine will undergo further transformation to glucuronide acid and sulfate ester conjugates, which excreted in urine (about 71% within 48 hours), while 24% was in feces.[1,4]

Levobupivacaine produces an intrathecal block with similar characteristics of sensory and motor block, and also recovery like bupivacaine.[1] The onset of sensory and motor block is hastened with the use of hyperbaric levobupivacaine as compared with isobaric levobupivacaine.[10] The regression of motor block occurs earlier with levobupivacaine as compared to bupivacaine.[11,12] Intrathecal administration of levobupivacaine with a dosage of 15 mg provides an adequate sensory and motor block lasting for approximately 6.5 hours. Dosage of 5-10 mg is used in daily case surgeries. At low concentration, levobupivacaine will produce a differential block with preservation of motor function, which provides benefits for ambulatory surgery. Minimum effective local anesthetic dose (MLAD) of levobupivacaine as recommend by an up and down sequential design study is 11.7 mg.[1,5]

Baricity is a measure of the relative density of local anesthetic solution when compared with cerebrospinal fluid (CSF). Local anesthetics have baricity which ranges from 0.9990 to 1.0010 are isobaric.[13] Local anesthetics are made hyperbaric by adding glucose, which increases its mass density. Hyperbaric solutions are generally preferred in intrathecal anesthesia, because they tend to spread according to gravity, and can achieve higher peak sensory level with faster onset.[14] Several reports have shown that isobaric bupivacaine spreads unexpectedly cephalad, even after a reasonable time is allowed for fixation, thus causes late complication such as hypotension and bradycardia due to high block.[15,16] It was explained that all plain anesthetic solutions are actually hypobaric in CSF, resulting in an excessively high spread.[17] In contrast, isobaric levobupivacaine is different in this aspect. Its block levels are distributed to a narrow range and do not spread to higher levels as observed in the various study.[18,19] Gori *et al.* described that specific gravity of isobaric levobupivacaine is very close to CSF, it acts indifferently to gravitational forces, both immediately after the injection and later on.[19] Therefore intrathecal isobaric levobupivacaine does not spread unexpectedly high, and levels of sensory block after spinal isobaric levobupivacaine are unaffected by the change in patient position following the injection. This might be the advantage over plain bupivacaine which tends to spread unexpectedly high.[14]

Transurethral endoscopic surgery requires a sensory block of at least thoracic 10 (T10).[18] In our case series, the highest level of sensory block ranged from thoracic 6 (T6) to thoracic 8 (T8). This is by the reports from Glaser *et al.*[20], Fattorini *et al.*[21], and Vellosillo *et al.*,[22] which said that peak sensory level achieved with isobaric levobupivacaine was around T8.

Sen *et al.*[23] performed a study on patients who received either 13.5 mg hyperbaric bupivacaine or 13.5 mg isobaric levobupivacaine for transurethral endoscopic surgery, found that the speed of onset and offset of motor and sensory blockade were significantly quicker with hyperbaric bupivacaine, while the extent of maximal block and occurrence side effects were similar between the groups. In our case series, 3 of 6 patients experienced shivering during the surgery, but no other side effects (nausea, vomiting, bradycardia, hypotension, or pruritus) were encountered during surgery.

Isobaric levobupivacaine was found effective for surgeries requiring a level of T10 or below like TURP,[24] lower limb orthopedic surgeries,[14] lower abdominal surgeries.[25,26] For cesarean section, isobaric levobupivacaine also proved effective as the spreading of spinal anesthetic was found to be more cephalic due to gravid uterus achieving desired T4/T6 level.[12,27] A study by Lee *et al.*[28], demonstrated 2.6 ml of 0.5% isobaric levobupivacaine or 0.5% racemic bupivacaine in urological surgery under spinal anesthesia and found that there were

no significant differences in the quality of sensory and motor block or in hemodynamic change.

Our case series shows that isobaric levobupivacaine is effective in intrathecal anesthesia for transurethral endoscopic surgery as it offers effective sensory-motor blockade and stable hemodynamics profile.

CONCLUSION

Levobupivacaine should be considered as an alternative to its racemic patent, bupivacaine due to better safety profile.

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