The Use of Levobupivacaine and Ropivacaine in Spinal Anaesthesia for Lower Limb and Urological Surgery

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ABSTRACT

Levobupivacaine and ropivacaine are two relatively new local anaesthetics which were developed in view of their potential for less cardiotoxicity in comparison with bupivacaine, the most common local anaesthetic used in spinal anaesthesia for many years. Both are produced in pure S(-) enantiomer form in contrast to bupivacaine which is a racemic mixture. They have been shown to be effective in peripheral nerve blocks, and epidural analgesia and anaesthesia; nevertheless, experience of their use in spinal anaesthesia is limited. The objective of this thesis was to evaluate their use in spinal anaesthesia for surgery in non-obstetric patients. My hypothesis was that *levobupivacaine and ropivacaine are effective local anaesthetic agents for spinal anaesthesia in lower limb and urological surgery.* In order to test this hypothesis, I conducted five clinical studies on 269 patients who had urological surgery or lower limb surgery under spinal or combined spinal-epidural anaesthesia. First, I investigated the efficacy and clinical characteristics of levobupivacaine and the mixture of levobupivacaine with fentanyl in spinal anaesthesia. Next, I compared the use of ropivacaine-fentanyl with bupivacaine-fentanyl in spinal anaesthesia. Finally, I defined the dose-response relationship of ropivacaine in spinal anaesthesia using traditional dose-response methodology and defined the relative potency among levobupivacaine, ropivacaine and bupivacaine by comparing the defined ED50 in spinal anaesthesia using up-down sequential allocation method.

I found that 2.6ml of 0.5% levobupivacaine had similar clinical characteristics as the same volume of 0.5% bupivacaine in spinal anaesthesia. Both were effective for

spinal anaesthesia in urological surgery, when a sensory block up to at least T10 dermatome was required. In comparing the use of levobupivacaine alone and levobupivacaine with fentanyl, there were no significant differences in haemodynamic changes and quality of sensory and motor block, when 2.6ml of levobupivacaine alone or 2.3ml of levobupivacaine with fentanyl 15mcg (0.3ml) were used in spinal anaesthesia. Both were effective for spinal anaesthesia in urological surgery. In comparing the use of ropivacaine 10mg and bupivacaine 10mg, both with fentanyl 15mcg in spinal anaesthesia for urological surgery, all the patients achieved adequate level of sensory block up to T10 dermatome or higher. The two drugs were similar in the onset time of motor block, the characteristics of sensory block and haemodynamic changes; however, the duration of motor block was shorter with ropivacaine. I concluded that both studied solutions, ropivacaine-fentanyl and bupivacaine-fentanyl, were effective for spinal anaesthesia in urological surgery and the duration of motor block was shorter with the ropivacaine-fentanyl solution. The dose-response relationship of ropivacaine in spinal anaesthesia for lower limb surgery requiring a sensory block up to at least the T12 dermatome was defined. Anaesthesia was successful in 0, 0, 42, 83 and 100% when ropivacaine at doses of 2, 4, 7, 10 and 14mg respectively were given. The derived values for ED50 and ED95 were 7.6mg and 11.4mg respectively. The cephalic level of sensory block and the degree of motor block increased with larger doses of ropivacaine. Finally, the median effective dose (ED50) of bupivacaine, levobupivacaine and ropivacaine in spinal anaesthesia for lower limb surgery were defined as 5.50mg (95% CI: 4.90-6.10mg), 5.68mg (95% CI: 4.92-6.44mg), and 8.41mg (95% CI: 7.15-9.67mg) respectively. The relative potency

ratios were 0.97 (95% CI: 0.81-1.17) for levobupivacaine/bupivacaine, 0.65 (95% CI: 0.54-0.80) for ropivacaine/bupivacaine and 0.68 (95% CI: 0.55-0.84) for ropivacaine/levobupivacaine.

In this series of studies, I have shown that levobupivacaine and ropivacaine are effective local anaesthetic agents for spinal anaesthesia in lower limb and urological surgery. This proved my hypothesis. Both are suitable alternatives to bupivacaine for spinal anaesthesia. Furthermore, these studies showed that ropivacaine is less potent than levobupivacaine and bupivacaine and the potency is similar between levobupivacaine and bupivacaine at median effective dose.

PREFACE

STATEMENT OF WORK

The work in this thesis was done at Kwong Wah Hospital, Kowloon, Hong Kong SAR, China during the period 2001-2010, while I was employed as consultant in the Department of Anaesthesiology and Operating Theatre Services. From the year 2004 to 2010, I was also appointed as Honorary Clinical Associate Professor in Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Shatin, Hong Kong. The work contained within this thesis is exclusively my own, except for the assistance in data collection, data analysis and manuscript preparation that was given by Professor Warwick D Ngan Kee, Professor Tony Gin, Dr K Muchhal, Dr HK Chang, Dr CL So, Dr SY Fong, Dr TC Liu and Ms Alice Cheung.

This thesis has not been accepted in whole or in part for any other degree or diploma and none of this work has been published elsewhere by other authors.

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PUBLICATIONS AND PRESENTATIONS

THE FOLLOWING PUBLICATIONS AROSE FROM THIS WORK

Lee YY, Muchhal K, Chan CK. Levobupivacaine versus racemic bupivacaine in spinal anaesthesia for urological surgery. Anaesth Intensive Care 2003;**31:**637-41.

Lee YY, Ngan Kee WD, Muchhal K, Chan CK. Randomized double-blind comparison of ropivacaine-fentanyl and bupivacaine-fentanyl for spinal anaesthesia for urological surgery. Acta Anaesthesiol Scand 2005; **49:**1477-82.

Lee YY, Muchhal K, Chan CK, Cheung AS. Levobupivacaine and fentanyl for spinal anaesthesia: a randomized trial. Eur J Anaesthesiol 2005; **22:**899-903.

Lee YY, Ngan Kee WD, Chang HK, So CL, Gin T. Spinal ropivacaine for lower limb surgery: a dose response study. Anesth Analg 2007;**105:**520-3.

Lee YY, Ngan Kee WD, Fong SY, Liu JT, Gin T. The median effective dose of bupivacaine, levobupivacaine, and ropivacaine after intrathecal injection in lower limb surgery. Anesth Analg 2009; **109:**1331-4.

The following presentations arose from this work

Lee YY. A dose-response study of spinal ropivacaine for lower limb surgery: preliminary report. Presented at 8th Asian and Oceanic Society of Regional Anesthesia and Pain Medicine, 2005, Chiba, Japan.

Lee YY. The use of levobupivacaine in spinal and epidural anaesthesia. Presented at Anaesthesiology refresher course, 2007, Macau, SAR, China.

Lee YY. The minimum effective local anaesthetic dose of bupivacaine, levobupivacaine and ropivacaine after intrathecal injection in lower limb surgery. Presented at XXVII European Society of Regional Anaesthesia Congress, 2008, Genoa, Italy.

Lee YY. The use of levobupivacaine in spinal and epidural anaesthesia. Presented at International Anaesthesia Summit, 2010, Guangzhou, China.

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LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologists
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
cm	Centimetre
CSF	Cerebrospinal fluid
EDx	Effective dose for x % of patients
F	Female
HR	Heart rate
Hg	Mercury
IV	Intravenous
Kg	Kilogram
l	litre
L	Lumbar level
M	Male
mg	Milligram
mcg	Microgram
min	Minute
ml	Millilitre
MLAC	Minimum local analgesic concentration
MLAD	Minimum local anaesthetic dose
mm	Millimetre

mV	Millivolt
n	Number
NS	Not significant
pKa	-log (dissociation constant)
SD	Standard deviation
TURBT	Transurethral resection of bladder tumour
TURP	Transurethral resection of prostate
Tx	x^{th} thoracic (dermatome)
vs	versus
yr	year

PART 1

INTRODUCTION

CHAPTER I HYPOTHESIS AND OBJECTIVE

CHAPTER II REVIEW OF LITERATURE

CHAPTER III RESEARCH PLAN

CHAPTER I

HYPOTHESIS AND OBJECTIVE

Due to its long duration of action, racemic bupivacaine is one of the commonest local anaesthetics and is used in a wide variety of clinical setting including peripheral nerve blocks, epidural anaesthesia and spinal anaesthesia. 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 (Albright 1979, Reiz and Nath 1986). This has led to research programmes to develop a local anaesthetic agent which is effective but with less cardiotoxicity (Whiteside and Wildsmith 2001). It is known that for bupivacaine, the S(-) enantiomer is less toxic than R(+) form (Albright 1979, Huang et al 1998, Mazoit et al 1993). Ropivacaine and levobupivacaine are two relatively new local anaesthetics which were developed in view of the potential of less cardiotoxicity. Both are produced in pure S(-) enantiomer form. Levobupivacaine is the S(-) enantiomer of bupivacaine and ropivacaine is the propyl analogue of bupivacaine. Both agents have been showed to be effective in nerve blocks, and epidural analgesia and anaesthesia. However, experience and research with their use in spinal anaesthesia for surgery are still limited.

Spinal anaesthesia is commonly used for lower limb and urological surgery. The objective of this thesis was to evaluate the use of levobupivacaine and ropivacaine, the two 'newer' local anaesthetics in spinal anaesthesia for

lower limb and urological surgery. The hypothesis was that '*levobupivacaine and ropivacaine are effective local anaesthetic agents for spinal anaesthesia in lower limb and urological surgery*'.

CHAPTER II

REVIEW OF LITERATURE

HISTORY OF SPINAL ANAESTHESIA

Spinal anaesthesia is produced by the intrathecal injection of a local anaesthetic solution into the cerebrospinal fluid (CSF) within the subarachnoid space which causes temporary interruption of the nerve transmission.

CSF was first discovered by Cotugno in 1764 (Atkinson et al 1987). The first intrathecal injection of local anaesthetic in animals was done by JL Corning, a neurologist, in New York in 1885. He inadvertently punctured the dura and injected cocaine, thus administering local anaesthetic to the spinal nerves of a dog (Atkinson et al 1987). The first spinal anaesthesia in a human was performed by Bier in 1898 using 3ml of 0.5% cocaine solution (Atkinson et al 1987). Following that, spinal anaesthesia with cocaine was reported by Bier and others between 1899 and 1905. Nevertheless, popularity of spinal anaesthesia was not gained due to the toxicity of cocaine and its short duration of action (Cousins and Bridenbaugh 1998). In 1904, procaine was synthesized and it was the first neurologically safe local anaesthetic. Following the introduction of procaine, spinal anaesthesia was widely used. In 1923, Labat published the book 'Regional Anesthesia' and documented the occurrence of transient headache, retention of urine and anal incontinence with no permanent neurological damage after spinal anaesthesia (Maltby et al 2000). The popularity of spinal anaesthesia became more in the 1930s with the introduction of tetracaine and dibucaine as

their duration of action was longer. It reached a peak by 1940. However, its use subsequently declined because of the improvement in the technique of general anaesthesia and the fear of permanent neurological damage after the publicized 'Woolley and Roe' cases of paralysis after spinal anaesthesia in United Kingdom in 1947 (Cousins and Bridenbaugh 1998). Woolley and Roe became paraplegic after spinal anaesthesia on the same day in the same hospital. Original, it was suggested to be caused by the contamination of the local anaesthetic with phenol through invisible cracks of the glass ampule. Recently, it was also suggested that the problem was caused by the contamination of the spinal needles or syringes with acidic descaling liquid during the sterilization process (Maltby et al 2000). The use of spinal anaesthesia has increased since the mid-1960s after the epidemiological studies of Driffs and Vandam which showed its safety if properly performed (Dripps and Vandam 1954). Its popularity accelerated with the availability of new amide-type local anaesthetics and the awareness of risks associated with general anaesthesia (Nimmo and Smith 1989).

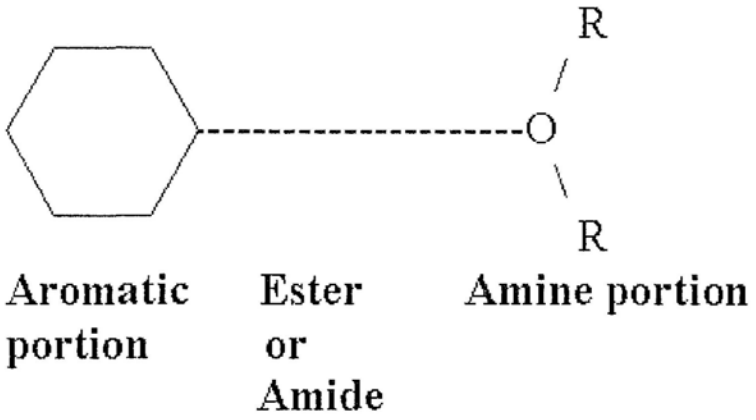
PHARMACOLOGY OF LOCAL ANAESTHETIC AGENTS

Local anaesthetics are drugs that when applied to nerve tissue can produce reversible blockade in the conduction of nerve impulses. The recovery of nerve conduction is complete and there is no structural damage to the nerve fibres.

A brief account on the mechanism of action of local anaesthetics is as follows. Neurons are highly specialized nerve cells. In the resting state, the neuronal membrane is permeable to both sodium and potassium ions. Potassium ions can move freely across the membrane while sodium ion can move in a semi-permeable manner with control in gates on the sodium channels. Potassium accumulates inside the neuron in order to maintain electrical neutrality. Higher concentration of sodium ion is maintained in the extracellular fluid on the outside of the cell membrane except when the sodium channels are open. In general, the interior of a neuron is electronegative (in the order of -80 mV) with respect to its outer surface. A nerve impulse may be activated in the neuron by a variety of stimuli. It is a physiochemical process with electrical changes on the cell membrane of the neuron. During the transmission of the nerve impulse, the sodium ion permeability increases. This will change the resting membrane potential to become less negative as sodium ions pass into the cell. An action potential will be triggered when the membrane potential is depolarized to a threshold level, which is usually about +15mV. The permeability to sodium ion will be greatly increased at the threshold membrane potential. At higher membrane potential the sodium permeability will not increase further as all the

sodium channels are opened. An action potential is of constant amplitude once a stimulus of threshold intensity has reached. It is an all or none response. After depolarization, sodium ion permeability will fall. This causes repolarization of the cell membrane to its resting level (Fee and Bovill 2004, Tetzlaff 2000). Local anaesthetics act as sodium ion channel blockers which inhibit the inward movement of sodium ions during depolarization. They will slow the rate of rise and the height of action potential. They do not affect the resting membrane potential.

Local anaesthetics are made up of a lipophilic part (usually an aromatic ring) and a hydrophilic part (usually a tertiary amide) linked up by an ester (-CO-) or amide (-NHC-) bond (Figure 1).



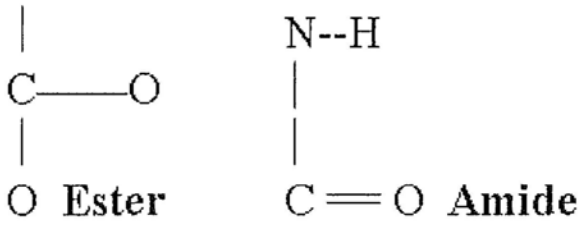


FIGURE 1 STRUCTURE OF A LOCAL ANAESTHETIC MOLECULE

The type of this linkage is the basis for classification of local anaesthetics as ester group or amide group. Amide local anaesthetics are eliminated mainly by liver metabolism, while ester local anaesthetics are eliminated faster due to rapid hydrolysis in the plasma and liver. Therefore, the elevation in the plasma concentration of amide local anaesthetics is more prolonged and systemic toxicity is more likely than ester local anaesthetics. Allergic reaction to local anaesthetics is commoner in ester local anaesthetics in comparison to amide local anaesthetics due to its metabolite of para-aminobenzoic acid.

Most amide local anaesthetics are chiral molecules. Each molecule has an asymmetric carbon atom which is bound to four different substitutes. For a molecule with chiral centre, there are two different three-dimensional structures (stereoisomers) with respect to each other. They are mirror images of one another, like the left and right hands which cannot overlap with each other. Enantiomers (a pair of stereoisomers) are optically active and rotate polarized light in different directions: dextrorotatory [clockwise rotation (+)] and levorotatory [counterclockwise rotation (-)]. Enantiomers are named 'R' or 'S' according to the three-dimensional arrangement of the substitutes around the chiral centre of the molecules. Enantiomers have identical physiochemical properties but their interactions with biological receptors are different due to the difference in their three-dimensional structures.

In spinal anaesthesia, the density of the local anaesthetics can be adjusted in additional to the drug dose for the achievement of desired level of block. This is usually done with the addition of dextrose. The baricity of a spinal

solution is the ratio of the density of the solution divided by that of the CSF. The density of normal CSF varies. For the spinal anaesthetic solution to behave persistently hypobaric or hyperbaric in all patients, its baricity needs to be less than 0.9990 and greater than 1.0010 respectively (Cousins and Bridenbaugh 1998). With the use of hyperbaric solution, the distribution of the spinal anaesthetic solution will be affected by gravity and hence can be manipulated by the position of the patient.

THE DEVELOPMENT AND CHEMISTRY OF BUPIVACAINE, LEVOBUPIVACAINE AND ROPIVACAINE

Bupivacaine (chemical name: 2-pipendineccarboxamide, 1-butyl-N-12, 6-diethylphenyl-monohydrochloride) is an amino-amide local anaesthetic. It is a racemic mixture with equimolar amounts of both dextro- and levorotatory enantiomers. It was first synthesized by Af Ekenstam in 1957 (Af Ekenstam 1957). It has been one of the most popular local anaesthetics for many years due to its long duration of action. Bupivacaine has a good safety record in terms of neurotoxicity since its introduction in 1965. Transient neurologic symptoms was interpreted as a sign of possible neurotoxicity of local anaesthetics after spinal anaesthesia. The incidence in bupivacaine was significantly less than that of lignocaine (Zaric et al 2005).

However, bupivacaine has a narrower difference of plasma concentration in the occurrence of central nervous system toxicity and cardiovascular toxicity in comparison with other local anaesthetics (Morishima et al 1985, Santos et al 1989). There were reports of cases of almost simultaneous convulsion and cardiac arrest after accidental intravascular injection of bupivacaine (Albright 1979). This means that bupivacaine has a narrower margin of safety in clinical use as convulsion usually precedes cardiac arrest in cases of overdose of other local anaesthetics (Whiteside and Wildsmith 2001). In view of this, there was a need to develop a local anaesthetic with the favourable blocking properties on nerve conduction similar to bupivacaine but with a greater margin of safety.

Both levobupivacaine and ropivacaine are synthesized as the levorotatory S(-) enantiomer instead of a racemic mixture. Ropivacaine (N-n-propyl 2', 6'-pipecroboxylidide hydrochloride) is an amino-amide local anaesthetic (Figure 2). It is the propyl analogue of bupivacaine. It was first synthesized in the 1950s, nevertheless, its clinical use was not explored fully until the 1970s when there was an interest in searching for a local anaesthetic with lower cardiotoxicity. Eventually it was registered for clinical use in 1996 (Whiteside and Wildsmith 2001). Levobupivacaine is the S(-) enantiomer of bupivacaine (Figure 2). It was developed after ropivacaine when it was recognized that the S(-) enantiomer of the local anaesthetics were less cardiotoxic. It was marketed for clinical use in 1999. Animal studies suggested that levobupivacaine and ropivacaine could be injected intrathecally without neurotoxicity (Malinovsky et al 2002, Muguruma et al 2006)

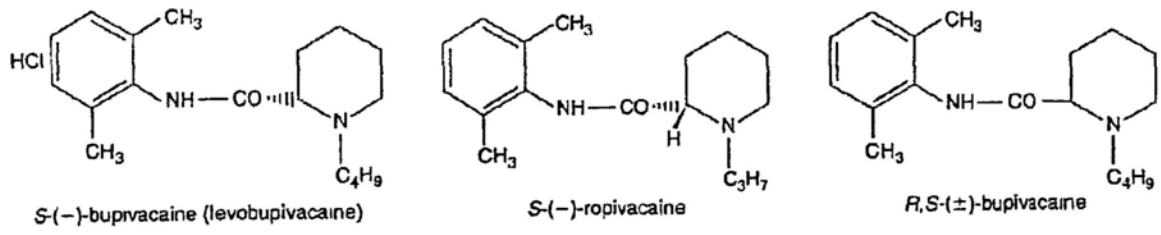


FIGURE 2 THE CHEMICAL STRUCTURE OF LEVOBUPIVACAINE, ROPIVACAINE AND BUPIVACAINE

The physical and chemical properties of these three local anaesthetics are summarized in Table 1.

TABLE 1 THE PHYSICAL AND CHEMICAL PROPERTIES OF BUPIVACAINE, LEVOBUPIVACAINE AND ROPIVACAINE

	Bupivacaine	Levobupivacaine	Ropivacaine
Molecular weight	288	288	274
pKa	8.1	8.1	8.1
Partition coefficient (octanol/buffer)	346	346	115
Protein binding (%)	95	95	94

As levobupivacaine is the S(-) enantiomer of bupivacaine, their physical and chemical properties are identical. In general, lipid solubility determines the anaesthetic potency of the local anaesthetics. Lipid solubility is assessed as partition coefficient, which is the relative solubility of the local anaesthetic in octanol compared with the solubility in aqueous solution. The partition coefficient and hence, the lipid solubility of ropivacaine is lower than that of bupivacaine and levobupivacaine. As a local anaesthetic with high lipid solubility can penetrate the nerve membrane more easily, fewer molecules are required for blocking the conduction of nerve impulses. This results in higher potency and longer duration of action (Miller 2005). As the lipid solubility of ropivacaine is less than that of levobupivacaine and bupivacaine (Table 1), it is predicted that its potency will be lower. The lower lipid solubility of ropivacaine also suggests that it may produce a more selective blockade for sensory fibres in comparison to bupivacaine (Wildsmith et al 1989, Whiteside and Wildsmith 2001). In simple terms, lower lipid solubility will reduce the affinity and penetration of the nerve membrane by ropivacaine. Hence, the blockade of the smaller sensory fibres (unmyelinated C fibres and smaller myelinated A fibres) is greater than the large motor fibres (larger myelinated A fibres), especially when a lower concentration is used.

COMPARISON OF BUPIVACAINE, LEVOBUPIVACAINE AND ROPIVACAINE IN PRE-CLINICAL STUDIES.

In the laboratory, studies have been done in animals and isolated nerves for comparing the properties of sensory and motor block for bupivacaine, levobupivacaine and ropivacaine.

Dyhre et al compared the duration of sensory and motor block of bupivacaine, levobupivacaine and ropivacaine in peripheral nerve block in the rat. They found that equimolar doses of these three local anaesthetics had similar duration of action (Dyhre et al 1997).

Kanai et al compared the dose-response of levobupivacaine, ropivacaine and bupivacaine after epidural and intrathecal injection in the rat at concentrations of 0.25-0.75%. It was found that the duration of sensory block was similar between levobupivacaine and bupivacaine and it was significantly longer than ropivacaine. Duration of motor block at lower concentration was similar between levobupivacaine and ropivacaine but it was significantly shorter than that of bupivacaine. At higher concentration, the duration of motor block for levobupivacaine and bupivacaine were longer than that of ropivacaine (Kanai et al 1999).

Kanai et al compared the anaesthetic potency of R(+) bupivacaine, S(-) bupivacaine (levobupivacaine) and ropivacaine by studying their effects on action potential amplitude and the maximal rate of rise of action potential in crayfish giant axon in vitro. They reported that levobupivacaine has a more potent phasic blocking effect than ropivacaine and R(+) bupivacaine (Kanai et al 2000).

Brau et al investigated the ability of the local anaesthetics in inhibiting the tetrodotoxin-sensitive sodium channels in peripheral nerves. These sodium channels are the major site of action of the local anaesthetics. It was found that ropivacaine was approximately 50% less potent than levobupivacaine and bupivacaine (Brau et al 2000).

Vladimirov et al studied the potency of stereoisomers of bupivacaine in rat for sciatic nerve block. They found that levobupivacaine is equipotent to R(+) or racemic bupivacaine (Vladimirov et al 2000). Sinnott and Strichartz compared ropivacaine and levobupivacaine at concentrations of 0.0625, 0.125 and 0.25% for sciatic nerve block in the rat. At 0.0625%, levobupivacaine produced a denser motor block and longer duration of sensory block compared with ropivacaine. At 0.125%, there was no difference between the two drugs. At 0.25%, levobupivacaine had a 30% longer duration of sensory and motor block compared with ropivacaine (Sinnott and Strichartz 2003).

These pre-clinical studies suggest that there are differences in potency among these three local anaesthetics. Although their findings are not always consistent due to differences in the experimental settings, they provide hints that ropivacaine may be less potent than bupivacaine and levobupivacaine.

THE USE OF LEVOBUPIVACAINE AND ROPIVACAINE IN PERIPHERAL NERVE BLOCK

In peripheral nerve block, both ropivacaine and levobupivacaine were first reported to be used for injection into the brachial plexus. Hickey et al reported the successful use of 0.5% ropivacaine for brachial plexus block using the subclavian approach while Cox et al reported that there was no significant difference in successful rate between 0.5% levobupivacaine and 0.5% bupivacaine in supraclavicular brachial plexus block (Hickey et al 1990, Cox et al 1998a). Since then, the use of levobupivacaine and ropivacaine for different types of peripheral nerve block has been studied extensively.

Their use in brachial plexus block was further studied. Casati et al compared the onset time and quality of interscalene brachial plexus block for open shoulder surgery using 30ml of 0.5% levobupivacaine or 0.5% ropivacaine. They found that the onset time and quality of block were similar (Casati et al 2003). Liisanantti et al compared the use of 45ml of 0.5% bupivacaine, 0.5% levobupivacaine or 0.5% ropivacaine in axillary brachial plexus block for hand and forearm surgery. The successful rate for surgery and the duration of the blocks were similar among the three studied solutions (Liisanantti et al 2004). Piangatelli et al compared the use of 30ml of 0.5% levobupivacaine and 0.75% ropivacaine in infraclavicular brachial plexus block. The duration of sensory block was longer in levobupivacaine. Both studied solutions were effective with no complications (Piangatelli et al 2006).

Levobupivacaine and ropivacaine have been used successfully in sciatic nerve block. Casati et al compared levobupivacaine and ropivacaine for sciatic nerve block. They conducted a study on 50 American Society of Anaesthesiologists (ASA) physical status I-II patients for hallux valgus repair. All patients received a femoral nerve block with 15ml of 2% mepivacaine. For sciatic nerve block, they were randomly allocated to receive 20ml of either 0.5% levobupivacaine or 0.5% ropivacaine. The median (range) time for the onset of surgical block was 30 min (5-60min) with levobupivacaine and 15min (5-60min) with ropivacaine (P = 0.63). There were no differences in the duration of sensory and motor block as well as post-operative analgesia. The median duration of post-operative analgesia was 16 hours for both of them. They concluded that 0.5% levobupivacaine and 0.5% ropivacaine have similar characteristics of sensory and motor block in sciatic nerve block (Casati et al 2002). Piangatelli et al compared the characteristics of sensory and motor block of lumbar plexus block and sciatic nerve block using either 0.5% levobupivacaine or 0.75% ropivacaine. They performed the lumbar plexus block with 30ml of the local anaesthetic solution and sciatic nerve block with 10ml of the local anaesthetic solution. The characteristics of the sensory and motor block were similar with faster onset of motor block and longer duration of sensory block with 0.5% levobupivacaine. The time of resolution of motor block was similar between the two groups (Piangatelli et al 2004). Casati et al studied the onset time and duration of sciatic nerve block in using 20ml of 0.5% levobupivacaine, 0.75% levobupivacaine or 0.75% ropivacaine. They concluded that 0.75%

levobupivacaine had faster onset than 0.5% levobupivacaine and longer duration of analgesia than both 0.5% levobupivacaine and 0.75% ropivacaine (Casati et al 2005).

These studies showed that levobupivacaine and ropivacaine with concentrations at or above 0.5% would provide effective anaesthesia in peripheral nerve plexus blocks.

THE USE OF LEVOBUPIVACAINE AND ROPIVACAINE IN EPIDURAL ANALGESIA FOR LABOUR PAIN

Both levobupivacaine and ropivacaine have been used successfully in epidural analgesia for labour pain. Clinical studies have compared the use of levobupivacaine, ropivacaine and bupivacaine in epidural analgesia.

Lyons et al compared the minimum local analgesic concentration (MLAC) of levobupivacaine and bupivacaine in epidural analgesia for labour pain in a randomized, double-blind study using up-down sequential allocation method. MLAC was median effective concentration of the study drug in 20ml for epidural analgesia in the first stage of labour. They found that MLAC of levobupivacaine was 0.083% (95% CI: 0.065-0.101) and the MLAC of bupivacaine was 0.081% (95% CI: 0.055-0.108). The potency ratio of levobupivacaine/bupivacaine was 0.98 (95% CI: 0.67-1.41). Hence, they concluded that there was no clinical important difference between levobupivacaine and bupivacaine in epidural analgesia (Lyons et al 1998).

Polley et al compared the relative analgesic potencies between ropivacaine and bupivacaine in epidural analgesia for labour pain using the up-down sequential allocation method. They found the MLAC of ropivacaine was 0.111% (95% CI: 0.100-0.122) and that of bupivacaine was 0.067% (95% CI: 0.052-0.082). Ropivacaine was significantly less potent than bupivacaine. The potency ratio was 0.6 (95% CI: 0.49-0.74) (Polley et al 1999). Similar potency ratio was also defined by Capogna et al (Capogna et al 1999).

Benhamou et al and Polley et al studied the relative potencies of levobupivacaine and ropivacaine for epidural analgesia in labour using the up-down sequential allocation method. Both studies found that the MLAC of levobupivacaine was less than that of ropivacaine. Nevertheless, the difference in MLAC was not statistically significant (Polley et al 2003, Benhamou et al 2003).

These studies suggest that in epidural analgesia for labour pain, bupivacaine is more potent than ropivacaine. Potency is similar between levobupivacaine and bupivacaine. Levobupivacaine may have similar or slightly higher potency in compared with ropivacaine.

THE USE OF LEVOBUPIVACAINE AND ROPIVACAINE IN EPIDURAL ANAESTHESIA FOR SURGERY.

Levobupivacaine and ropivacaine have been used successfully in epidural anaesthesia for surgery. Brown et al had compared the use of 20ml of 0.5% ropivacaine and 0.5% bupivacaine for epidural anaesthesia in lower limb surgery. They concluded that the sensory and motor blocking characteristics were similar between the two drugs (Brown et al 1990). Katz et al compared the use of 20ml of 0.75% ropivacaine and 0.5% bupivacaine in epidural anaesthesia for lower limb surgery. There were no significant differences in the clinical properties of the two studied solutions (Katz et al 1990). Tuttle et al compared the use of 20ml of 0.75% ropivacaine and 0.75% bupivacaine in epidural anaesthesia for gynaecologic surgery. Both studied solutions would provide adequate surgical anaesthesia. 0.75% ropivacaine had a shorter duration of sensory and motor block (Tuttle et al 1995). McGlade et al compared the use of 20ml of 0.5% bupivacaine and 0.5% ropivacaine in epidural anaesthesia for lower limb surgery. There were no differences in clinical characteristics between the two drugs (McGlade et al 1997). These studies suggested that ropivacaine in 0.75% or 0.5% would provide effective anaesthesia, which was similar to bupivacaine, for surgery in epidural injection.

Kopacz et al compared the use of 20ml of 0.75% levobupivacaine and 0.75% bupivacaine in epidural anaesthesia for lower abdominal surgery. Both agents were effective and there were no significant clinical differences between them (Kopacz et al 2000).

Comparative study has been done for ropivacaine and levobupivacaine. Peduto et al compared the use of 15ml of 0.5% levobupivacaine and 0.75% ropivacaine in epidural anaesthesia for lower limb surgery. They concluded that the clinical profile were the same for these two studied solutions (Peduto et al 2003).

These studies suggested that the clinical profiles of 0.5% or 0.75% levobupivacaine, ropivacaine and bupivacaine were similar and they were effective agents for epidural anaesthesia. This was in contrast to the potency studies done in epidural analgesia for labour pain which suggested that ropivacaine has a lower potency (Capogna et al 1999, Polley et al 1999). These apparently conflicting results may be accounted for by the differences in patients' population, end point of the results between analgesia and surgical anaesthesia, and the doses of local anaesthetic agents used.

THE USE OF LEVOBUPIVACAINE AND ROPIVACAINE IN INTRATHECAL INJECTION FOR LABOUR ANALGESIA

As the site of application of local anaesthetic is different between epidural and intrathecal injection, the results from epidural injection may not be extrapolated directly to intrathecal injection in spinal analgesia and anaesthesia.

The potencies of levobupivacaine, ropivacaine and bupivacaine have been compared in intrathecal injection for labour analgesia. Sia et al performed a random dose allocation dose-response study of levobupivacaine and ropivacaine with five doses studied, namely 1, 1.5, 2, 2.5 or 3mg. They found that levobupivacaine was more potent than ropivacaine with calculated values for ED50 of 1.07 and 1.4mg, respectively (Sia et al 2005). Using up-down sequential allocation method, Camorcia et al determined ED50 values for ropivacaine, levobupivacaine and bupivacaine as 3.64, 2.94 and 2.37mg respectively. The relative analgesic potency ratios were 0.65 for ropivacaine/bupivacaine, 0.80 for ropivacaine/levobupivacaine and 0.81 for levobupivacaine/bupivacaine. Their results suggested a potency hierarchy of bupivacaine>levobupivacaine>ropivacaine (Camorcia et al 2005). Van de Velde et al determined the full dose-response relationship of these three local anaesthetics when they were given with sufentanil 1.5mcg. The doses of the study drug given were 1.0, 1.5, 2.0, 2.5, 3.0, or 3.5mg respectively. The ED95 values defined were 3.3, 5.0 and 4.8mg for bupivacaine, levobupivacaine and ropivacaine respectively (Van de Velde et al 2007). Their results suggested a potency hierarchy of bupivacaine>levobupivacaine=ropivacaine, although of note,

the ED95 values for levobupivacaine and ropivacaine were larger than the maximum doses actually given (3.5mg) and were estimated by extrapolation. Furthermore, the co-administration of sufentanil might have had an effect on the potency hierarchy among these three local anaesthetics and hence, the result might not be identical to when the local anaesthetics were administered alone.

The conflicting results in these studies on the potency hierarchy among these three local anaesthetics might be due to different inclusion criteria of subjects, study methodology and co-administration of other analgesic drugs.

The use of levobupivacaine and ropivacaine in spinal anaesthesia for general surgery (Studies before 2002, the time that this thesis was planned)

The use of ropivacaine in spinal anaesthesia for general surgery was first reported in 1994. Early reports on the effectiveness of its use in spinal anaesthesia were disappointing. Van kleef et al reported the use of 3 ml of 0.5% ropivacaine and 0.75% ropivacaine in spinal anaesthesia for lower limb surgery; they found that there was a wide variable spread in the level of sensory block. The median (range) of the upper level of analgesia were T11 (L4–T5) and T10-11 (L4–T4) with 0.5% and 0.75% ropivacaine respectively (Van kleef et al 1994). Wahedi et al found that there was a failure rate of 20% for surgery in using 3 ml of 0.5% ropivacaine for spinal anaesthesia (Wahedi et al 1996). Malinovsky et al found that ropivacaine 15mg was less potent than bupivacaine 10mg in spinal anaesthesia for urological surgery and supplementary analgesia was required in 16% of the patients (Malinovsky et al 2000). Nevertheless, the use of ropivacaine in spinal anaesthesia was successful in some other studies. Gautier et al reported that the clinical effects of ropivacaine 12 mg were similar to bupivacaine 8 mg in spinal anaesthesia for lower limb surgery (Gautier et al 1999). McNamee et al found that ropivacaine in doses of 18.75mg and 25mg for spinal anaesthesia in total hip arthroplasty were effective (McNamee et al 2001). McNamee et al compared the use of ropivacaine 17.5mg and bupivacaine 17.5mg in spinal anaesthesia for total hip arthroplasty. It was found that the anaesthesia was adequate in both groups with more rapid recovery of sensory and motor function in the ropivacaine group (McNamee et al 2002). Among the

results of the above studies, there are controversies in the use of ropivacaine in terms of the effectiveness and consistency in the spread of sensory block, the optimal dose and equivalent dose between ropivacaine and bupivacaine.

The early reports on the efficacy on the use of levobupivacaine in spinal anaesthesia were conflicting. Burke et al conducted an open, non-comparative study of 0.5% levobupivacaine 3ml in spinal anaesthesia for lower limb surgery in twenty patients. The quality of anaesthesia was adequate in only 90% (18/20) of cases. They concluded that the spread of the 0.5% levobupivacaine solution was unpredictable (Burke et al 1999). Glaser et al performed a prospective, randomized, double-blind study comparing 3.5 ml of 0.5% levobupivacaine and 3.5 ml of 0.5% bupivacaine for spinal anaesthesia for elective hip replacement. Both drugs were effective and their clinical effects, including sensory and motor block, were similar (Glaser et al 2002).

CHAPTER III

RESEARCH PLAN

Five clinical studies were planned. As levobupivaine and ropivacaine are only available commercially in plain solution, I used plain solution for the three local anaesthetics, bupivacaine, levobupivacaine and ropivacaine in all my studies.. I first conducted a study to compare the use of levobupivacaine and bupivacaine in spinal anaesthesia for urological surgery. The study investigated the clinical efficacy, and characteristics of sensory and motor block in using 2.6 ml of 0.5% levobupivacaine and 0.5% bupivacaine in spinal anaesthesia for urological surgery requiring sensory block up to at least the tenth thoracic (T10) dermatome.

Fentanyl is a lipophilic opioid which has been commonly used as an adjunct to bupivacaine for enhancement of analgesia without intensifying motor and sympathetic block during spinal anaesthesia (Ben-David et al 1997, Ben-David et al 2000). The addition of fentanyl to levobupivacaine may form a mixture for spinal anaesthesia with minimal motor block and hypotension. I planned my second study to compare the clinical efficacy, motor block and haemodynamic effects of using 2.3ml of 0.5% levobupivacaine with fentanyl 15mcg (0.3ml) and 2.6ml of 0.5% levobupivacaine alone in spinal anaesthesia for urological surgery.

My third study compared the use of ropivacaine 10mg and bupivacaine 10mg, both with fentanyl 15mcg for spinal anaesthesia for urological surgery. I compared their efficacy and characteristics of sensory and motor block during the onset and recovery of the spinal block.

In the fourth study, I planned to use traditional dose-response methodology in defining the dose-response relationship of ropivacaine for spinal anaesthesia in lower limb surgery, which required the upper level of sensory block up to T12 dermatome. The ED50 and ED95 of ropivacaine in intrathecal injection were defined.

In the fifth study, I planned to compare the relative potencies between levobupivacaine, ropivacaine and bupivacaine in spinal anaesthesia. The up-down sequential allocation method and the technique of Dixon and Massey were used to define the ED50 of these three local anaesthetics in spinal anaesthesia for lower limb surgery (Dixon and Massey 1983).

PART 2:

METHODOLOGY

CHAPTER IV METHODS

CHAPTER IV

METHODS

RESEARCH METHOD

I. Ethical consent

All studies were approved by the Ethics Committee of Kwong Wah Hospital or Kowloon West Cluster, Hospital Authority, Hong Kong. All patients gave written informed consent before the study.

II. Patient selection and Anaesthesia

Adult patients of ASA physical status I-III were studied. ASA I denotes 'a normal healthy individual'. ASA II denotes 'a patient with mild systemic disease'. ASA III denotes 'a patient with severe systemic disease that is not incapacitating'. Patients, who were scheduled to have lower limb or urological surgery under spinal or combined spinal-epidural anaesthesia, were eligible for recruitment. Patients were excluded if they had known hypersensitivity to any of the studied drugs, any contraindication to spinal or epidural anaesthesia, or unable to understand English or Chinese. In the comparative studies between levobupivacaine and bupivacaine as well as that between levobupivacaine alone and levobupivacaine with fentanyl, additional inclusion criteria were age 50-75, body weight 45-80 Kg. In the dose-response study for ropivacaine, other inclusion criteria were, body weight 45-85 Kg and height ≥150 cm. In the

study for median effective dose of bupivacaine, levobupivacaine and ropivacaine, other inclusion criteria were body weight 40-90 Kg, height ≥145 cm.

All the patients had an intravenous catheter of size 18G or 16G placed before the intrathecal injection. Intravenous fluid preload of normal saline or Hartmann's solution at a volume of 500 ml or 10 ml kg^{-1} was given. In the comparative studies between levobupivacaine and bupivacaine, and that between levobupivacaine alone and levobupivacaine with fentanyl, the intrathecal injections were given with 25-gauge Quincke needles using the single shot spinal anaesthesia technique under aseptic condition at the L3–L4 interspace while the patients were put in a lateral position. In other studies, a combined spinal-epidural technique with a combined kit (BD Durasafe Plus, Becton Dickension Medical Device Company, Suzhan, China or Franklin Lakes, NJ, USA) was used. Under aseptic condition, the epidural space at the L3-4 or L2-3 interspace was identified with a 17-gauge Tuohy needle using loss of resistance to air technique. A 25-gauge Whitacre spinal needle was then passed through the epidural needle and after confirming free flow of cerebrospinal fluid, the study solution was injected intrathecally. All the study solutions were prepared by an anaesthesiologist who was not involved in the assessment of the respective patient. All patients were monitored with compliance to the minimum standards set by the Hong Kong College of Anaesthesiologists. The monitoring included

electrocardiography, pulse oximetry, non-invasive blood pressure (Datex AS3 physiological monitor, Datex Instrumentarium Corp, Helsinki, Finland). Sensory block was recorded by assessing the loss of cold sensation to ethyl chloride spray according to a standard dermatome chart (Figure 3). It was assessed bilaterally. Motor block were assessed using modified Bromage scale (0 = no paralysis, able to flex hip, knee, and ankle; 1 = able to flex knee, unable to raise extended leg; 2 = able to flex ankle, unable to flex knee; 3 = unable to flex ankle, knee and hip) (Bromage 1965). It was assessed bilaterally in urological cases and on the non-operative side in cases for lower limb surgery.

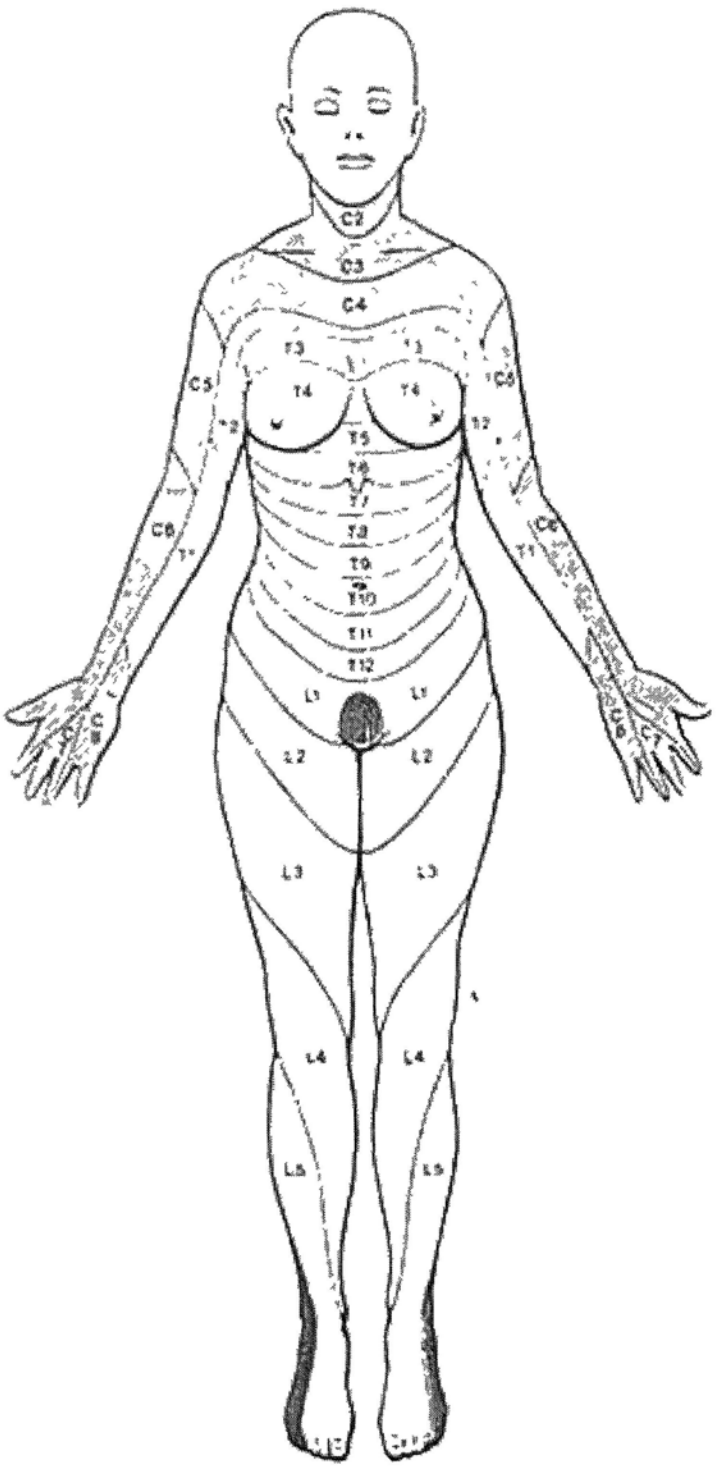


Figure 3. Dermatome chart

Baseline blood pressure was taken as the first recording in the operating theatre before any intervention. Hypotension was defined as a decrease in systolic blood pressure (BP) of more than 30% from baseline or less than 100 mmHg. This was treated with IV boluses of ephedrine or phenylephrine and further boluses of intravenous fluid as required. Bradycardia, defined as heart rate (HR) < 50 bpm, was treated with IV atropine 0.3-0.6mg. The incidence of adverse effects, such as nausea, vomiting and shivering, were recorded. For patients who had received a combined spinal-epidural injection, a follow-up visit was done on the day after the surgery and they were assessed for complete recovery of sensory and motor function as well as the occurrence of post-dural puncture headache.

All studies were randomized according to computer-generated random numbers using the sealed envelope technique. The random number was generated by 'random number generator' in www.random.org. All studies were double-blind with the observers, the surgeons and the study subjects blinded to the intrathecal drug given. The randomization codes and envelopes were prepared by a registered nurse who was not involved in the preparation of the study solutions or assessment of the patients. The codes were revealed only after the completion of the respective studies. Other specific details are stated in the method section of the individual studies.

III. Statistical Methods

The specific statistical methods used in this thesis were stated in the 'methods' section in each study. Parametric and non-parametric tests were used as appropriate to the type of the data. Parametric tests used were Student's t-test and analysis of variance. Non-parametric tests used were Fisher's exact test, the Chi-squared test and the Mann-Whitney U-test.

Probit analysis was used in defining the dose-response relationship for spinal ropivacaine. This is a specialized regression model for binomial response variables. The binary response (success/failure) of different cohorts of patients under different doses was measured. The dose-response relationship curve is sigmoid in nature thus it is impossible to generate a regression graph. Probit analysis acts as a transformation from sigmoid to linear relationship. The proportion of the successful response at each dose was transformed into a 'working probit value' so that the relationship between the 'working probit value' and the log (dose) became linear. Hence, a linear regression graph could be generated with the measured responses and the doses studied. The dose-response relationship was defined with the log(dose) vs. working-probit linear regression plot. Hence, ED50 and ED95 were calculated (Tallarida 2000).

The up-down sequential allocation method as described by Dixon and Massey was used to determine the ED50 of the local anaesthetics. It

is a simple, efficient study methodology which allows the ED50 to be estimated with a smaller sample size as all the data points are clustered near the ED50 in comparison to the traditional dose-response study which has the data points scattered along the entire dose-response curve (Dixon and Massey 1983). I defined the ED50 of bupivacaine, levobupivacaine and ropivacaine for spinal anaesthesia and derived the relative potency ratios among them at ED50.

PART 3:

LEVOBUPIVACAINE

CHAPTER V

LEVOBUPIVACAINE VERSUS RACEMIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

INTRODUCTION

Due to its long duration of action, racemic bupivacaine is one of the commonest local anaesthetics 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 (Albright 1979, Reiz and Nath 1986). Levobupivacaine is the S(-) enantiomer of racemic bupivacaine. The cardiotoxicity of levobupivacaine is less than that of racemic bupivacaine, due to the lower affinity of the S(-) enantiomer than the R(+) enantiomer for the inactivated state of the cardiac sodium channel (Valenzuela et al 1995). In view of this potential decrease in cardiotoxicity, levobupivacaine appears to be an attractive alternative to racemic bupivacaine. Clinical studies comparing levobupivacaine and racemic bupivacaine in epidural and infiltration anaesthesia show that both are equally effective (Cox et al 1998b, Lyons et al 1998, Bader et al 1999, Bay-Nielsen et al1999, Kopacz et al 2000). At the time of designing this study there were only four published trials of intrathecal administration of levobupivacaine. The results on clinical efficacy and motor block were not consistent (Burke et al 1999, Vercauteren et al 2001, Glaser et al 2002, Alley et

al 2002). The first publication was a non-comparative study using 0.5% levobupivacaine for lower limb surgery (Burke et al 1999). The second was a randomized controlled trial of 0.5% levobupivacaine versus racemic bupivacaine for spinal anaesthesia in hip replacement surgery (Glaser et al 2002). The other two studies compared hyperbaric 0.25% levobupivacaine and 0.125% levobupivacaine with racemic bupivacaine (Vercauteren et al 2001, Alley et al 2002). No study had investigated 0.5% levobupivacaine for spinal anaesthesia for lower abdominal or urological surgery. Therefore I performed this clinical trial to investigate the clinical efficacy and motor block of 0.5% levobupivacaine and 0.5% racemic bupivacaine in spinal anaesthesia for urological surgery requiring sensory block to at least T10 dermatome.

MATERIALS AND METHODS

This prospective, randomized, double-blind trial was approved by the Ethics Committee, Kwong Wah Hospital. Fifty patients scheduled for elective transurethral resection of the prostate (TURP) and/or bladder tumour (TURBT) were recruited after giving written informed consent.

The inclusion criteria were (i) age 50 to 75 years, (ii) ASA physical status I-III, and (iii) body weight 45-80Kg. The exclusion criteria were (i) known hypersensitivity to amide local anaesthetic, (ii) contraindication to spinal anaesthesia, and (iii) lack of understanding of English or Chinese.

The patients were randomly assigned into one of two groups, receiving 2.6ml plain solution of either 0.5% levobupivacaine (Antigen Pharmaceutical Limited, Tipperary, Ireland for Abbott Laboratories) or 0.5% racemic bupivacaine (Marcain 0.5%, AstraZeneca Pty Ltd, North Ryde, Australia) intrathecally, according to a computer-generated randomization table. Diazepam 5mg was given orally at least two hours before surgery as premedication and an IV infusion of Hartmann's solution 10ml Kg^{-1} given over 10 -20 min immediately before spinal anaesthesia. The insertion of the spinal needle was performed under aseptic conditions with the patient in left lateral position. A 25 gauge Quincke needle was used at L3-L4 interspace with a midline or paramedian approach. The study solutions were injected intrathecally with the orifice of the needle oriented towards the right side of the patients. Barbotage technique was not used and the intrathecal injection was done in approximately 20 s. The

patients were turned supine and placed in horizontal position immediately after injection of the spinal drug and were given supplementary nasal oxygen 2 L min^{-1}.

Parameters monitored included (i) continuous electrocardiogram, heart rate and pulse oximetry; (ii) non-invasive blood pressure before the conduct of spinal anaesthesia, then every 2.5 minutes for 15 minutes and every 5 minutes thereafter; (iii) sensory block, which was monitored using loss of sensation to cold spray (ethyl chloride) every 2.5 minutes for 15 minutes after the initiation of spinal anaesthesia and at the end of operation; (iv) motor block, assessed according to a modified Bromage scale (0=no paralysis, able to flex hip, knee, and ankle; 1=able to flex knee, unable to raise extended leg; 2=able to flex ankle, unable to flex knee; 3=unable to flex ankle, knee and hip) every 2.5 minutes for 15 minutes and at the end of the operation (Bromage 1965).

The operation was started 15 minutes after the initiation of spinal anaesthesia if the level of sensory block had reached T10 dermatome or above. If the level of analgesia was inadequate, general anaesthesia was to be given.

Baseline blood pressure was the first reading taken in the oprating theatre before any intervention. Hypotension was defined as a systolic blood pressure less than 100mmHg or a decrease of more than 30% from baseline and was treated with incremental doses of ephedrine 5mg IV and/or intravenous Hartmann's solution. Bradycardia was defined as a heart rate <50 beats per minute and was treated with atropine 0.3-0.6mg IV.

The onset of adequate sensory block was defined as the time interval from completion of the spinal drug injection to the achievement of a sensory block at

T10. The incidence of motor block at the start and end of the operation and the addition of any sedative drug were recorded. At the end of surgery, the patient's satisfaction was assessed as good, fair or poor. The adequacy of anaesthesia was assessed as good, fair or inadequate by the attending anaesthesiologist.

The sample size was calculated to provide 80% power to detect a 25% reduction in the incidence of complete motor block in the levobupivacaine group compared with the bupivacaine group. The estimated incidence of complete motor block in bupivacaine group was 100%. Statistical analyses were performed using Student's t-test (for parametric data) and Chi-squared or Fisher's exact tests (for frequency data such as incidence). A significance level of 5% was considered statistically significant.

RESULTS

Fifty patients were recruited (levobupivacaine group n=24; bupivacaine group n=26). One patient in the levobupivacaine group was excluded due to technical failure, with no evidence of sensory and motor block at 30 minutes after intrathecal injection. There were no significant differences between the levobupivacaine and bupivacaine groups for demographic data, baseline haemodynamic parameters, ASA classification or type of operation (Table 2, 3). There were no significant differences between the two groups in the quality of sensory and motor block or in haemodynamic changes (Table 4, 5, Figure 4, 5).

Side-effects of anaesthesia were infrequent and minor. The incidence of hypotension was 4% (2/49) with both cases in the bupivacaine group. Three patients (levobupivacaine group n=2 and bupivacaine group n=1) experienced shivering. One patient in the bupivacaine group had nausea and vomiting.

The efficacy of both levobupivacaine and bupivacaine was good. Anaesthesia was adequate and patient satisfaction good in all cases. Two patients in the bupivacaine group and one patient in the levobupivacaine group required sedation with midazolam 1mg IV in the intraoperative period.

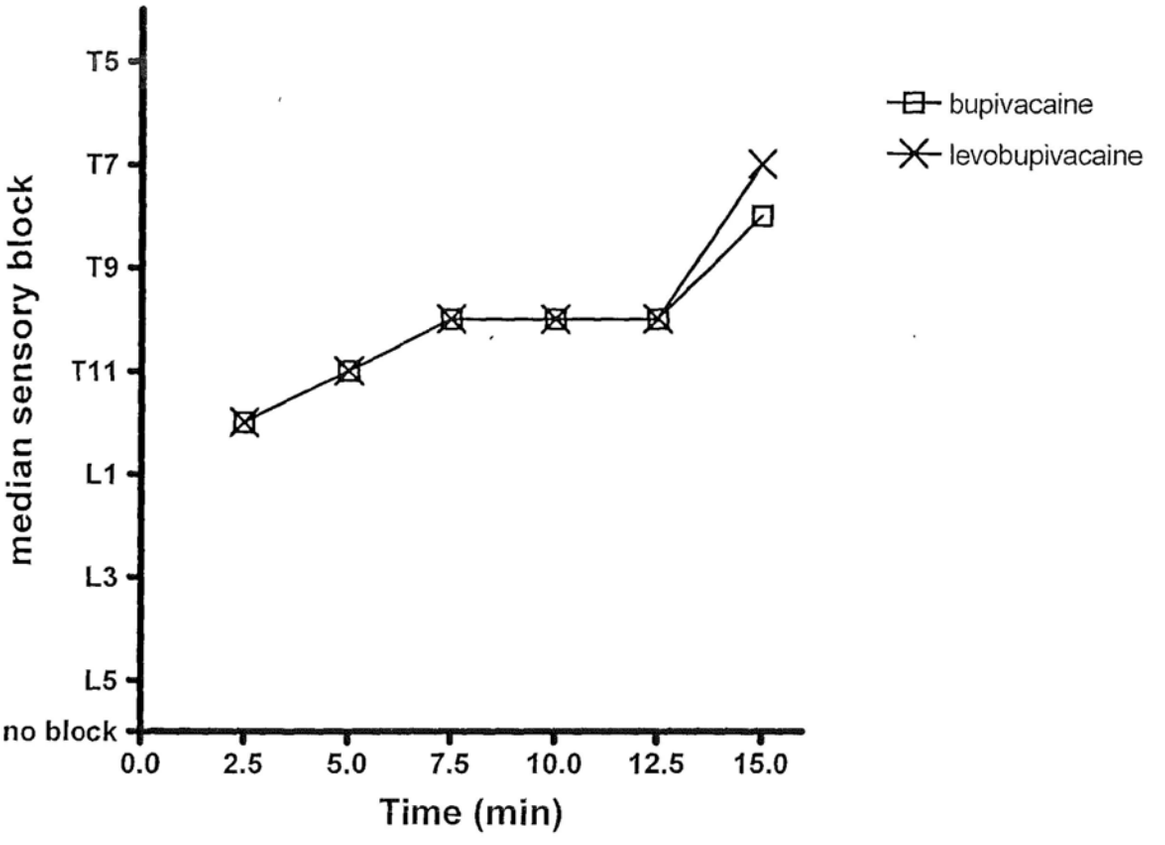


FIGURE 4 PROGRESSION OF UPPER DERMATOMAL LEVEL OF SENSORY BLOCK [Median] OVER TIME.

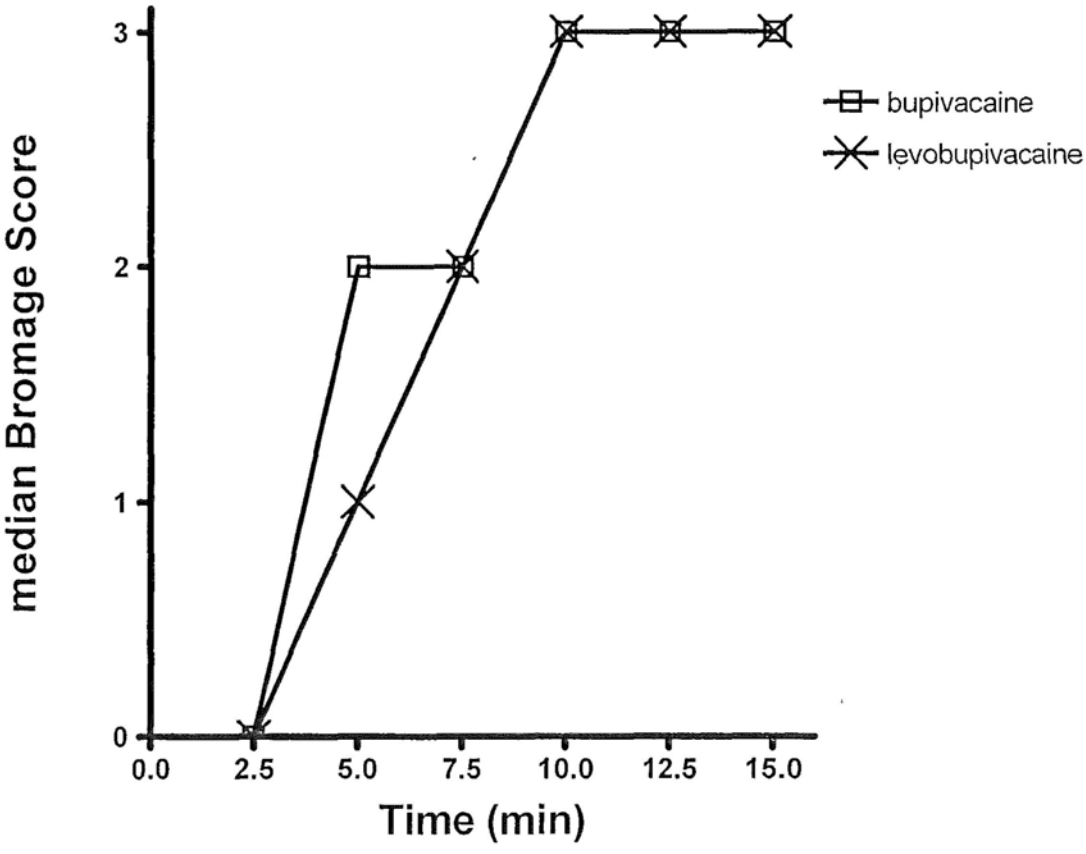


FIGURE 5 PROGRESSION OF MOTOR BLOCK [MEDIAN] OVER TIME.

TABLE 2. DEMOGRAPHIC DATA AND BASELINE HAEMODYNAMIC PARAMETERS.

	Bupivacaine Group	Levobupivacaine Group
Number of patients	26	23
Age (yrs)	68 ± 5	67 ± 5
Body weight (kg)	58 ± 8	61 ± 9
Body height (cm)	165 ± 6	164 ± 5
Baseline systolic blood pressure (mmHg)	140 ± 24	153 ± 25
Baseline heart rate (bpm)	72 ± 12	72 ± 13

Data are mean ± SD. No significant differences between groups.

TABLE 3 ASA CLASSIFICATION AND TYPE OF OPERATION

	Bupivacaine Group	Levobupivacaine Group
ASA I	8 (31%)	7 (30%)
ASA II and III	18 (69%)	16 (70%)
TURP	22 (85%)	17 (74%)
TURBT	4 (15%)	6 (24%)

Data are number of patients (percentage). No significant differences between groups.

TABLE 4 COMPARISON OF SENSORY BLOCK AND MOTOR BLOCK

	Bupivacaine Group	Levobupivacaine Group
Time to achieve sensory block of T10 (min)	8 ± 4	10 ± 6
Highest level of sensory block	T8 (T3 – T10)	T7 (T3 – T10)
Motor block less than Bromage 3 at the start of operation	2 (8%)	5 (22%)
Motor block of Bromage 3 at the start of operation	24 (92%)	18 (78%)
Motor block less than Bromage 3 at the end of operation	1 (4%)	2 (9%)
Motor block of Bromage 3 at the end of operation	25 (96%)	21 (91%)

Time to achieve sensory block of T10 expressed in mean ± SD, highest level of sensory block expressed in median (range), and motor block expressed in number of patients (percentage). No significant differences between groups.

TABLE 5. COMPARISON OF HAEMODYNAMIC EFFECTS

	Bupivacaine Group	Levobupivacaine Group
Systolic blood pressure at 5 min (mmHg)	140 ± 25	148 ± 22
Systolic blood pressure at 10 min (mmHg)	135 ± 24	140 ± 21
Lowest systolic blood pressure (mmHg)	119 ± 21	124 ± 16
Heart rate at 5 min (bpm)	73 ± 15	75 ± 17
Heart rate at 10 min (bpm)	71 ± 13	74 ± 15

Data are mean ± SD. No significant differences between groups.

Discussion

This study found that 2.6 ml of 0.5% levobupivacaine was an effective local anaesthetic for spinal anaesthesia for urological surgery that required a sensory block to the T10 dermatome. The onset time, degree of sensory and motor block and haemodynamic changes were similar to those for 0.5% racemic bupivacaine.

The use of levobupivacaine for other routes of administration, including epidural anaesthesia and nerve plexus blocks, indicates that the anaesthetic potency of levobupivacaine is similar to racemic bupivacaine (Cox et al 1998a, Cox et al 1998b, Lyons et al 1998, Bader et al 1999, Bay-Nielsen et al 1999, Kopacz et al 2000). Lyons et al reported that the potency ratio of levobupivacaine to racemic bupivacaine was 0.98 for epidural analgesia in labour pain (Lyons et al 1998). Levobupivacaine administered via these routes has the advantage of less cardiotoxicity should accidental intravascular injection occur. Since the dose of bupivacaine used in spinal anaesthesia 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 anaesthesia. Furthermore, if levobupivacaine completely replaces racemic bupivacaine for other routes of administration, demand for racemic bupivacaine may drop, such that it may cease to be manufactured for economic reasons.

There are only a few studies involving intrathecal levobupivacaine. Burke et al conducted an open, non-comparative study of 0.5% levobupivacaine 3ml for

spinal anaesthesia for lower limb surgery in twenty patients (Burke et al 1999). The quality of anaesthesia was adequate in only 90% (18/20) of cases. They concluded that the spread of the 0.5% levobupivacaine solution was unpredictable. It was suggested that the variable sensory block might have been due to the hypobaric property of 0.5% levobupivacaine at 37°C (McLeod and Burke 2001). Glaser et al performed a prospective, randomized, double-blind study comparing 0.5% levobupivacaine and racemic bupivacaine 3.5ml for spinal anaesthesia for elective hip replacement (Glaser et al 2002). They found similar clinical effects, including sensory and motor block. Vercauteren et al used 2ml of 0.125% levobupivacaine or racemic bupivacaine as the initial subarachnoid injection for combined spinal-epidural analgesia in labour (Vercauteren et al 2001). They found similar clinical effects in these two drugs except that levobupivacaine produced no motor block, compared with 34% of patients in the bupivacaine group having motor block equivalent to Bromage score 1. Clinical studies of epidural levobupivacaine also suggest that motor block with levobupivacaine may be less than that of an equivalent dose of racemic bupivacaine. Cox et al compared epidural 0.5% levobupivacaine or bupivacaine for lower limb surgery (Cox et al 1998b). They found a trend towards less motor block with an equivalent dose of levobupivacaine. Convery et al compared 0.125% levobupivacaine and 0.125% racemic bupivacaine for epidural analgesia during labour and noted a trend towards less motor block with levobupivacaine (Convey et al 1999). If intrathecal levobupivacaine produces dense sensory block with minimal motor block, it could facilitate early ambulation after spinal

anaesthesia in day surgery. Confirmation and determination of optimal doses and concentrations of levobupivacaine requires further study. Alley et al conducted a randomized, double-blind, cross-over study in eighteen healthy volunteers to compare 0.25% hyperbaric levobupivacaine and racemic bupivacaine in doses of 4 to 12mg for spinal anaesthesia (Alley et al 2002). Levobupivacaine and racemic bupivacaine showed equivalent efficacy in terms of sensory and motor block.

Ropivacaine is the S(-) enantiomer of the propyl analogue of bupivacaine and is also less cardiotoxic than racemic bupivacaine. Its lower lipid solubility potentially confers greater differential block of sensory and motor fibres (Whiteside and Wildsmith 2001) but it is less potent than bupivacaine in epidural anaesthesia (Capogna et al 1999). The equipotent ratio with bupivacaine has not been defined for the intrathecal route. McDonald et al reported it was half as potent as bupivacaine as a 0.25% hyperbaric solution (McDonald et al 1999) and Gautier et al found that ropivacaine 12mg was equipotent to bupivacaine 8mg in isobaric solution (Gautier et al 1999). The efficacy of isobaric ropivacaine for spinal anaesthesia for urological and abdominal operations appears disappointing. Intrathecal ropivacaine 15mg was associated with inadequate anaesthesia in 16% of patients having transurethral resection of the bladder tumour or prostate and in 20% of patients undergoing abdominal surgery (Wahedi et al 1996, Malinovsky et al 2000). Whiteside et al found that hyperbaric 0.5% ropivacaine 3ml provided reliable spinal anaesthesia for a shorter duration than did hyperbaric 0.5% bupivacaine 3ml (Whiteside et al 2003). They stressed

that intrathecal ropivacaine needed to be administered as a hyperbaric solution to produce reliable spinal anaesthesia. The presence of greater differential block for sensory and motor fibres in ropivacaine is also controversial. Malinovsky et al found less potent anaesthesia but similar motor block after 0.3% ropivacaine 15mg in comparison with 0.2% bupivacaine 10mg given intrathecally (Malinovsky et al 2000), while McNamee et al found a shorter duration of complete motor block and sensory block from 17.5mg of 0.5% ropivacaine in comparison with the same dose of bupivacaine (McNamee et al 2002). Nevertheless, Ogun et al found that in obstetric patients, intrathecal ropivacaine 15mg had a shorter duration of motor block and a similar duration of sensory block when compared with the same dose of bupivacaine (Ogun et al 2003). It is uncertain whether there is a real difference in the clinical profile of the block or just a difference in potency between the two drugs.

Plain solution of bupivacaine and levobupivacaine at concentration of 0.5% were used in this study. 0.5% plain bupivacaine is very slightly hypobaric. 0.5% plain levobupivacaine has a higher density than 0.5% plain bupivacaine and it is either slightly hypobaric or isobaric as the density of the human CSF varies. Both behave in an isobaric manner after intrathecal injection (Mcleod 2004). Plain levobupivacaine has been licensed for intrathecal use. Hyperbaric solutions of levobupivacaine or ropivacaine are not commercially available.

Most anaesthesiologists have extensive experience with intrathecal bupivacaine, however, the relative intrathecal potency for levobupivacaine, ropivacaine and bupivacaine is not known. The clinical use of levobupivacaine or

ropivacaine as isobaric or hyperbaric solutions to replace racemic bupivacaine for spinal anaesthesia requires further evaluation.

In conclusion, I found 2.6ml of 0.5% levobupivacaine to be effective for spinal anaesthesia in urological surgery requiring sensory block to at least the T10 dermatome. This was consistent with the finding of Glaser et al but differed from that of Burke et al who reported unpredictable spread of intrathecal 0.5% levobupivacaine (Burke et al 1999, Glaser et al 2002). I believe the larger sample size and randomized controlled design of this study and that of Glaser et al better reflect the clinical picture. This study supports that 0.5% levobupivacaine is an effective alternative to racemic bupivacaine in spinal anaesthesia for surgery that requires a sensory block to at least T10 dermatome.

CHAPTER VI

THE USE OF LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

INTRODUCTION

Racemic bupivacaine is one of the most common local anaesthetics used for spinal anaesthesia and levobupivacaine is the S(-) enantiomer of racemic bupivacaine. Clinical studies comparing levobupivacaine and racemic bupivacaine in epidural and spinal analgesia, show that both are equally effective (Cox et al 1998b, Lyons et al 1998, Bader et al 1999, Kopacz et al 2000, Glaser et al 2002, Lee et al 2003). During epidural use, levobupivacaine and racemic bupivacaine have the same analgesic potency, however levobupivacaine is 13% less potent on a percentage weight per volume basis for motor block (Lacassie and Columb 2003). Hence, in the epidural route, levobupivacaine has greater sensory-motor dissociation in blockade than racemic bupivacaine. It is likely that similar sensory-motor dissociation is also present in the intrathecal use of levobupivacaine. Fentanyl is a lipophilic opioid which has been used as an adjunct to local anaesthetics, including racemic bupivacaine, for enhancement of analgesia without intensifying motor and sympathetic block in spinal analgesia (Ben-David et al 1997; Ben-David et al 2000). It is possible that the addition of fentanyl to levobupivacaine may result in a mixture for spinal anaesthesia with minimal motor block and hypotension.

At the time this study was designed, no study had been published on the intrathecal use of 0.5% levobupivacaine with fentanyl. I performed this clinical study to compare the clinical efficacy, motor block, and haemodynamic effects of using 2.3ml of 0.5% levobupivacaine with fentanyl 15mcg (0.3ml) and 2.6ml of 0.5% levobupivacaine alone in spinal anaesthesia for urological surgery requiring sensory block to at least T10 dermatome.

METHODS

This prospective, randomized, double-blind study was approved by the Ethics Committee of Kwong Wah Hospital. After obtaining informed consent, fifty patients who were scheduled for elective transurethral resection of the prostate or bladder tumour were recruited.

The inclusion criteria were age between 50 and 75, ASA physical status I–III, and body weight between 45kg and 80kg. The exclusion criteria were known hypersensitivity to amide local anaesthetics, contraindications against spinal anaesthesia, or lack of understanding of English or Chinese.

The patients were then randomly assigned into two groups for spinal anaesthesia according to computer-generated random numbers inserted into sealed envelopes. Group L received 2.6ml of 0.5% levobupivacaine (Antigen Pharmaceutical Limited, Tipperary, Ireland for Abbott Laboratories) alone and group LF received 2.3ml of 0.5% levobupivacaine with fentanyl 15mcg (0.3ml) (Mayne Pharma Pty Ltd, Melbourne, Australia). Diazepam 5mg was given orally as pre-medication on the morning of the operation and an intravenous infusion of 10 ml kg^{-1} of Hartmann's solution was given before initiation of the spinal anaesthesia. The anaesthesiologist who performed the intrathecal injection and assessment of the spinal block, was blinded to the group of study solution. The study solution was prepared by another anaesthesiologist who was not involved in the clinical care of the patient. Insertion of the spinal needle was undertaken in aseptic conditions using a 25-gauge Quincke needle at the L3-L4 interspace with midline or paramedian approach. The patient was in the left lateral position

when the spinal needle was inserted. The study solutions were injected intrathecally with the orifice of the needle oriented towards the right side of the patients. Barbotage technique was not used and the intrathecal injection was done in approximately 20 s.

Upon completion of the intrathecal injection, the patient was immediately turned back to a supine position. All patients were given supplementary nasal oxygen of 2 l min^{-1}.

During the procedure, electrocardiogram, heart rate, and pulse oximetry were monitored continuously. Noninvasive blood pressure was taken before the conduct of spinal anaesthesia, every 2.5 minutes for 15 minutes after the initiation of spinal anaesthesia and every 5 minutes thereafter. Sensory blockade was monitored using loss of sensation to a cold spray of ethyl chloride, which was performed every 2.5 minutes for 15 minutes after the initiation of spinal anaesthesia and again at the end of the procedure. Motor blockade was assessed according to a modified Bromage scale (0=no paralysis, able to flex hip, knee and ankle; 1=able to flex knee, unable to raise extended leg; 2=able to flex ankle, unable to flex knee; 3=unable to flex ankle, knee and hip).

The operation was started 15 minutes after the initiation of spinal anaesthesia if the level of sensory block reached T10 or above. If the level of sensory block was inadequate, then general anaesthesia was given.

Hypotension was defined as a decrease in the systolic blood pressure of more than 30% from the baseline or less than 100mmHg. This was treated with intravenous infusion of Hartmann's solution or IV boluses of ephedrine 5mg.

Bradycardia was defined as a heart rate of less than 50 beats per minutes and was treated with IV injection of atropine 0.3mg–0.6mg.

The onset of adequate sensory block was defined as the achievement of a sensory block level of T10 dermatome or higher. The addition of any sedative drugs, if required, was recorded. Patient's satisfaction was assessed as good, fair, or poor at the end of the operation. Adequacy of anaesthesia was assessed by the attending anaesthetist as good, fair or bad.

Sample size was calculated to provide 80% power to detect a 25% reduction in the incidence of complete motor block in the LF group compared with the L group. The estimated incidence of complete motor block in levobupivacaine group was 100%. Statistical analyses were performed using student t-test (for parametric data), Mann-Whitney U test (for non-parametric data) and Chi-squared or Fisher's exact tests (for frequency data such as incidence). $P < 0.05\%$ was considered statistically significant.

RESULTS

Twenty-five patients were recruited in each group. There were no significant differences between the two groups for patient characteristic data, ASA classification and type of operation (Table 6). The baseline and intra-operative haemodynamic parameters were found to be similar in both groups (Table 7). The onset time for adequate level of sensory block, the highest level of sensory block and degree of motor block were also similar in both groups (Table 8, Figure 6 & 7).

The efficacy of both levobupivacaine alone and levobupivacaine with fentanyl was good. Anaesthesia was adequate and patient satisfaction was good in all cases. Two patients, one in each group, required supplementary sedation with IV midazolam 1mg and 2mg respectively.

Side-effects of anaesthesia with these two regimes were minor and infrequent. Three patients (12%) in the Group L had shivering. Hypotension occurred in four patients (16%), one in Group L and three in Group LF. No patient had nausea, vomiting or pruritus.

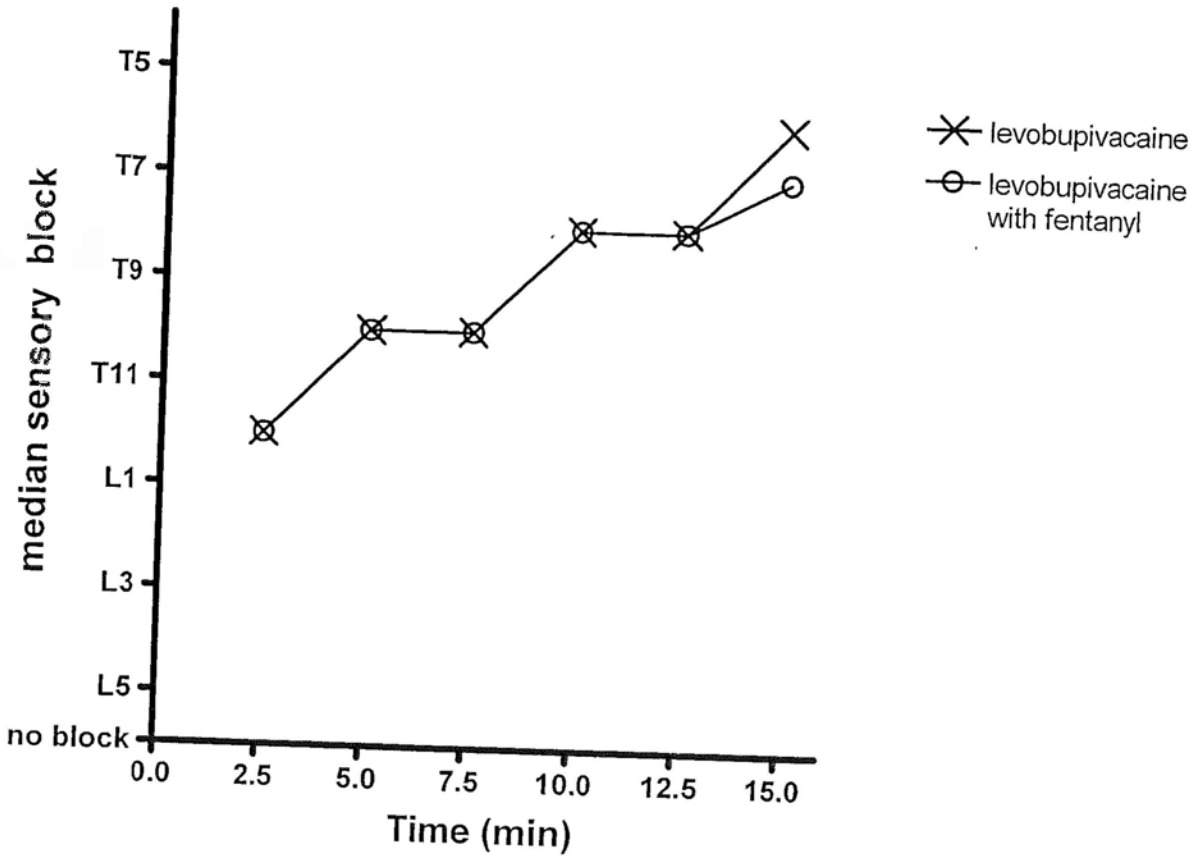


FIGURE 6 PROGRESSION OF UPPER DERMATOMAL LEVEL OF SENSORY BLOCK [Median] OVER TIME.

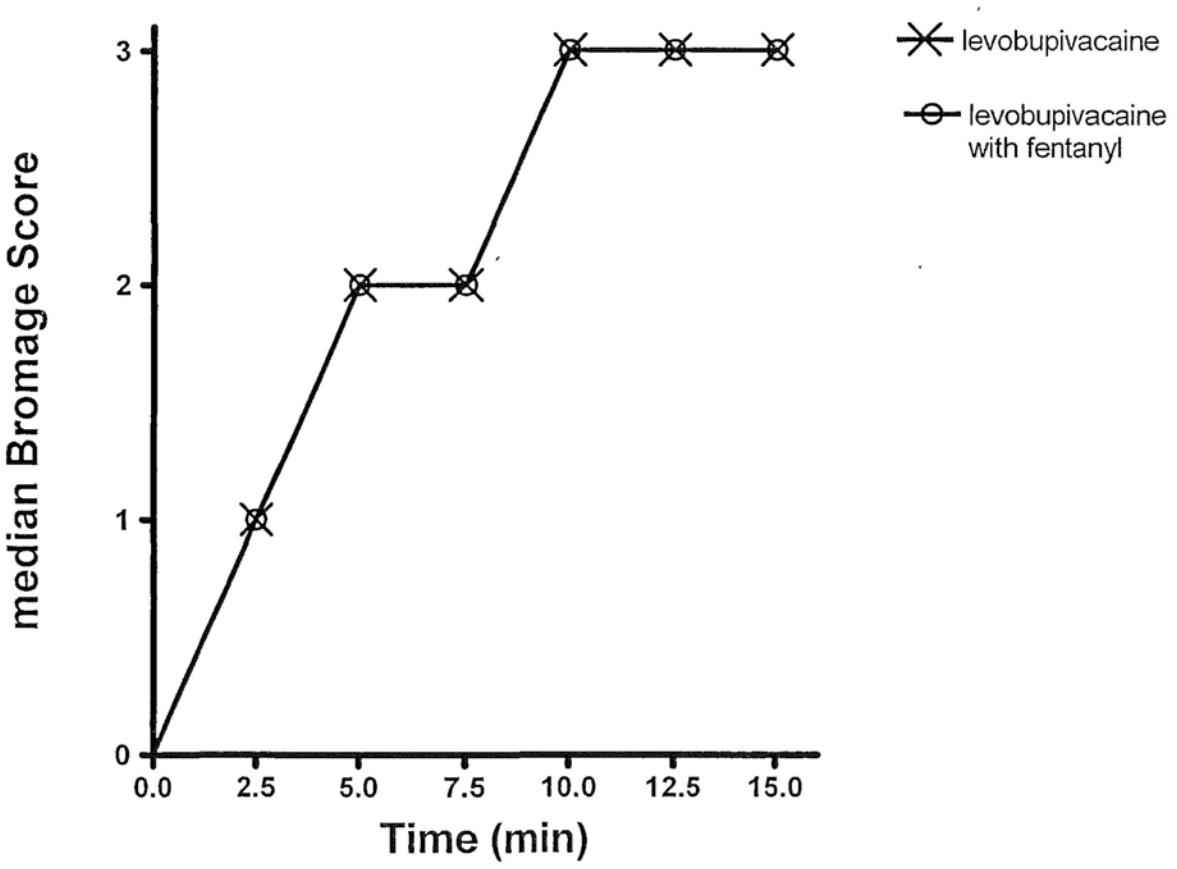


FIGURE 7 PROGRESSION OF MOTOR BLOCK [MEDIAN] OVER TIME.

TABLE 6 PATIENT CHARACTERISTIC DATA

	Levobupivacaine (n = 25)	Levobupivacaine with fentanyl (n = 25)
Age (yrs)	68 ± 6	69 ± 5
Body weight (kg)	62 ± 8	65 ± 9
Body height (cm)	163 ± 6	165 ± 7
ASA (I/II/III)	7/17/1	9/15/1
Type of operation:		
TURP	17	16
TURBT	8	9
Time interval from intrathecal injection to the end of surgery (min)	54 ± 25	61 ± 32

Data are mean ± SD or number of patients. No significant differences between groups.

TABLE 7 HAEMODYNAMIC DATA

	Levobupivacaine	Levobupivacaine with fentanyl
Baseline systolic blood pressure (mmHg)	150 ± 18	149 ± 19
Baseline mean blood pressure (mmHg)	109 ± 13	111 ± 15
Baseline heart rate (bpm)	72 ± 11	73 ± 11
Systolic blood pressure at 5 min (mmHg)	141 ± 23	139 ± 18
Mean blood pressure at 5 min (mmHg)	101 ± 16	101 ± 14
Heart rate at 5 min (bpm)	75 ± 15	75 ± 12
Systolic blood pressure at 10 min (mmHg)	135 ± 20	134 ± 20
Mean blood pressure at 10 min (mmHg)	99 ± 14	99 ± 15
Heart rate at 10 min (bpm)	74 ± 12	74 ± 12
Lowest mean blood pressure (mmHg)	86 ± 14	85 ± 11

Data are mean ± SD. No significant differences between groups.

TABLE 8 COMPARISON OF SENSORY BLOCK AND MOTOR BLOCK

	Levobupivacaine	Levobupivacaine with fentanyl
Time to achieve sensory block of T10 (min)	8 ± 5	7 ± 3
Highest level of sensory block	T6 (T3–T10)	T7 (T4–T10)
Maximum motor block with Bromage score 2	1	4
Maximum motor block with Bromage score 3	24	21
Motor block at the start of operation with Bromage score<3	4	7
Motor block at the start of operation with Bromage score 3	21	18
Motor block at the end of operation with Bromage score< 3	1	4
Motor block at the end of operation with Bromage score 3	24	21

Data are expressed as mean ± SD, median (range) or number of patients. No significant differences between groups.

Discussion

This study found that 2.3 ml of 0.5% levobupivacaine with fentanyl 15mcg was an effective mixture for spinal anaesthesia in urological surgery that required a sensory block to the T10 dermatome. The onset time, level of sensory block, degree of motor block and haemodynamic effects were similar between 2.6ml of 0.5% levobupivacaine alone and 2.3ml of 0.5% levobupivacaine with fentanyl 15mcg.

Levobupivacaine has been found to be as effective as racemic bupivacaine in spinal anaesthesia (Glaser et al 2002, Lee et al 2003). The effect of adding fentanyl to bupivacaine for spinal anaesthesia has been studied. Ben-David et al compared the use of 0.17% bupivacaine 3 ml with and without fentanyl 10mcg in spinal anaesthesia for arthroscopy (Ben-David et al 1997). The sensory blockade was significantly more intense with a lower failure rate in the group with fentanyl. Ben-David et al compared the use of bupivacaine 4 mg with fentanyl 20mcg and bupivacaine 10mg in spinal anaesthesia for surgical repair of hip fracture in geriatric patients (Ben-David et al 2000). Both regimes were effective with less hypotension in the group with fentanyl. It was suggested that the intrathecal use of fentanyl had a synergistic effect with the low-dose bupivacaine in the achievement of a functional sensory blockade for surgical anaesthesia. The use of a low dose of bupivacaine was associated with a less sympathetic blockade resulting in lower incidence of hypotension. Choi et al found that the intrathecal use of hyperbaric bupivacaine 8mg with 10mcg of fentanyl was as effective as hyperbaric bupivacaine 12mg in Caesarean section

(Choi et al 2000). The addition of fentanyl had the advantage of low incidence of excessive high block. Martyr and Clark compared the use of 7.5mg hyperbaric bupivacaine with fentanyl 20mcg and 12.5mg hyperbaric bupivacaine alone (Martyr and Clark 2001). Both groups were equally effective with no differences in the incidence or severity of hypotension. Korhonen et al found that 3 mg of hyperbaric bupivacaine with 10mcg of fentanyl was as effective as 4 mg of hyperbaric bupivacaine for knee arthroscopy (Korhonen et al 2003). The recovery of motor function was faster in the group with fentanyl. These studies confirmed the local anaesthetic dose-sparing effect of fentanyl when it was added to bupivacaine for intrathecal use. This might be associated with less hypotension during spinal anaesthesia.

The use of racemic bupivacaine with fentanyl in spinal anaesthesia for urological surgery is effective. . Kuusniemi et al studied the effect of adding fentanyl 25mcg to bupivacaine for spinal anaesthesia (Kuusniemi et al 2000). They found that the addition of fentanyl 25mcg to 5 mg of bupivacaine resulted in effective anaesthesia with motor block of short duration. The addition of fentanyl 25mcg to 10 mg of bupivacaine increased the intensity and duration of motor block in comparison to bupivacaine 10mg alone. The incidence of pruritus in all patients with fentanyl was 30%. Goel et al studied the addition of fentanyl to bupivacaine 5mg in spinal anaesthesia (Goel et al 2003). It was concluded that the addition of fentanyl 12.5mcg provided better surgical anaesthesia and improved the reliability of block than fentanyl 7.5 or 10mcg. Haemodynamic stability was good in all patients. The incidence of pruritus was 33%. Kararmaz

et al compared the intrathecal injection of bupivacaine 4mg with fentanyl 25mcg (Group F) and bupivacaine 7.5mg (Group B) (Kararmaz et al 2003). The density and duration of motor block were more in Group B. Both groups had adequate sensory block for surgery. Hypotension was more significant in the Group B (25% versus 0%). The incidence of pruritus was 75% in Group F. These studies showed that the addition of fentanyl to bupivacaine for spinal anaesthesia would augment the effect of bupivacaine. This would allow the reduction in the dose of bupivacaine used and would increase the reliability of lower dose of bupivacaine used for spinal anaesthesia. This might result in less intensity of motor block and less hypotension. However, the use of intrathecal fentanyl was associated with significant incidence of pruritus.

The addition of fentanyl to levobupivacaine has been found to have a dose-sparing effect on the requirement of levobupivacaine for epidural analgesia in labour (Robinson et al 2001). Intrathecal use of levobupivacaine has been studied. My previous study with 2.6ml of 0.5% levobupivacaine and that of Glaser et al, both found that 0.5% levobupivacaine and 0.5% bupivacaine have similar clinical effects, including sensory and motor block (Glaser et al 2002, Lee et al 2003). Intrathecal injection of an opioid with levobupivacaine had been studied (Vercauteren et al 2001). 2ml of 0.125% levobupivacaine or racemic bupivacaine with sufentanil 0.75mcg ml^{-1} and epinephrine 1:800,000 were used as the initial intrathecal injection for combined spinal-epidural analgesia in labour. It was found that levobupivacaine produced no motor block in comparison with 34% of patients in the bupivacaine group had motor block of Bromage score 1.

This study found that 2.3ml of 0.5% levobupivacaine with fentanyl 15mcg was as effective as 2.6ml of 0.5% levobupivacaine alone in spinal anaesthesia. The haemodynamic effects, the characteristics of sensory and motor block were similar. Nevertheless, the potential advantages of less motor block and less hypotension were not unveiled in the dose used in this study. This was probably due to the relatively large dose of levobupivacaine used in this study. Extrapolated from the use bupivacaine and fentanyl in spinal anaesthesia, such advantages of less motor block and less hypotension might be unveiled with the use of lower dose of levobupivacaine (Ben-David et al 2000). The potential side-effects of spinal fentanyl such as the pruritus, nausea and vomiting did not occur in the patients of this study.

The potency ratio of levobupivacaine to racemic bupivacaine was 0.98 for epidural analgesia in labour pain (Lyons et al 1998). Their potency ratio in intrathecal use has not been determined. My choice of comparing 2.6ml of levobupivacaine with 2.3 ml of levobupivacaine and fentanyl 15mcg was based on my previous study on the efficacy of 2.6ml of levobupivacaine in spinal anaesthesia for urological surgery and published result in the use of fentanyl with bupivacaine (Goel et al 2003, Lee et al 2003). Further studies can be directed to find the optimal combination of levobupivacaine and opioid with maximal haemodynamic stability and least motor block, which may be useful for spinal anaesthesia in ambulatory surgery.

In conclusion, I found that the haemodynamic effects and the characteristics of sensory and motor blockade were similar between 2.6ml of

0.5% levobupivacaine alone and 2.3ml of 0.5% levobupivacaine with fentanyl 15mcg in spinal anaesthesia for urological surgery requiring sensory block to at least T10 dermatome. Both regimes are effective with minimal side-effects. The addition of fentanyl has a dose-sparing effect with 0.5% levobupivacaine in spinal anaesthesia.

PART 4:

ROPIVACAINE

CHAPTER VII RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

CHAPTER VIII SPINAL ROPIVACAINE FOR LOWER LIMB SURGERY: A DOSE-RESPONSE STUDY

CHAPTER VII

RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

INTRODUCTION

Several recent studies have described the use of ropivacaine for spinal anaesthesia (Gautier et al 1999, Malinovsky et al 2000, Khaw et al 2001, McNamee et al 2001). Because early in-vitro and animal studies have shown that ropivacaine causes less motor block than bupivacaine (Feldman and Covino 1988; Bader et al 1989), ropivacaine may be a potentially useful agent for spinal anaesthesia when a quick recovery of motor function is desirable. However, only limited data from clinical studies are available to support this (Danelli et al 2004, Kallio et al 2004a). Fentanyl is a lipophilic opioid which has been used as an adjunct to local anaesthetics for enhancement of analgesia without intensifying motor block in spinal anaesthesia (Ben-David et al 1997, Ben-David et al 2000). Its use will allow the use of lower dose of local anaesthetics for effective spinal anaesthesia. This will allow any difference in the motor blocking property of different local anaesthetics more likely to be shown. The aim of this randomized, double-blinded study was to compare the use of plain ropivacaine 10 mg with plain bupivacaine 10 mg, both with fentanyl 15 mcg, for spinal anaesthesia for

urological surgery. I hypothesized that both drug mixtures would provide adequate anaesthesia but that motor recovery would be faster after ropivacaine.

METHODS

This was a prospective randomized double-blind study. The study protocol was approved by Ethics Committee of Kowloon West Cluster, Hospital Authority, Hong Kong. Thirty-four ASA physical status I–III patients scheduled for elective transurethral resection of prostate or bladder tumour were recruited after obtaining written informed consent. Patients were excluded if they had a known hypersensitivity to ropivacaine, bupivacaine or fentanyl, any contraindication to spinal anaesthesia, or were not able to understand English or Chinese.

Diazepam 5 mg was given orally as premedication on the morning of operation. On arrival in the operating room, standard monitoring was attached and 10 ml kg^{-1} lactated Ringer's solution was given intravenously. Patients were randomly assigned into one of two groups according to computer–generated random number codes that were placed in sealed envelopes. Patients in the bupivacaine group received 2 ml of plain bupivacaine 5 mg ml^{-1} (Marcain 0.5%, AstraZeneca Pty Ltd, North Ryde, Australia) and fentanyl 15 mcg (0.3 ml) (Mayne Pharma Pty Ltd, Melbourne, Australia) and patients in the ropivacaine group received 2 ml of plain ropivacaine 5 mg ml^{-1} (prepared by mixing 1 ml of Naropin 1%, AstraZeneca Pty Ltd (Sodertalje, Sweden) and 1 ml of Normal Saline) and fentanyl 15 mcg (0.3ml) intrathecally using a combined spinal-epidural technique with a combined kit (BD Durasafe Plus, Becton Dickinson Medical Device Company Ltd, Franklin Lakes, NJ, USA). The study solutions were prepared in identical syringes by an anaesthesiologist who was not involved in subsequent

patient care or assessment.

After turning the patient to the left lateral position, the skin was disinfected and the epidural space at the L3-4 interspace was identified with a 17-gauge Tuohy needle using loss-of-resistance to air. A 25-gauge Whitacre spinal needle was then passed through the epidural needle and after confirming free flow of CSF, the study solution was injected intrathecally with the orifice of the needle orientated towards the right side of the patient. Barbotage technique was not used and the intrathecal injection was done in approximately 20 s.

After removing the spinal needle, an epidural catheter was inserted 3–4 cm into the epidural space and secured with tape. The patient was then turned to the supine position for 15 min after which he or she was placed in the lithotomy position. All patients received oxygen 2 l min^{-1} by nasal cannulae.

After intrathecal injection, sensory block was recorded by assessing loss of cold sensation to ethyl chloride spray, and motor block using a modified Bromage scale (0 = no paralysis, able to flex hip, knee and ankle; 1 = able to flex knee, unable to raise extended leg; 2 = able to flex ankle, unable to flex knee; 3 = unable to flex ankle, knee and hip) (Bromage 1965) every 2.5 minutes for 15 min, at the end of operation and then every 15 min until the end of the study period. Other monitored parameters included continuous electrocardiogram, heart rate, pulse oximetry and non-invasive blood pressure cycled every 5 minutes.

The operation was allowed to start after the level of sensory block had reached the T10 dermatome or above at 15 min. If the sensory block had not reached T10 dermatome by 15 min, the block was supplemented via the epidural

catheter. These cases were considered failures. All patients were kept in lithotomy position during surgery, after which they were returned to the supine position.

Hypotension was defined as a decrease in systolic BP of more than 30% from baseline or less than 100 mmHg. This was treated with IV boluses of ephedrine and further intravenous infusion of lactated Ringer's solution as required. Bradycardia was defined as HR < 50 bpm. This was treated with IV atropine 0.3 – 0.6 mg as required. We recorded the occurrence of side-effects including nausea/vomiting, shivering and respiratory depression (as observed by the anaesthesiologist) and pruritus (as reported by patients). All of these side-effects were managed by the attending anaesthesiologists as clinically indicated. If the patient complained of pain during the operation, the level of sensory block was assessed and supplementation via the epidural catheter was given.

The end of the study period was defined as the time at which the sensory block had regressed to below the T10 dermatome and the Bromage score was 0. The duration of motor block was defined as the time from intrathecal injection to regression of motor block to Bromage score 0. Complete motor block was defined as a Bromage score of 3 and the duration of complete motor block was defined as the time from intrathecal injection to regression of the block to a Bromage score < 3.

At the end of the study period, patients were asked to rate their satisfaction as good, fair or poor. At the same time, the adequacy of anaesthesia was assessed by the attending anaesthesiologist as good, fair or poor. All

patients had a follow up visit on the day after the operation to look for full recovery of sensory and motor function, post-dural puncture headache and transient neurological symptoms.

Power analysis was based on the primary outcome, which was defined as the duration of motor block. Based on data from published studies (Malinovsky et al 2000; Ogun et al 2003), the standard deviation in the duration of motor block for bupivacaine was estimated to be 32 min. We calculated that a sample size of 16 patients per group would have 80% power to detect a 30 min difference in the duration of motor block at the 5% significance level. Data were analyzed using Student's t-test (for demographic data), the Chi-square test and Fisher's exact test (for categorical data), and the Mann-Whitney U-test (for characteristics of sensory and motor block). A value of $P < 0.05$ was considered as statistically significant.

RESULTS

All patients achieved sensory block to the T10 dermatome or higher at 15 min after intrathecal injection. One patient in the ropivacaine group was excluded from analysis because of unexpectedly prolonged surgery that lasted 3.2 h. This patient required epidural supplementation 1.8 hours after the initiation of spinal anaesthesia. Of the remaining patients, there were no differences in patient characteristics and surgical time between the groups (Table 9).

TABLE 9 CHARACTERISTICS OF PATIENTS AND DURATION OF SURGERY

	Ropivacaine group (n = 16)	Bupivacaine group (n = 17)	*P* value
Sex (M/F)	14/2	15/2	NS
Age (yr)	68 ± 8	70 ± 6	NS
Height (cm)	164 ± 7	162 ± 8	NS
Weight (Kg)	64± 10	62 ± 9	NS
ASA (I/II/III)	6/8/2	9/4/4	NS
Duration of operation (min)	40 ± 27	57 ± 28	NS

Data are mean ± SD or number. NS = not significant.

The details of motor block are shown in Table 10 and Figure 8. The primary outcome, the duration of motor block, was shorter (P = 0.003) in the ropivacaine group (median: 126 min; interquartile range: 93-162 min) compared with the bupivacaine group (median: 189 min; interquartile range: 157-234 min; Table 10). The difference between medians was 71 min (95% CI: 28 - 109 min). In addition, the duration of complete motor block was shorter in the ropivacaine group (median: 92 min; interquartile range: 63 – 120 min) compared with the bupivacaine group (median: 164 min; interquartile range: 126–183 min; $P < 0.001$; Table 10). There was no difference in the onset time of motor block (Table 10). One patient in the ropivacaine group had no measurable motor block for the duration of the study. All other patients achieved a modified Bromage score of 3.

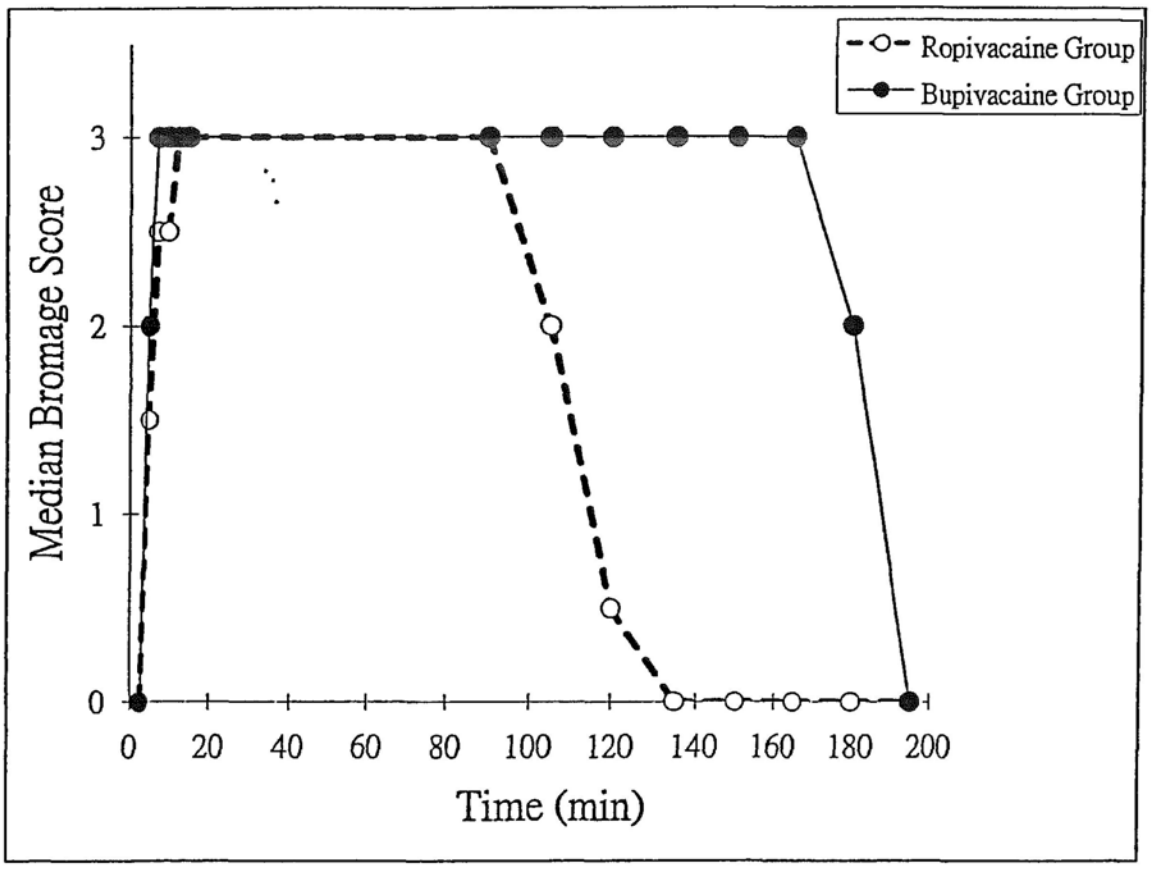


FIGURE 8 PROGRESSION OF MOTOR BLOCK [MEDIAN] OVER TIME.

TABLE 10. ONSET AND DURATION OF MOTOR BLOCK.

	Ropivacaine group	Bupivacaine group	*P* value
Onset time to Bromage score of 1 (min)	5 [2.5 – 9.4]	5 [2.5 – 6.3]	0.61
Duration of motor block (min)	126 [93 - 162]	189 [157 - 234]	0.003
Duration of complete motor block (min)	92 [63 – 120]	164 [126 – 183]	< 0.001

Data are median [interquartile range].

The details of sensory block are shown in Table 11 and Figures 9 and 10. Sensory block to the T10 dermatome or above was achieved and was sufficient for surgery in all patients. There were no differences in the highest level of sensory block, the onset time of sensory block to the T10 dermatome and time from injection to regression of sensory block to below the T10 dermatome.

TABLE 11 DEVELOPMENT AND REGRESSION OF SENSORY BLOCK.

	Ropivacaine group	Bupivacaine group	*P* value
Highest level of sensory block (dermatome)	T5 [T4 - T6]	T5 [T4 - T6]	NS
Onset time of sensory block to T10 (min)	5 [2.5 - 9.4]	5 [5 - 7.5]	NS
Time to regression of sensory block to below T10 (min)	164 [141 - 211]	174 [154 – 209]	NS

Data are median [interquartile range]. NS = not significant.

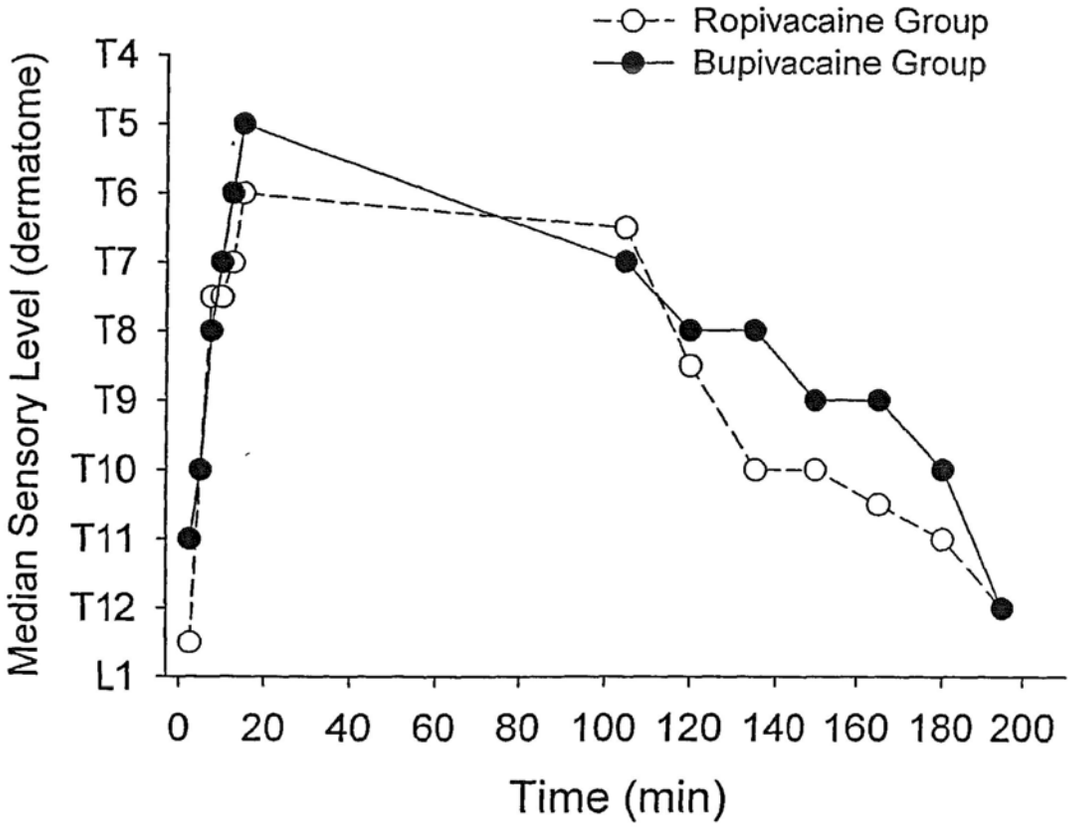


FIGURE 9 PROGRESSION OF UPPER DERMATOMAL LEVEL OF SENSORY BLOCK [MEDIAN] OVER TIME.

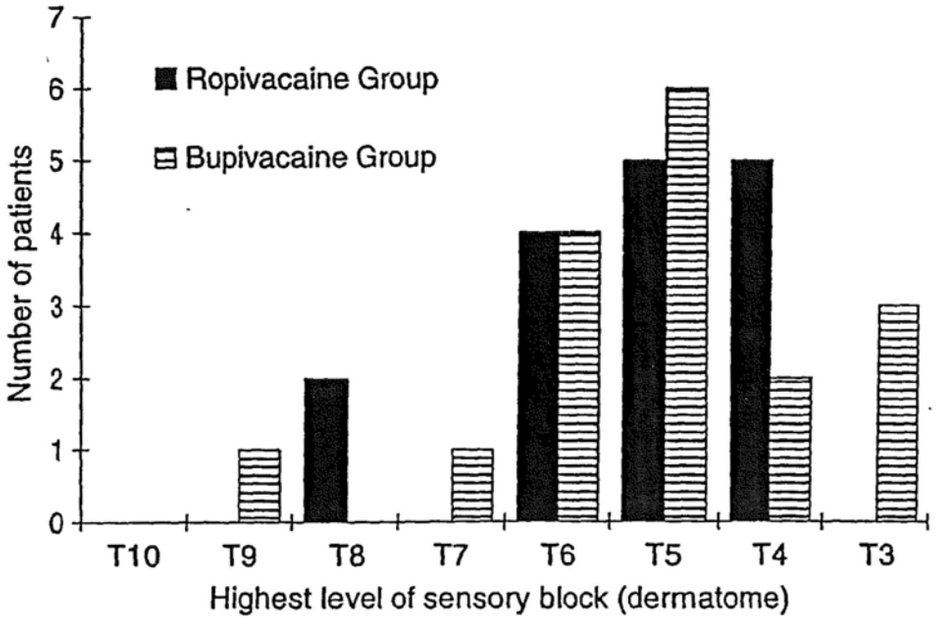


FIGURE 10 HIGHEST LEVEL OF SENSORY BLOCK (DERMATOME). THERE WAS NO SIGNIFICANT DIFFERENCE BETWEEN GROUPS.

Haemodynamic changes were similar between the two groups. There were no significant differences in heart rate or systolic and diastolic blood pressure between the groups in the first 15 min after the initiation of spinal anaesthesia. One patient in the ropivacaine group who had a highest recorded sensory block at the T4 dermatome developed hypotension. No patients in the bupivacaine group had hypotension. Bradycardia did not occur in any patient in either group.

The satisfaction of the patients and the adequacy of anaesthesia were rated as good in all cases in both groups. No patient had pruritus, shivering, respiratory depression or nausea and vomiting. No patient had residual neurological deficit, post-dural puncture headache or transient neurological symptoms at the post-operative follow up.

DISCUSSION

This study showed that plain ropivacaine 10 mg plus fentanyl 15 mcg provided similar sensory anaesthesia but with a shorter duration of motor block, compared with plain bupivacaine 10 mg plus fentanyl 15 mcg when used for spinal anaesthesia in urological surgery. This combination may be useful for lower abdominal and lower limb surgery of limited duration when early mobilization is required, for example in ambulatory surgery.

Rapid recovery after spinal anaesthesia is useful for the facilitation of early mobilization after urological and other surgery of short duration. However, the best drugs and combinations to achieve this are controversial. Previously, hyperbaric lignocaine 50 mg ml^{-1} was a common local anaesthetic used for short surgical procedures. However, its use has declined because of concerns about cauda equina syndrome and transient neurological symptoms (Gaiser 2000). This has aroused interest in alternative local anaesthetics and combinations which can produce spinal anaesthesia of relatively short duration. The potential suitability of ropivacaine in this respect was initially suggested by in vitro and animal studies (Feldman and Covino 1988; Bader et al 1989). Subsequently, a clinical study also showed that spinal ropivacaine was associated with motor block of shorter duration when compared with bupivacaine (Ogun et al 2003). The results of my study are in agreement with these findings.

The shorter duration of motor block with spinal ropivacaine compared with bupivacaine can be explained by two possible mechanisms: a difference in potency and a difference in differential sensory:motor block. Previous in-vitro

studies suggested a small difference in potency between ropivacaine and bupivacaine (Wildsmith et al 1989). Subsequently, clinical trials of both epidural (Capogna et al 1999, Polley et al 1999) and spinal (McDonald et al 1999, Camorcia et al 2005) administration have also shown that ropivacaine appears to be less potent than bupivacaine. In this study, because I used equal doses of ropivacaine and bupivacaine, this may in part account for some of the difference found in the duration of motor block. However, because there were no significant differences in the characteristics of sensory block, this suggests that potency alone does not account for my findings. Although this study was not powered to detect differences in sensory block and therefore the possibility of a type II error exists, nonetheless my findings may be partly explained by a difference in differential sensory:motor block. The latter was suggested by early in-vitro and animal studies (Feldman and Covino 1988, Bader et al 1989) and has been confirmed by some clinical comparisons of spinal ropivacaine and bupivacaine that have accounted for differences in potency by comparing relatively larger doses of ropivacaine (Danelli et al 2004, Kallio et al 2004a). For example, Kallio et al reported that based on duration per milligram dose, the duration of motor block of ropivacaine was half that of bupivacaine, whereas the duration of sensory block was two thirds (Kallio et al 2004a).

A wide range of doses of ropivacaine for spinal anaesthesia have been described. For example, doses from 17.5 mg to 25 mg have been reported to be effective for spinal anaesthesia in lower limb surgery (McNamee et al 2001, McNamee et al 2002). Conversely, Wahedi et al obtained a failure rate of 20%

with intrathecal injection of plain ropivacaine 15 mg in abdominal surgery (Wahedi et al 1996) and Malinovsky et al found that plain ropivacaine 15 mg was associated with inadequate spinal anaesthesia in 16% urological surgery patients (Malinovsky et al 2000). In view of this, the addition of fentanyl to ropivacaine was planned in this study. It was well documented that intrathecal fentanyl has a dose-sparing effect when used with local anaesthetics in spinal anaesthesia as based on the studies with bupivacaine. It was extrapolated that similar effect was present with ropivacaine. As the difference in motor block between bupivacaine and ropivacaine would be more likely shown at lower doses in compared to a supramaximal dose, the addition of fentanyl allowed the use of lower doses of local anaesthetics for effective anaesthesia. The addition of fentanyl 15 mcg to both study groups were for standardization so that the only variable between the two groups was the local anaesthetic, bupivacaine and ropivacaine, only. This study found that a small dose of plain ropivacaine (10 mg) provided an adequate sensory block for all patients, with the exception of one patient in whom surgery was unduly prolonged. This probably reflects the effect of the addition of fentanyl. Experience with bupivacaine has shown that the addition of intrathecal fentanyl increases the level and duration of sensory block without prolonging the duration of motor block (Ben-David et al 1997). This allows the use of smaller doses of local anaesthetic with shorter duration of motor block and a lower incidence of excessively high block (Ben-David et al 2000). The addition of fentanyl to ropivacaine for spinal anaesthesia has also been described. Yegin et al described the addition of fentanyl 25 mcg to

hyperbaric ropivacaine 18 mg in urological patients. They found that fentanyl improved the quality and prolonged the duration of analgesia compared with ropivacaine alone (Yegin et al 2005). Kallio et al found that a mixture of hyperbaric ropivacaine 10 mg plus fentanyl 20 mcg resulted in equal onset and duration of analgesia, but faster mobilization, compared with hyperbaric ropivacaine 15 mg (Kallio et al 2005). In my study I used a plain rather than hyperbaric solution and found the results to be consistent with the last two studies.

Ropivacaine is now approved for spinal anaesthesia by the manufacturer and many studies have now been published attesting to the safety of its use for this purpose. Although a case of possible transient neurological symptoms following intrathecal ropivacaine has been reported (Ganapathy et al 2000), the significance of this report has been questioned.

In this study, I only tested the motor power on a modified Bromage scale. However, a Bromage score of 0 is not necessarily an adequate criterion to signify the ability to ambulate. Other tests that should be considered include assessment of partial knee bends while standing, tests of proprioception and a supervised trial walk. I did not test ambulation in our patients for practical reasons because most of them required continuous urinary irrigation after surgery. Further work is required to determine whether the shorter duration of motor block with ropivacaine in comparison with bupivacaine can be translated to earlier ambulation.

In conclusion, I found that plain ropivacaine 10 mg with fentanyl 15 mcg provided effective spinal anaesthesia for urological surgery. The quality of block was similar to that of plain bupivacaine 10 mg with fentanyl 15 mcg but the median duration of motor block with ropivacaine group was shorter than that with bupivacaine. This shorter duration of motor block may be useful when early ambulation after brief surgery is required. Further studies are indicated to determine the optimal combination of ropivacaine with fentanyl for early ambulation and discharge.

CHAPTER VIII

SPINAL ROPIVACAINE FOR LOWER LIMB SURGERY: A DOSE-RESPONSE STUDY

INTRODUCTION

Many reports have described the use of intrathecal ropivacaine (McNamee et al 2002, Gautier et al 2003, Ogun et al 2003, Whiteside et al 2003, Casati et al 2004, Danelli et al 2004, Kallio et al 2004b, Fettes et al 2005, Lee et al 2005). However, a number of different doses of ropivacaine have been used for spinal anaesthesia and the dose-response relationship has not been fully determined. Previously, Khaw et al described the dose-response relationship for spinal ropivacaine in obstetric patients (Khaw et al 2001), but their findings cannot be fully extrapolated to the general surgical population because of differences in pharmacodynamic response and block requirement between pregnant and non-pregnant patients. The objective of this study was to define the dose-response relationship for ropivacaine in patients having spinal anaesthesia for lower limb surgery. Traditional dose-response methodology was used and values for ED50 and ED95 were determined.

METHODS

This study was a prospective, randomized, double-blind trial of 60 patients scheduled for a range of lower limb surgeries under combined spinal-epidural anaesthesia. No attempt was made to select or stratify patients according to the operation or the use of a tourniquet. Approval was obtained from the Ethics Committee, Kowloon West Cluster, Hospital Authority, Hong Kong, China and all patients gave written informed consent. Inclusion criteria were ASA physical status I–III, age ≥ 18 years, body weight 45–85 kg and height ≥ 150 cm. For the patients who could not stand or sit, the recent body weight taken from history was used. Exclusion criteria were known hypersensitivity to amide local anaesthetics, contraindications to spinal or epidural anaesthesia and inability to understand English or Chinese.

After enrollment, patients were randomly assigned to receive 1 of 5 doses of intrathecal ropivacaine using a combined spinal-epidural technique: 2, 4, 7, 10 or 14 mg (n = 12 per group). A combined kit (BD Durasafe plus variable extension set, Becton Dickinson Medical Devices Co. Ltd, Suzhou, China) was used for the spinal-epidural injection. Randomization was performed according to computer-generated random numbers using the sealed envelope technique. All study solutions were prepared in identical syringes by mixing ropivacaine 10 mg ml^{-1} (Naropin, Astra Zeneca Pty. Ltd, Sodertalje, Sweden) and normal saline to a final volume of 2.8 ml. Study solutions were prepared by an anaesthesiologist not involved with subsequent administration and patient assessment.

All patients received intravenous prehydration with 500 ml lactated Ringer's solution. With patients in the lateral position, under aseptic conditions, the epidural space was identified at the L3-4 or L2-3 interspace using a 17 gauge Tuohy needle and loss-of-resistance to air. A 25-gauge Whitacre spinal needle was passed through the epidural needle and observed for free flow of cerebrospinal fluid before injecting the study solution intrathecally with the orifice facing cephalad. The spinal needle was removed and an epidural catheter was inserted. The epidural catheter was gently aspirated and observed for the presence of blood or cerebrospinal fluid but no test dose was administered. Patients were placed in the supine position and were monitored using continuous electrocardiography and pulse oximetry and non-invasive blood pressure, cycled every 5 minutes, until the end of surgery.

Sensory block was assessed using the loss of cold sensation with ethyl chloride spray, and motor block using a modified Bromage scale (0, no paralysis, able to flex hip, knee and ankle; 1, able to flex knee, unable to raise extended leg; 2, able to flex ankle, unable to flex knee, 3, unable to flex ankle, knee and hip) every 2.5 min for 20 min (Bromage 1965). Surgery was initiated when the level of sensory block reached the 12th thoracic (T12) dermatome or above. If the block did not reach the required level or if pain occurred during surgery, epidural supplementation using ropivacaine 7.5 mg ml^{-1} was given at the anaesthesiologist's discretion.

Our primary endpoint was the success or failure of spinal anaesthesia. For the purposes of the study, a success was recorded if a bilateral sensory

block to the T12 dermatome was attained within 20 min after intrathecal injection and surgery was completed, or proceeded until at least 50 min after the intrathecal injection, without epidural supplementation.

Hypotension defined as a decrease in systolic blood pressure by more than 30% from baseline or to less than 100 mmHg, was treated with incremental IV doses of ephedrine 5 mg or phenylephrine 50 mcg and further boluses of intravenous fluid as required. Bradycardia defined as heart rate < 50 bpm, was treated with IV atropine 0.3 mg – 0.6 mg. The incidences of adverse effects such as nausea, vomiting, and shivering were recorded. All patients received a follow-up visit on the day after the operation and were assessed for complete recovery of sensory and motor function.

A sample size of 12 patients in each group was determined using Tallarida's suggestion for efficient design of a dose-response study (Tallarida et al 1997). Data for age and height of the patients are presented as mean and standard deviation. Intergroup comparisons were performed using one-way analysis of variance. Data on the type of surgery were analyzed using Fisher's exact test. Levels of sensory and motor block are presented as median values. The dose-response relationship for spinal ropivacaine was determined using probit analysis. Probit analysis was used in defining the dose-response relationship. The binary response (success / failure) in different groups of patients were measured. The dose-response relationship curve is sigmoid in nature thus it is impossible to generate a regression graph. Probit analysis acts as a transformation from sigmoid to linear relationship. The proportion of the

successful responses in each dose group was transformed into a 'working probit value'. These values were used to construct a working probit-log(dose) plot, its relationship was linear. Linear regression was performed and interpolation was used to determine values for ED50 and ED95 (Tallarida 2000). Data were analyzed using SPSS 10.0 for Windows (Chicago, IL), PharmTools Pro 1.1.27 (The McCary Group, Emmaus, PA) and GraphPad Prism 4.00 (GraphPad Software, San Diego CA). $P < 0.05$ was considered statistically significant.

RESULTS

Sixty patients completed the study and were included for data analysis. In one additional case both spinal injection (intrathecal ropivacaine 7 mg) and epidural supplementation failed to produce adequate sensory block and general anaesthesia was required. This case was regarded as a technical failure and whilst maintaining blinding, another patient was recruited as a replacement. There were no differences in age and height of the patients as well as type of surgery (Tables 12 and 13). The spinal needle was inserted at L3-L4 interspace in 58 patients and the L2-L3 interspace in 2 patients.

Anaesthesia was successful in 0 (0%), 0 (0%), 5 (42%), 10 (83%) and 12 (100%) patients in the 2-, 4-, 7-, 10- and 14-mg groups, respectively. Unsuccessful cases are described in Table 14. The percentage of successful cases in each group was transformed into a working probit value. Linear regression analysis showed a regression coefficient (r) of 0.99 and a coefficient of determination (r^2) of 0.97 (Figure 11). The calculated value for ED50 was 7.6 mg (95% CI: 6.2 – 8.7 mg) and for ED95 was 11.4 mg (95% CI: 9.7 – 18.3 mg) (Figure 12).

The cephalic level of sensory block and the degree of motor block increased with larger doses of ropivacaine (Figure 13 and 14). No patient had bradycardia. Four patients (1 in 7 mg group, 1 in 10 mg group and 2 in 14 mg group) had hypotension which recovered promptly with IV boluses of ephedrine and phenylephrine. Three patients (1 in 10 mg group and 2 in 14 mg group) had shivering. No patients experienced nausea and vomiting. There were no

residual neurological changes and no post-dural puncture headaches in any patient at the follow-up visit on the day after the surgery.

TABLE 12 PATIENT DEMOGRAPHICS

	Ropivacaine				
	2 mg (n = 12)	**4 mg (n = 12)**	**7 mg (n = 12)**	**10 mg (n = 12)**	**14 mg (n = 12)**
Sex, M/F	7/5	5/7	5/7	6/6	6/6
Age (yrs)	69 (9.4)	63 (10.5)	61 (14.9)	68 (9.1)	65 (13.1)
Weight (Kg)	61 (12)	61 (15)	63 (8)	66 (9)	62 (11)
Height (cm)	164 (9.6)	158 (7.0)	162 (7.0)	163 (7.9)	158 (6.8)

Values are mean (standard deviation) for age, weight and height and number of patients for sex. There were no significant differences among the groups in age , weight and height.

TABLE 13 TYPE OF SURGERY

	Ropivacaine				
	2 mg (n = 12)	**4 mg (n = 12)**	**7 mg (n = 12)**	**10 mg (n = 12)**	**14mg (n = 12)**
Hip or above knee surgery	7 (0/7)	5 (0/5)	7 (0/7)	7 (0/7)	7 (0/7)
Knee or above ankle surgery	2 (2/0)	4 (3/1)	2 (2/0)	3 (3/0)	4 (4/0)
Ankle or foot surgery	3 (3/0)	3 (2/1)	3 (2/1)	2 (2/0)	1 (0/1)

Values are number of patients (with / without thigh tourniquet applied). There were no significant differences among the groups.

TABLE 14. DETAILS OF UNSUCCESSFUL CASES

	Ropivacaine				
	2 mg (n = 12)	**4 mg (n = 12)**	**7 mg (n = 12)**	**10 mg (n = 12)**	**14 mg (n = 12)**
Inadequate level of block at 20 min	8 (67%)	11 (92%)	6 (50%)	2 (17%)	0 (0%)
epidural supplementation required in first 50 min, for patients who had an adequate level of block at 20 min	4 (33%)	1 (8%)	1 (8%)	0 (0%)	0 (0%)
Total number of unsuccessful cases	12 (100%)	12 (100%)	7 (58%)	2 (17%)	0 (0%)

Values are number of patients (percentage within the group)

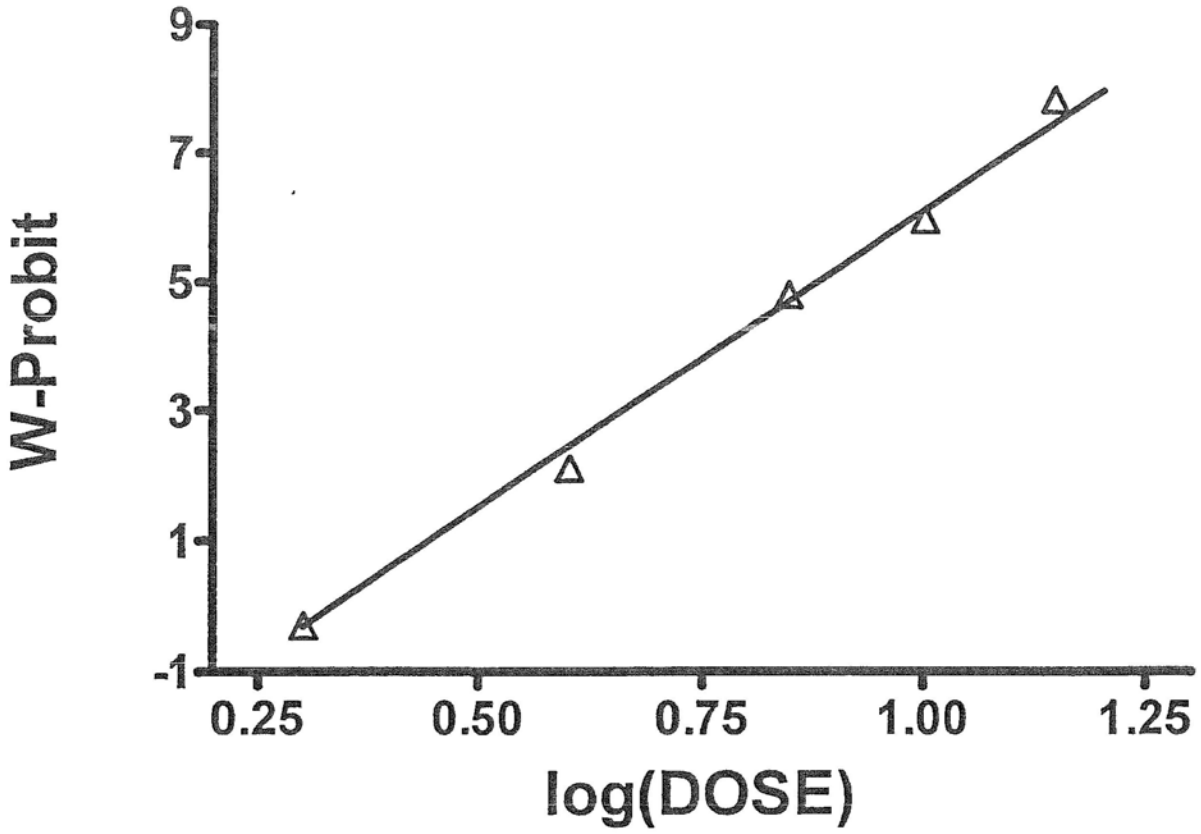


FIGURE 11 LINEAR REGRESSION PLOT OF WORKING PROBIT VALUE AGAINST LOG(DOSE).

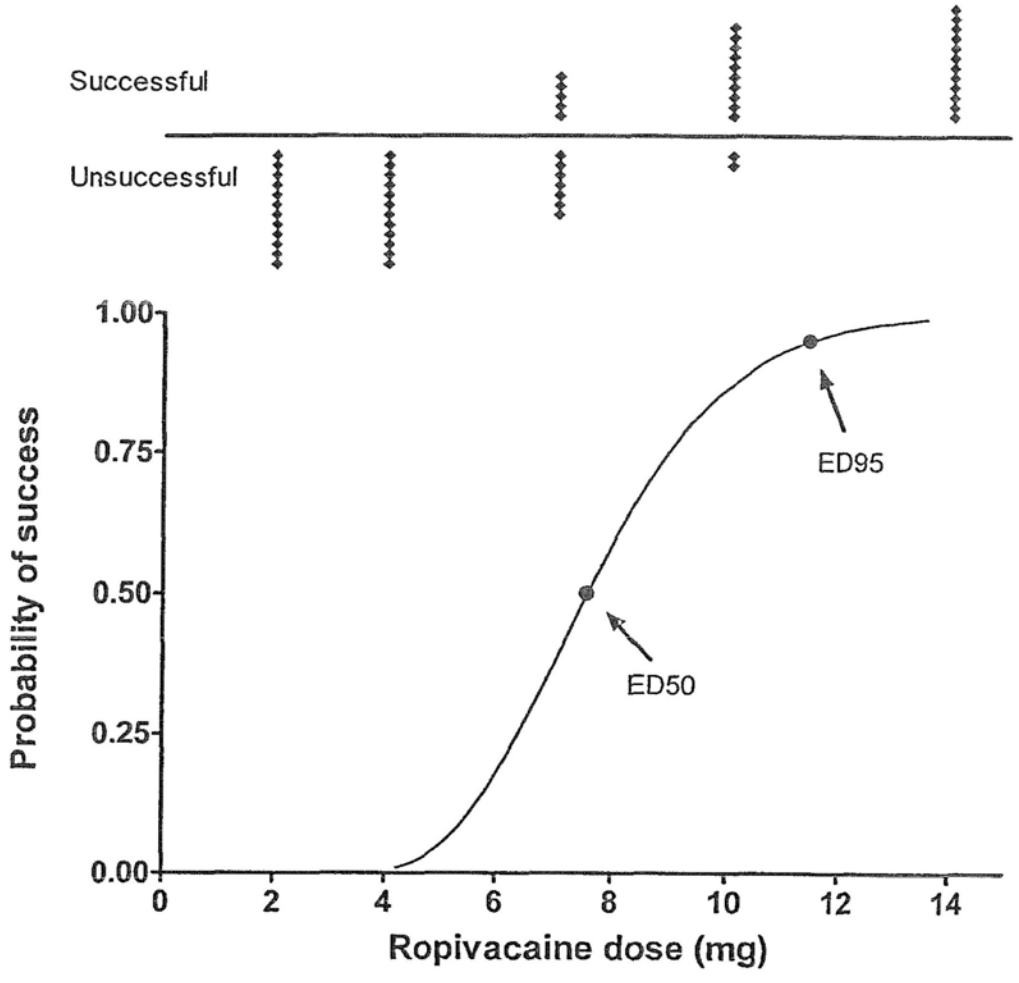


FIGURE 12 SIGMOID DOSE-RESPONSE CURVE OF SPINAL ROPIVACAINE. THE ED50 AND ED95 WERE 7.6 MG AND 11.4 MG RESPECTIVELY.

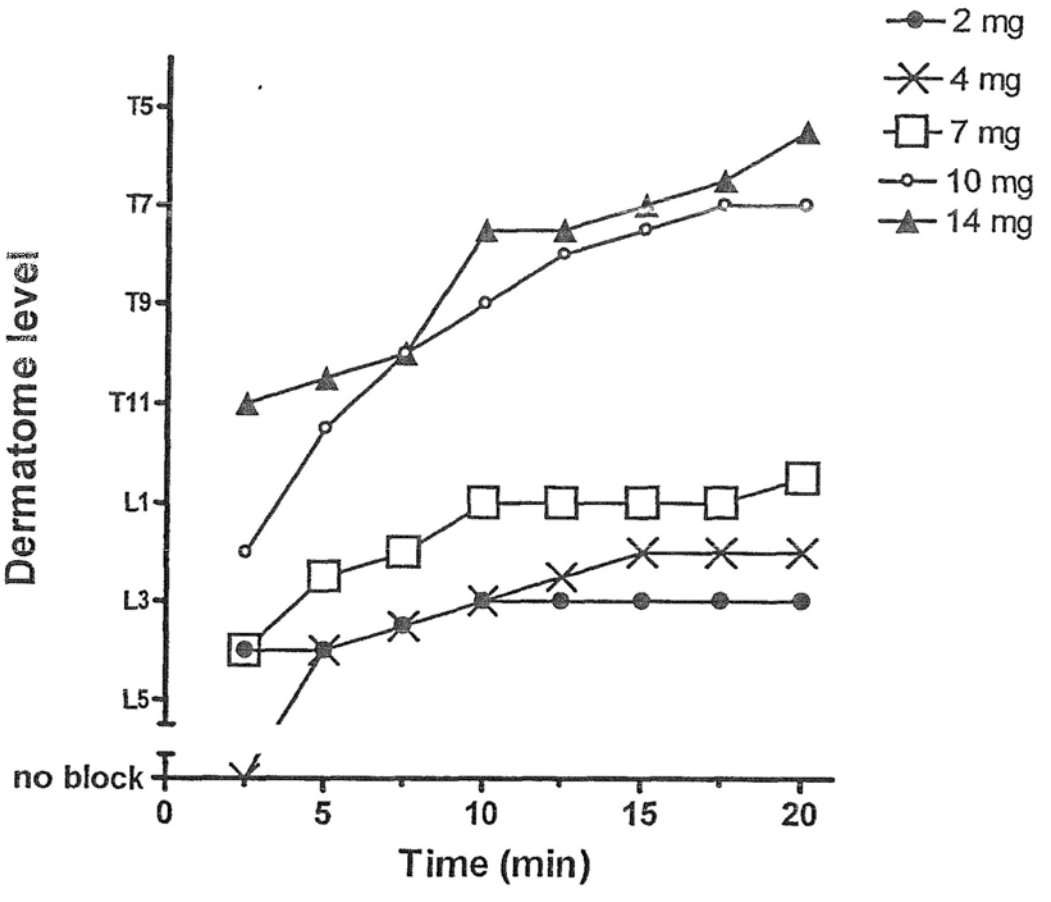


FIGURE 13 TIME COURSE OF CHANGES IN UPPER LEVEL OF SENSORY BLOCK (MEDIAN).

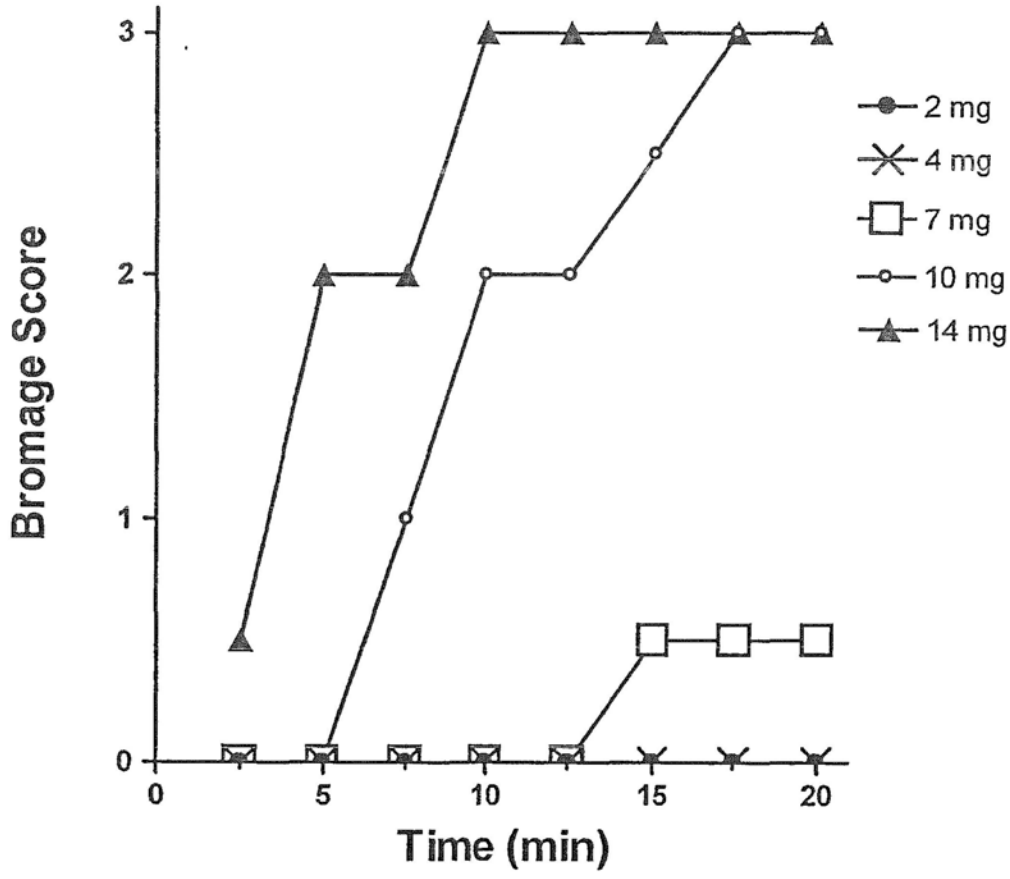


FIGURE 14 TIME COURSE OF CHANGES IN BROMAGE SCORE (MEDIAN).

Discussion

In this study, I investigated the dose-response relationship for intrathecal ropivacaine for patients having lower limb surgery of 50 minutes or less which required sensory block to the T12 dermatome. I determined the ED50 to be 7.6 mg (95% CI: 6.2 – 8.7 mg) and the ED95 to be 11.4 mg (95% CI: 9.7 – 18.3 mg).

The estimation of dose requirements for intrathecal ropivacaine from this study was surprisingly small. Sell et al used the technique of continuous spinal anaesthesia with spinal catheters and up-down sequential analysis to define the ED50 of ropivacaine for patients having hip replacement surgery as 12.8 mg (95% CI 12.2 – 13.4 mg) (Sell et al 2005). Nevertheless, their criteria for success included loss of sensation to pinprick and tetanic electrical stimulation at the T12 dermatome as well as complete motor block at 20 minutes after intrathecal injection and the use of spinal catheter would produce a different spread of local anaesthetic compared with injection through needle. These differences in successful criteria and the technique of intrathecal injection of study solutions render the direct comparison of our results impossible. The doses used in previous reports on the use of ropivacaine for spinal anaesthesia for lower extremity surgery have ranged from 15 mg to 33.75 mg, which are greater than our calculated value for the ED95 (11.4 mg) (Malinovsky et al 2000, McNamee et al 2002, Kallio et al 2004a, Kallio et al 2004b, Wong et al 2004). This suggests that commonly-used doses may be greater than required. With the construction of the dose-response curve, our data may be a useful guide for clinicians to choose the optimal dose for spinal anaesthesia under different clinical situations;

for example, a dose equal to or greater than the ED95 when a single-injection technique is used, and a smaller dose nearer to the ED50 when a catheter technique is used.

The ED50 and ED95 of spinal ropivacaine defined in our study only gave an approximation of the true values as our sample size was small and the confidence intervals were wide. Because one potential benefit of the use of spinal ropivacaine would be for ambulatory surgery of short duration, we used successful conduct of surgery up to 50 min as one of the criteria defining success. Unfortunately, we did not monitor the progression and regression of sensory and motor block after the first 20 min of intrathecal injection. Further studies defining the time course of the sensory and motor block with different doses of ropivacaine would be of interest. Because patients were chosen from the routine operating lists and the study included a range of surgeries for which there was variation in the use of tourniquets. A better design may have been to apply more stringent selection criteria in order to reduce the heterogeneity among patients. Thus, although our results provide an indication of dose requirement for spinal ropivacaine for lower limb surgery, this should be considered a generalized estimate. Actual dose requirements for different subsets of lower limb surgery may vary.

In conclusion, I found that the ED50 and ED95 for spinal ropivacaine in lower limb surgery of 50 minutes duration or less were 7.6 mg and 11.4 mg respectively.

PART 5

COMPARISON OF ROPIVACAINE, LEVOBUPIVACAINE AND BUPIVACAINE

CHAPTER IX THE MEDIAN EFFECTIVE DOSE OF BUPIVACAINE, LEVOBUPIVACAINE AND ROPIVACAINE AFTER INTRATHECAL INJECTION IN LOWER LIMB SURGERY

CHAPTER IX

THE MEDIAN EFFECTIVE DOSE OF BUPIVACAINE, LEVOBUPIVACAINE AND ROPIVACAINE AFTER INTRATHECAL INJECTION IN LOWER LIMB SURGERY

INTRODUCTION

Levobupivacaine and ropivacaine have been described previously as alternatives to bupivacaine for spinal anaesthesia (Glaser et al 2002, Lee et al 2003, Kallio et al 2004b, Lee et al 2005, Boztug et al 2006). The relative potencies of these agents when given intrathecally for labour analgesia have been determined previously (Camorcia et al 2005; Van de Velde et al 2007), but because there are differences in pharmacodynamic response and block requirement between pregnant and non-pregnant patients, the results of these studies may not be applicable to other surgical populations. This study compared the potencies of levobupivacaine, ropivacaine and bupivacaine when given intrathecally using a combined spinal-epidural technique in patients having lower-limb surgery. For each local anaesthetic, the up-down sequential allocation method (Dixon and Massey 1983) was used to determine and then compare the median effective dose (ED50), which is also referred to as the minimum local anaesthetic dose (Sell et al 2005; Parpaglioni et al 2006).

METHODS

This study was a prospective randomized double-blinded trial of 75 patients scheduled for lower limb surgery under combined spinal-epidural anaesthesia. Approval was obtained from Clinical Research Ethics Committee, Kowloon West Cluster, Hospital Authority, Hong Kong Special Administrative Region, China. All patients gave written informed consent. Inclusion criteria were (i) ASA physical status I – III; (ii) age $\geq$18; (iii) body weight 40 – 90 kg; (iv) height $\geq$145 cm and (v) lower limb surgery involving the hip or knee area. For the patients who could not stand or sit, the recent body weight taken from history was used. Exclusion criteria were (i) known hypersensitivity to amide local anaesthetics; (ii) contraindications to spinal or epidural anaesthesia; (iii) inability to speak English or Chinese, and (iv) body mass index >35 kg m^{-2} . After enrollment, the patients were randomly assigned into one of three groups (n = 25 per group) to receive an intrathecal dose of bupivacaine, levobupivacaine or ropivacaine according to computer generated random numbers using the sealed envelope technique.

A standard combined spinal-epidural technique was used with a commercial kit (BD Durasafe plus variable extension set, Becton Dickinson Medical Devices Co. Ltd., Suzhan, China). An intravenous infusion of 10 ml kg^{-1} of normal saline was given as prehydration. With the patient in lateral position and using full aseptic precautions, the epidural space was identified at the L3-4 or L2-3 interspace with a 17-gauge Tuohy needle using the loss of resistance to air technique. A 25-gauge Whitacre spinal needle was then passed through the

epidural needle and free flow of CSF from the spinal needle indicated the correct position. Intrathecal injection of the study solution was done with orifice of the Whitacre needle facing cephalad. After the intrathecal injection, the spinal needle was removed and an epidural catheter was inserted 3 – 4 cm into the epidural space and then secured with tape. No drug was injected via the epidural catheter. The patient was then returned to the supine position.

The study solutions were prepared by an anaesthesiologist who was not involved with subsequent patient assessment using 0.5% bupivacaine (AstraZeneca Pty Ltd, North Ryde, NSW, Australia), 0.5% levobupivacaine (Nycomed Pharma AS, Elverum, Norway for Abbott Laboratories) or 1% ropivacaine (Naropin, AstraZeneca Pty Ltd, Soterlaje, Sweden). A different anaesthesiologist, who was blinded to the drug and dose, administered anaesthesia and assessed patients. The dose of intrathecal local anaesthetic administered to patients was varied according to the up-down sequential allocation method (Dixon and Massey 1983). In each group, the dose used for the first patient was 8 mg. For each subsequent patient, the dose was determined by the outcome of the previous patient in the group with the dosing increment set at 1 mg. For the purposes of the study, a successful block was defined using criteria we used in a previous study of patients having lower limb surgery (Lee et al 2007). Accordingly, a success was recorded if a bilateral sensory block to the T12 dermatome was attained within 20 min after intrathecal injection and surgery was completed, or proceeded until at least 50 min after the intrathecal injection, without epidural supplementation. After successful

anaesthesia, the dose of the study drug for the next patient was decreased by 1 mg in that group. Conversely, if a failure was recorded, the dose of the study drug for the next patient was increased by 1 mg in that group. All study drugs were diluted to a volume of 2.5 ml with normal saline to facilitate blinding.

In cases of failure, patients received top-up epidural injection of local anaesthetic as decided by the attending anaesthesiologist. If repeated top-up doses of epidural injection failed to provide adequate level of anaesthesia, general anaesthesia would be given. Patients were followed up on the day after the operation for the complete recovery of sensory and motor function and any adverse events.

The monitored variables included continuous electrocardiogram, pulse oximetry and noninvasive blood pressure cycled every 5 min from the start of spinal anaesthesia until the operation was finished. Sensory blockade was monitored using loss of sensation to cold spray of ethyl chloride every 2.5 min for 20 min after the initiation of spinal anaesthesia and at the end of operation. Motor blockade was assessed according to the modified Bromage scale (0 = no paralysis, able to flex hip, knee and ankle; 1 = able to flex knee, unable to raise extended leg; 2 = able to flex ankle, unable to flex knee; 3 = unable to flex ankle, knee and hip), every 2.5 min for 20 min and at the end of operation (Bromage 1965).

Demographic data were collected and are presented as count or mean ± SD as appropriate. Nominal data were analyzed using the chi-square test and continuous data were analyzed using one-way analysis of variance for inter-

group differences. Values for ED50 were calculated using the technique of Dixon and Massey (Dixon and Massey 1983). Sample size estimation was determined by the method as recommended by Dixon and Massey and based on the result of previous published studies (Sell et al 2005; Parpaglioni et al 2006). A sample size of 25 patients for each group was determined to account for cases of failure and the potential deviation of the initial test dose from ED50. Analyses were performed using SPSS 15.0 for Windows (SPSS Inc, Chicago, IL), Excel 2003 (Microsoft Corporation, Redmond, WA) and Graph Pad Prism 4.00 (Graphpad Software, San Diego, CA). Values of $P < 0.05$ were considered statistically significant.

RESULTS

Demographic data were similar among groups (Table 15). No patient had residual neurological changes or post-dural puncture headache when seen at the follow-up visit on the day after the surgery. The sequences of patients with successes and failures are shown in Figure 15. The calculated values for ED50 were 5.50 mg for bupivacaine (95% CI: 4.90-6.10 mg), 5.68 mg for levobupivacaine (95% CI: 4.92-6.44 mg) and 8.41 mg for ropivacaine (95% CI: 7.15-9.67 mg). The relative potency ratios among the different drugs were: levobupivacaine/bupivacaine 0.97 (95% CI: 0.81-1.17), ropivacaine/bupivacaine 0.65 (95% CI: 0.54-0.80) and ropivacaine/levobupivacaine 0.68 (95% CI: 0.55-0.84). The potency of the local anaesthetics was: bupivacaine = levobupivacaine > ropivacaine.

Table 15 Patient Demographics

	Bupivacaine Group (n=25)	Levobupivacaine Group (n=25)	Ropivacaine Group (n=25)
Sex (M/F)	14/11	9/16	13/12
Age (yr)	62 (16)	66 (11)	62 (14)
Height (m)	1.63 (0.09)	1.61 (0.08)	1.63 (0.09)
Body weight (kg)	63 (10)	61 (11)	62 (11)
Body mass index ($Kg\ m^{-2}$)	23.8 (2.9)	23.5 (3.8)	23.5 (3.6)

Values are mean (SD) for age, height, body weight and body mass index, and number of patients for sex. There were no significant differences among the groups.

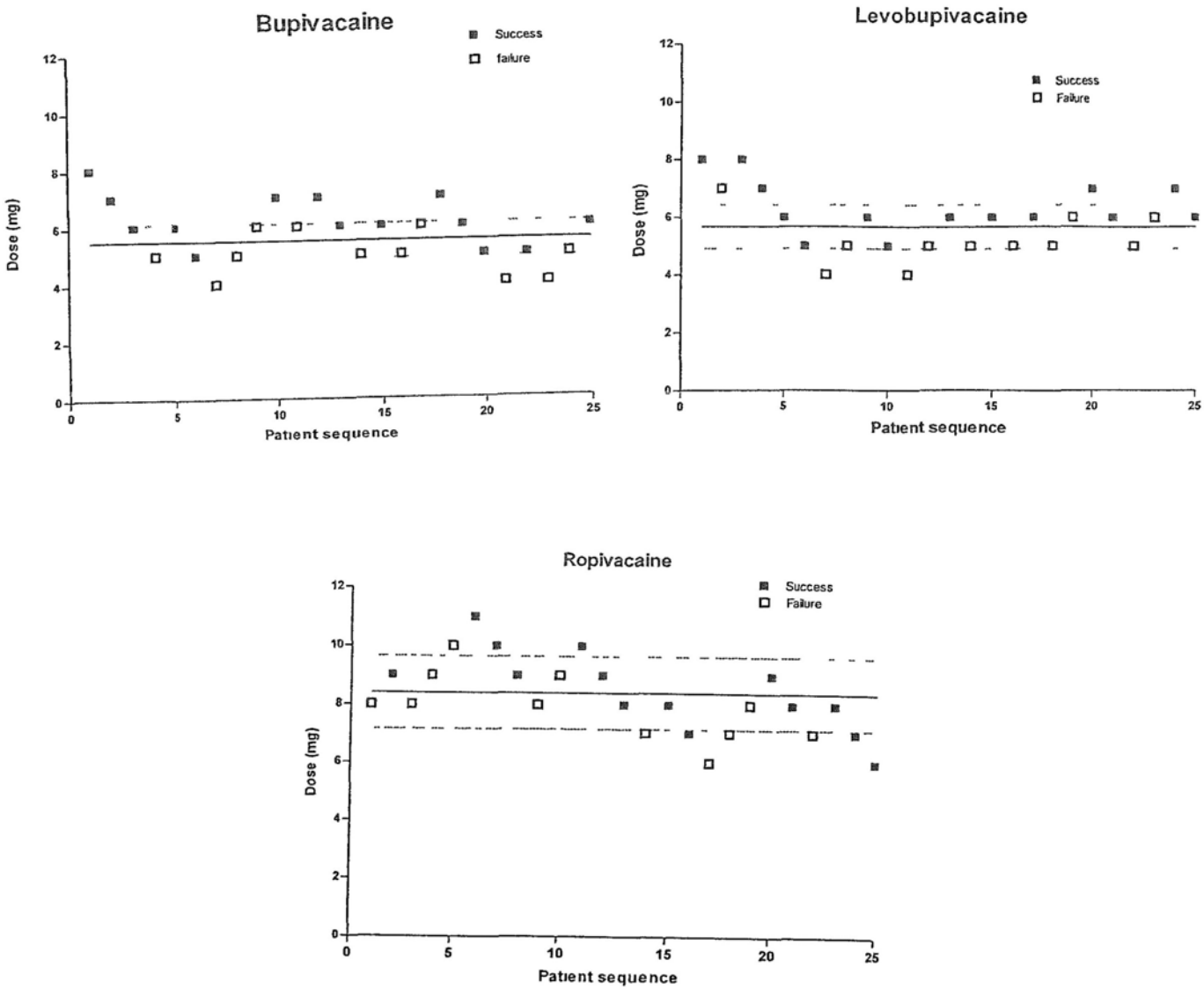


Figure 15 THE MEDIAN EFFECTIVE DOSE OF INTRATHECAL BUPIVACAINE, LEVOBUPIVACAINE AND ROPIVACAINE AS DETERMINED BY THE TECHNIQUE OF UP-DOWN SEQUENTIAL ALLOCATION. THE MEDIAN EFFECTIVE DOSES WERE **5.50** MG **(95% CI: 4.90** TO **6.10** MG) FOR BUPIVACAINE, **5.68** MG **(95% CI: 4.92** TO **6.44** MG) FOR LEVOBUPIVACAINE AND **8.41** MG **(95% CI: 7.15** TO **9.67** MG) FOR ROPIVACAINE

Discussion

This study investigated the ED50 of intrathecal ropivacaine, levobupivacaine and bupivacaine for lower limb surgery with duration up to 50 min. Under these study conditions, the potency determined was: bupivacaine = levobupivacaine > ropivacaine.

Two previous studies have compared ED50 values of levobupivacaine / ropivacaine and ropivacaine / bupivacaine when given intrathecally for surgical anaesthesia. Sell et al defined the ED50 of intrathecal levobupivacaine and ropivacaine for hip replacement surgery by continuous spinal anaesthesia using spinal catheters (Sell et al 2005). The calculated values were 11.7 mg (95% CI: 11.1-12.4 mg) and 12.8 mg (95% CI: 12.2-13.4 mg) respectively and they concluded that there was no significant difference between the drugs, which conflicts with our finding that levobupivacaine was more potent than ropivacaine. However, of note, Sell et al. based their conclusion on the overlapping of 95% CIs for the two sets of calculated values of ED50. This is a conservative comparison that lacks power for detecting a significant difference between the two drugs. It has been suggested that non-overlapping of 83% or 84% CIs is more appropriate for rejecting the null hypothesis at an α of approximately 0.05 (Payton et al 2003; Pace and Stylianou 2007). Michalek-Sauberer et al defined the ED50 of intrathecal bupivacaine and ropivacaine for brachytherapy of the lower abdomen by continuous spinal anaesthesia. The ED50 of intrathecal bupivacaine and ropivacaine were 11.2 mg and 22.6 mg respectively, with a potency ratio of 0.5 for ropivacaine / bupivacaine (Michalek-Sauberer et al 2008).

This is comparable to our finding that ropivacaine was less potent than bupivacaine. Parpaglioni et al defined the ED50 of intrathecal levobupivacaine and ropivacaine for caesarean delivery (Parpaglioni et al 2006). Similar to our findings, they determined that levobupivacaine was more potent than ropivacaine, with calculated values for ED50 of 10.58 mg and 14.22 mg for levobupivacaine and ropivacaine respectively.

Several studies have also compared the potencies of these three local anaesthetics when given intrathecally for labour analgesia, with conflicting results. Sia et al (2006) performed a random dose allocation dose-response study of levobupivacaine and ropivacaine and consistent with our results, noted that levobupivacaine was more potent than ropivacaine, with calculated values for ED50 of 1.07 mg and 1.4 mg respectively. Camorcia et al (2005) using up-down sequential allocation determined ED50 values for ropivacaine, levobupivacaine and bupivacaine as 3.64 mg, 2.94 mg and 2.37 mg respectively. Their results suggested a potency hierarchy of bupivacaine > levobupivacaine > ropivacaine. Van de Velde et al (2007) determined the full dose-response relation of the three local anaesthetics given with sufentanil 1.5 mcg. Their calculated values for ED95 of bupivacaine, levobupivacaine and ropivacaine were 3.3 mg, 5.0 mg and 4.8 mg respectively. Their results suggested a potency hierarchy of bupivacaine > levobupivacaine = ropivacaine, although of note the ED95 values for levobupivacaine and ropivacaine were greater than the maximum doses actually given (3.5 mg) and were estimated by extrapolation.

A comparison of local anaesthetic potency in different studies is made difficult by differences among the studies in criteria defining success, type of surgery and patient population. However, the ED50 of ropivacaine defined in our present study is comparable to that determined by dose-response methodology in our previous study in which we used similar criteria to define success (Lee et al 2007). In both these studies, we defined success as bilateral sensory block to the T12 dermatome within 20 min and ability for surgery to be performed for at least 50 min after intrathecal injection. These were relatively objective and well-defined criteria which were chosen to minimize subject and observer bias.

Up-down sequential allocation study is a simple and efficient method to define ED50. It allows the estimation of ED50 with greater precision and requires fewer subjects compared with traditional dose-response studies (Dixon and Massey 1983; Columb and D'Angelo 2006). Although ED50 is commonly used to define and compare the potency of different local anaesthetics (Sell et al 2005; Parpaglioni et al 2006; Michalek-Sauberer et al 2008), values of ED50 estimated in up-down sequential allocation studies represent only a single point (quantile) along the dose-response curve. Information on higher quantiles such as ED90 or ED95 that may be of more clinical relevance is not defined, and when comparing potencies of drugs, the assumption is often made that their dose-response curves are parallel. The potency ratio of local anaesthetics may vary at different points on the dose-response curve or when different responses are measured, which might partly explain the differences between our result and the finding of those studies for labour analgesia (Camorcia et al 2005; Van de Velde et al 2007).

In summary, I suggest that for intrathecal anaesthesia for lower limb surgery, ropivacaine is less potent than levobupivacaine and bupivacaine, whereas the potency is similar between levobupivacaine and bupivacaine. Although it is controversial whether calculated values for ED50 can be directly translated to clinical practice when doses closer to ED95 (Columb and D'Angelo 2006) are usually used, the information is useful for planning of future studies. Prospective comparative randomized trial can be conducted to define any difference in potencies among these three local anaesthetics at higher doses which arw commonly used in single-shot spinal anaesthesia during daily clinical practice.

PART 6:

SUMMARY AND CONCLUSIONS

CHAPTER X SUMMARY

CHAPTER XI CONCLUSIONS

CHAPTER X

SUMMARY

SUMMARY

The objective of this thesis was to evaluate the use of levobupivacaine and ropivacaine, the two 'newer' local anaesthetics in spinal anaesthesia for lower limb and urological surgery. My hypothesis was that '*levobupivacaine and ropivacaine are effective local anaesthetic agents for spinal anaesthesia in lower limb and urological surgery*'.

PHARMACOLOGY

Local anaesthetics drugs can produce reversible blockade of conduction of nerve impulses. The recovery of nerve conduction is complete with no structural damage to the nerve fibres. Bupivacaine has been the most popular local anaesthetic for many years due to its long duration of action. Nevertheless, bupivacaine has a narrower margin of safety in case of accidental intravenous injection as central nervous system and cardiovascular system toxicity occurs at similar plasma concentration. Furthermore, resuscitation from bupivacaine-induced cardiovascular collapse has been found to be difficult and may be unsuccessful. In view of this, there is clinical need to develop a local anaesthetic with similar nerve blocking properties of bupivacaine and a greater margin of safety in case of accidental intravascular injection.

Bupivacaine is a racemic mixture with equimolar amount of both S(-) and R(+) enantiomers. It was found that S(-) enantiomer of bupivacaine had less cardio-depressant effect than the R(+) enantiomer. Both levobupivacaine and ropivacaine are synthesized as the S(-) enantiomer only instead of racemic mixture. Levobupivacaine is the S(-) enantiomer of bupivacaine. Ropivacaine is the S(-) enantiomer of a propyl analogue of bupivacaine. Studies showed that levobupivacaine and ropivacaine are effective for use in peripheral nerve block, epidural analgesia and anaesthesia. My studies in this thesis investigate the use of levobupivacaine and ropivacaine in spinal anaesthesia for lower limb and urological surgery.

CLINICAL STUDIES

Levobupivacaine versus bupivacaine in spinal anaesthesia

There were controversies on whether levobupivacaine is a suitable local anaesthetic for intrathecal injection in spinal anaesthesia (Burke et al 1999, Glaser et al 2002). I performed a randomized, double-blind study to compare the clinical efficacy and motor-block using 2.6ml of either 0.5% levobupivacaine or 0.5% bupivacaine in spinal anaesthesia for urological surgery, when a sensory block to at least T10 dermatome was required. There were no significant differences between the two groups in the quality of sensory and motor block or haemodynamic change. Anaesthesia was adequate and patient satisfaction was good in all cases.

Addition of fentanyl to levobupivacaine

Fentanyl is a lipophilic opioid which has been used as an adjunct to bupivacaine in spinal anaesthesia for enhancement of analgesia without intensifying motor and sympathetic block. In epidural route, levobupivacaine has greater sensory-motor dissociation in blockade than bupivacaine (Lacassie and Columb 2003). Similar effect might be present in intrathecal injection. It is possible that the addition of fentanyl to levobupivacaine may form a mixture for spinal anaesthesia with minimal motor block and hypotension. I performed a prospective, randomized, double-blind study compared the clinical efficacy, motor block and haemodynamic effects of using 2.6ml of 0.5% levobupivacaine alone and 2.3ml of 0.5% levobupivacaine with fentanyl 15mcg in 0.3ml for spinal anaesthesia in urological surgery. There were no significant differences between the two groups in the haemodynamic change, and quality of sensory and motor block. Anaesthesia was adequate and patient satisfaction was good in all cases. Side-effects were minor and infrequent with both regimens.

Ropivacaine-fentanyl versus bupivacaine-fentanyl for spinal anaesthesia

In vitro and animal studies have shown that ropivacaine causes less motor block than bupivacaine (Bader et al 1989, Feldman and Covino 1988). Ropivacaine may be a potentially useful agent for spinal anaesthesia with a rapid recovery of motor function. I conducted a randomized double-blind study to compare the use of ropivacaine 10mg and bupivacaine 10mg, both with fentanyl

15mcg for spinal anaesthesia in urological surgery. Anaesthesia was successful in all the patients in both groups. The duration of motor block, was shorter in the ropivacaine group (median: 126 min, interquartile range: 93-162min) compared with the bupivacaine group (median: 189min, interquartile range: 157-234min, difference between medians: 71 min, 95% CI: 28-109 min, p=0.003). The duration of complete motor block was also shorter in the ropivacaine group compared with the bupivacaine group. There was no difference in the onset time of motor block. The characteristics of sensory block and the haemodynamic changes were similar between the groups.

Dose-response study for ropivacaine in spinal anaesthesia

A number of different doses of ropivacaine have been used for spinal anaesthesia; nevertheless, the dose-response relationship has not been fully determined in the general surgical population. I conducted a study to define the dose-response relationship for ropivacaine in patients having spinal anaesthesia for lower limb surgery requiring sensory block up to at least T12 dermatome. Traditional dose-response methodology was used. Anaesthesia was successful in 0, 0, 42, 83 and 100% of the 2, 4, 7, 10 and 14mg groups respectively. The derived value for ED50 was 7.6mg (95% CI: 6.2-8.7mg) and for ED95 was 11.4mg (95% CI: 9.7-18.3mg). The cephalic level of sensory block and the degree of motor block increased with larger doses of ropivacaine.

The median effective dose of bupivacaine, levobupivacaine and ropivacaine

Although levobupivacaine and ropivacaine have been successfully used as alternatives to bupivacaine for spinal anaesthesia, their relative potencies in the general surgical population have not been determined. Using the up-down sequential allocation method, I conducted a study to determine the median effective dose (ED50) of these three local anaesthetics for spinal anaesthesia in lower limb surgery which required a sensory block up to at least T12 dermatome. The ED50 was calculated using the method of Dixon and Massey (Dixon and Massey 1983).

The ED50s were 5.5mg for bupivacaine (95% CI: 4.90-6.10mg), 5.68mg for levobupivacaine (95% CI: 4.92-6.44mg), and 8.41mg for ropivacaine (95% CI: 7.15-9.67mg) in intrathecal anaesthesia. The relative anaesthetic potency ratios are 0.97 (95% CI: 0.81-1.17) for levobupivacaine/bupivacaine, 0.65 (95% CI: 0.54-0.80) for ropivacaine/bupivacaine, and 0.68 (95% CI: 0.55-0.84) for ropivacaine/levobupivacaine.

Finally, I have shown in this thesis that '*levobupivacaine and ropivacaine are effective local anaesthetic agents for spinal anaesthesia in lower limb and urological surgery*' and therefore prove my hypothesis. At a dose of 2.6ml, 0.5% levobupivacaine can be used as an alternative to 0.5% bupivacaine to be an effective local anaesthetic for spinal anaesthesia in urological surgery. 2.3ml of 0.5% levobupivacaine with fentanyl 15μg (0.3ml) is as effective as 2.6ml of 0.5% levobupivacaine alone in spinal anaesthesia for urological surgery. Their clinical

characteristics are similar. Ropivacaine 10mg with fentanyl 15mcg is an effective mixture for spinal anaesthesia in urological surgery. It provides similar sensory anaesthesia, but with a shorter duration of motor block, compared with bupivacaine 10mg with fentanyl 15mcg. For spinal anaesthesia using ropivacaine for lower limb surgery of 50 min duration or less, the ED50 and ED95 are 7.6 and 11.4mg respectively as defined by traditional dose-response methodology. For spinal anaesthesia in lower limb surgery, the ED50s were 5.5mg for bupivacaine (95% CI: 4.90-6.10mg), 5.68mg for levobupivacaine (95% CI: 4.92-6.44mg), and 8.41mg for ropivacaine (95% CI: 7.15-9.67mg) as defined by up-down sequential allocation method. Ropivacaine is less potent than levobupivacaine and bupivacaine, whereas the potency is similar between levobupivacaine and bupivacaine. Further areas of interest for future research would include defining the optimal mixture of different doses of levobupivacaine or ropivacaine with fentanyl for a more rapid recovery of motor function to suit the clinical situation when early mobilization is required and the mapping of the full dose-response relationship of levobupivacaine, ropivacaine and bupivacaine so that their relative potencies can be compared at different doses.

CHAPTER XI

CONCLUSIONS

1. 2.6ml of 0.5% levobupivacaine is effective for spinal anaesthesia in urological surgery requiring sensory block to at least the T10 dermatome. 0.5% levobupivacaine is an effective alternative to racemic bupivacaine in spinal anaesthesia.

2. The characteristics of sensory and motor blockade are similar between 2.6ml of 0.5% levobupivacaine alone and 2.3ml of 0.5% levobupivacaine with fentanyl 15mcg in spinal anaesthesia for urological surgery requiring sensory block to at least T10 dermatome. Both regimens are effective with minimal side-effects.

3. Ropivacaine 10 mg with fentanyl 15 mcg provided effective spinal anaesthesia for urological surgery. The quality of block was similar to that of bupivacaine 10 mg with fentanyl 15 mcg but the median duration of motor block with ropivacaine group was shorter than that with bupivacaine. This shorter duration of motor block may be useful when early ambulation after brief surgery is required.

4. The ED50 and ED95 for spinal ropivacaine in lower limb surgery of 50 minutes duration or less is defined as 7.6 mg and 11.4 mg respectively using the traditional dose-response methodology.

5. For spinal anaesthesia in lower limb surgery, the ED50s are 5.5mg for bupivacaine (95% CI: 4.90-6.10mg), 5.68mg for levobupivacaine (95% CI: 4.92-6.44mg), and 8.41mg for ropivacaine (95% CI: 7.15-9.67mg) as defined by up-down sequential allocation method. Ropivacaine is less potent than levobupivacaine and bupivacaine, whereas the potency is similar between levobupivacaine and bupivacaine in spinal anaesthesia for lower surgery as defined by median local anaesthetic doses.

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APPENDICES

APPENDIX A

LETTERS OF APPROVAL FROM ETHICS COMMITTEE FOR ALL STUDIES

APPENDIX B

RAW DATA FROM ALL STUDIES

APPENDIX A

LETTERS OF APPROVAL FOR ALL STUDIES FROM THE CLINICAL RESEARCH ETHICS COMMITTEE OF KWONG WAH HOSPITAL OR KOWLOON WEST CLUSTER, HOSPITAL AUTHORITY, HONG KONG.

A1 CHAPTER V LEVOBUPIVACAINE VERSUS RACEMIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

A2 CHAPTER VI THE USE OF LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

A3 CHAPTER VII RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

A4 CHAPTER VIII SPINAL ROPIVACAINE FOR LOWER LIMB SURGERY: A DOSE-RESPONSE STUDY

A5 CHAPTER IX THE MEDIAN EFFECTIVE DOSE OF BUPIVACAINE, LEVOBUPIVACAINE AND ROPIVACAINE AFTER INTRATHECAL INJECTION IN LOWER LIMB SURGERY

廣華醫院外科部
KWONG WAH HOSPITAL
DEPARTMENT OF SURGERY

17 April 2002

Dr Y Y Lo
Consultant
Department of Anaesthesiology & OIS
Kwong Wah Hospital
Kowloon

Dear Dr Lo

Re: EC Proposal 02016 –
Levobupivacaine versus Racemic Bupivacaine for Spinal Anaesthesia in elderly patients for urological operation

I write to inform you that approval has been given for you to proceed with the research project entitled "Levobupivacaine versus Racemic Bupivacaine for Spinal Anaesthesia in elderly patients for urological operation" in accordance with the protocol submitted.

Yours sincerely

Dr Yip Wai Chan
Chairman
Ethics Committee KWH

Y w

KWONG WAH HOSPITAL
DEPARTMENT OF SURGERY

25 Waterloo Road, Kowloon, Hong Kong
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25 October 2002

Dr Y Y Lee
Consultant
Department of Anaesthesiology & OTS
Kwong Wah Hospital
Kowloon

Dear Dr Lee

Re: EC Proposal 02046 –
"The use of Levobupivacaine and Fentanyl for spinal anaesthesia in elderly patients for urological operation"

I write to inform you that approval has been given for you to proceed with the research project entitled "The use of Levobupivacaine and Fentanyl for spinal anaesthesia in elderly patients for urological operation" in accordance with the protocol submitted.

Yours sincerely

Dr Yip Wai Chun
Chairman
Ethics Committee, KWH

YWC/cw

HOSPITAL AUTHORITY

Our Ref. : (in KWC GR/KHC ER 03-025 17 November 2003

Dr H H Yiu
Consultant (Anaesthesiology and OPS)
Kwong Wah Hospital

Dear Dr YIU

KWC CREC Reference: KW ER/03-025
Spinal Anaesthesia: A Comparison of Isobaric 0.5% Ropivacaine with 0.5% Bupivacaine Plus 15 µg Fentanyl for Urological Surgery

I am pleased to inform you that the above recent-submitted research application has been approved by the Clinical Research Ethics Committee of the Kowloon West Cluster (KWC CREC) on 12 November 2003 through Expedited Review process.

You are required to adhere to the following conditions:

1. Do not deviate from or make changes to the research protocol without prior written approval of the KWC CREC except when it is necessary to eliminate immediate hazards to research subjects or when the changes involve only logistical or administrative aspects of the research.
2. Report to the KWC CREC in the event of the following:
   a) change in research protocol or consent documents;
   b) unanticipated problems or serious adverse events; and
   c) new information that may adversely influence the risk-benefit ratio or affect the subject's willingness to continue participation in the research.
3. Report research progress to the KWC CREC at 12 monthly intervals or upon research closure if the research duration is less than 12 months.
4. Send a copy of your final report to the KWC CREC for record upon research completion.

Please quote the KWC CREC Reference in all your future correspondences with the KWC CREC including submission of progress reports and requesting for amendments to the research protocol. If you have any enquiry please feel free to contact Mr Linus HU, Secretary of the KWC CREC on 2990 1880. Thank you for your attention.

Yours sincerely,

(Dr Lawrence TANG)
Chairperson
Clinical Research Ethics Committee
Kowloon West Cluster

c.c. Hospital Chief Executive, KWH

醫院管理局
HOSPITAL AUTHORITY

Quality Patient-Centred Care Through Teamwork

Our Ref : ( ) in KWC/GR/REC/EX/05-021

14 April 2005

Dr LEE Ying-yin
Consultant
Department of Anaesthesiology & OTS
Kwong Wah Hospital

Dear Dr LEE,

KWC-CREC Ref. : KW/EX/05-021

Spinal Anaesthesia for Lower Limb Surgery: Dose-response Study of Ropivacaine

The Kowloon West Cluster Clinical Research Ethics Committee (KWC-CREC) is authorized by the Cluster Chief Executive to review and monitor clinical research. It serves to ensure that research complies with the Declaration of Helsinki, local regulations and HA policy. It has the authority to approve, require modifications in (to secure approval), or disapprove research. This Committee has power to terminate / suspend a research at any time if there is evidence to indicate that the above principles and requirements have been violated.

KWC-CREC has reviewed/approved, as appropriate, your research application on 12 April 2005 by expedited review, and reached the following decision basing on the documents submitted as shown below. You are required to adhere to the attached conditions.

Study site(s)	Kwong Wah Hospital
Document(s) approved	I Protocol Review Application Form II Study Protocol III. Subject Information Sheet & Consent Form-English and Chinese versions, (Version as enclosed in PI's email dated 16/3/2005)
Document(s) reviewed	I. Brief CV of Principal Investigator
Conditions	1 Do not deviate from, or make changes to the study protocol without prior written KWC-CREC approval, except when it is necessary to eliminate immediate hazards to research subjects or when the change involves only logistical or administrative issues. 2. Apply a clinical trial certificate from department of health if indicated 3 Report the followings to KWC-CREC* : (i) study protocol or consent document change, (ii) serious adverse event, (iii) study progress (iv) new information that may be relevant to a subject's willingness to continue participation in the study. 4. Report first study progress to KWC-CREC at 12-monthly intervals until study closure. [*Forms are available from KWC-CREC intranet webpage]

Please quote the CREC Reference ***(KW/EX/05-021)*** in all your future correspondences with the KWC-CREC, including submission of progress reports and requesting for amendments to the research protocol.

If you have any enquiry, please feel free to contact Miss Dawn LEUNG on 2990 1039. Thank you for your attention.

Yours sincerely,

(Dr TSAO Yen-chow)
Chairperson
Clinical Research Ethics Committee
Kowloon West Cluster

c.c COS(Anaes & OTS), KWH

Secretariat of Clinical Research Ethics Committee, Kowloon West Cluster
Room 133, Block J, Princess Margaret Hospital, 1 Lai Chi Kok, Kowloon, Hong Kong Tel (852) 2990 1039 Fax (852) 2990 1059

醫院管理局
HOSPITAL AUTHORITY

群策研力爲病人・優質醫護兩吉林
Quality Patient-Centred Care Through Teamwork

5 January 2006

Dr LEE Ying-yin
Consultant
Department of Anaesthesiology & OTS
Kwong Wah Hospital

Dear Dr LEE,

KWC-CREC Reference : KW/FR/05-025

Minimum local anaesthetic dose for intrathecal anaesthesia: a randomized comparison between levobupivacaine, ropivacaine and bupivacaine

The Kowloon West Cluster Clinical Research Ethics Committee (KWC-CREC) is authorized by the Cluster Chief Executive to review and monitor clinical research. It serves to ensure that research complies with the Declaration of Helsinki, local regulations and HA policy. It has the authority to approve, require modifications in (to secure approval), or disapprove research. This Committee has power to terminate / suspend a research at any time if there is evidence to indicate that the above principles and requirements have been violated.

KWC-CREC has reviewed / approved, as appropriate, your research application on 21 December 2005 by full review process, and reached the following decision basing on the documents submitted as shown below. You are required to adhere to the attached conditions.

Study site(s)	Kwong Wah Hospital
Document(s) approved	I. Clinical Research Ethics Approval Application Form II. Protocol III. Subject Information Sheet and Consent Form (Chinese and English Versions)
Document(s) reviewed	I. CV of Investigator
Conditions	1. Do not deviate from, or make changes to the study protocol without prior written REC approval, except when it is necessary to eliminate immediate hazards to research subjects or when the change involves only logistical or administrative issues. 2. Apply a clinical trial certificate from Department of Health if indicated. 3. Report the followings to KWC-CREC* : (i) study protocol or consent document change, (ii) serious adverse event, (iii) study progress (iv) new information that may be relevant to a subject's willingness to continue participation in the study. 4. Report first study progress to KWC-CREC at 12-monthly intervals until study closure. [* Forms are available from KWC-CREC intranet webpage]

Please quote the CREC Reference (**KW/FR/05-025**) in all your future correspondences with the KWC-CREC, including submission of progress reports and requesting for amendments to the research protocol.

If you have any inquiry, please feel free to contact Mr Lewis LI, Secretary of the KWC-CREC, on 2990 3749. Thank you for your attention.

Yours sincerely,

(Dr TSAO Yen-chow)
Chairperson
Clinical Research Ethics Committee
Kowloon West Cluster

c.c. COS(Anaes & OTS), KWH

APPENDIX B

RAW DATA FROM ALL STUDIES

B1 CHAPTER V LEVOBUPIVACAINE VERSUS RACEMIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

B2 CHAPTER VI THE USE OF LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

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B4 CHAPTER VIII SPINAL ROPIVACAINE FOR LOWER LIMB SURGERY: A DOSE-RESPONSE STUDY

B5 CHAPTER IX THE MEDIAN EFFECTIVE DOSE OF BUPIVACAINE, LEVOBUPIVACAINE AND ROPIVACAINE AFTER INTRATHECAL INJECTION IN LOWER LIMB SURGERY

CODING FOR RAW DATA IN 'SENSORY BLOCK' AND 'MOTOR BLOCK'

MOTOR BLOCK IN MODIFIED BROMAGE SCALE
0 = no paralysis, able to flex hip, knee and ankle
1 = able to flex knee, unable to raise extended leg
2 = able to flex ankle, unable to flex knee
3 = unable to flex ankle, knee and hip

Sensory block
1–12 = 1st–12th thoracic dermatome respectively
13–17 = 1st–5th lumbar dermatome respectively
18 = No detectable sensory block

APPENDIX B1

LEVOBUPIVACAINE VERSUS RACEMIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No.	GROUP: 1=bupivacaine, 2=levobupivacaine	Age (year)	Body weight (Kg)	Height (cm)	ASA	Operation: 1=TURP, 2=TURBT	Baseline HR (bpm)	HR at 5 min (bpm)	HR at 10 min (bpm)	Baseline systolic BP (mmHg)	Systolic BP at 5 min (mmhg)	Systolic BP at 10 min (mmHg)
1	1	71	65	167	2	1	54	50	53	186	189	199
2	1	58	64	163	1	2	68	67	67	105	90	107
3	1	69	57	173	2	1	90	79	77	168	147	145
4	1	65	52	177	1	1	54	50	54	146	144	142
5	1	57	65	159	1	1	90	104	105	161	173	165
6	1	72	52	163	2	2	87	82	70	118	121	125
7	1	59	46	159	1	2	63	56	53	100	103	101
8	1	72	80	168	2	1	62	61	62	112	131	123
9	1	68	46	176	2	1	82	82	86	170	178	159
10	1	70	60	159	2	1	74	67	63	180	185	167
11	1	68	67	164	3	1	79	77	77	122	130	122
12	1	68	55	159	2	1	80	85	87	137	144	153
13	1	70	57	166	2	1	68	72	77	139	140	131
14	1	68	64	169	1	1	65	67	58	165	147	138
15	1	75	52	165	3	1	88	80	76	145	151	151
16	1	67	55	169	2	1	55	59	54	162	156	151
17	1	66	50	167	2	2	63	63	62	144	133	141
18	1	59	70	165	1	1	60	113	82	119	119	103
19	1	68	62	164	2	1	80	82	92	130	122	120
20	1	65	59	160	3	1	66	75	73	140	145	120
21	1	66	53	157	1	1	60	60	61	102	113	108
22	1	72	54	159	2	1	79	88	69	133	103	92
23	1	73	60	166	2	1	79	78	75	154	155	147
24	1	73	64	158	2	1	63	60	57	131	153	154
25	1	74	55	164	2	1	85	79	77	138	143	129

APPENDIX B1

LEVOBUPIVACAINE VERSUS RACEMIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No.	GROUP: 1=bupivacaine, 2=levobupivacaine	Age (year)	Body weight (Kg)	Height (cm)	ASA	Operation: 1=TURP, 2=TURBT	Baseline HR (bpm)	HR at 5 min (bpm)	HR at 10 min (bpm)	Baseline systolic BP (mmHg)	Systolic BP at 5 min (mmhg)	Systolic BP at 10 min (mmHg)
26	1	67	55	172	1	1	72	74	67	130	132	128
27	2	69	64	167	1	1	88	99	90	145	147	131
28	2	63	66	168	2	1	62	70	66	175	150	145
29	2	75	75	168	3	2	60	62	58	156	149	124
30	2	64	55	170	2	2	84	107	97	144	158	142
31	2	71	51	170	2	1	76	78	74	159	162	150
32	2	70	56	165	1	1	58	53	60	138	136	133
33	2	75	55	169	2	1	85	82	76	183	158	166
34	2	64	66	155	2	1	60	52	66	184	180	177
35	2	70	64	162	2	1	55	55	56	145	125	129
36	2	60	80	165	1	1	72	94	80	163	157	154
37	2	74	64	167	2	2	62	63	69	137	116	112
38	2	72	52	162	2	2	66	55	60	156	139	150
39	2	56	45	160	2	2	88	88	83	100	109	107
40	2	69	66	170	1	1	95	97	101	155	148	146
41	2	72	65	163	2	1	60	61	59	158	193	166
42	2	59	63	158	2	1	84	79	80	133	152	122
43	2	69	72	162	2	2	78	78	87	159	132	139
44	2	60	58	160	2	1	69	77	76	129	119	127
45	2	64	59	170	1	1	64	65	63	125	143	137
46	2	68	46	165	1	1	88	84	87	131	132	127
47	2	73	75	167	3	1	53	47	48	215	189	194
48	2	67	55	160	2	1	87	100	100	146	132	127
49	2	62	57	155	1	1	70	73	73	190	179	124

APPENDIX B1

LEVOBUPIVACAINE VERSUS RACEMIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No.	Time to achieve sensory block of T10 (min)	Highest level of sensory block achieved: thoracic level	Motor block at the start of operation (Bromage score)	Motor block at the end of operation (Bromage score)	Lowest systolic BP (mmHg)	Side-effects: 1= nausea & vomiting , 2=shivering	Hypotension
1	5.0	9	3	3	184	0	No
2	5.0	6	3	3	81	0	Yes
3	10.0	9	3	3	133	0	No
4	10.0	9	2	3	138	0	No
5	5.0	6	3	3	127	2	No
6	2.5	6	3	3	110	0	No
7	5.0	4	3	3	101	0	No
8	10.0	10	3	3	107	0	No
9	15.0	5	3	3	128	1	No
10	10.0	8	3	3	149	0	No
11	10.0	9	3	3	104	0	No
12	5.0	5	3	3	132	0	No
13	5.0	8	3	3	112	0	No
14	5.0	3	3	3	122	0	No
15	15.0	9	3	3	104	0	No
16	15.0	9	3	3	145	0	No
17	7.5	6	3	3	107	0	No
18	10.0	8	3	3	103	0	No
19	5.0	8	3	3	112	0	No
20	5.0	6	3	3	120	0	No
21	10.0	7	2	2	108	0	No
22	10.0	4	3	3	92	0	Yes
23	10.0	9	3	3	122	0	No
24	12.5	9	3	3	135	0	No
25	5.0	8	3	3	119	0	No

APPENDIX B1

LEVOBUPIVACAINE VERSUS RACEMIC BUPIVACAINE IN SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No.	Time to achieve sensory block of T10 (min)	Highest level of sensory block achieved: thoracic level	Motor block at the start of operation (Bromage score)	Motor block at the end of operation (Bromage score)	Lowest systolic BP (mmHg)	Side-effects: 1= nausea & vomiting , 2=shivering	Hypotension
26	7.5	6	3	3	104	0	No
27	15.0	8	1	3	102	2	No
28	15.0	10	3	3	120	0	No
29	5.0	7	3	3	127	0	No
30	2.5	6	3	3	138	2	No
31	12.5	9	3	3	121	0	No
32	15.0	8	2	3	108	0	No
33	15.0	10	3	3	155	0	No
34	12.5	6	2	3	140	0	No
35	5.0	10	3	3	120	0	No
36	2.5	3	3	3	108	0	No
37	15.0	10	3	3	100	0	No
38	5.0	6	3	3	139	0	No
39	2.5	6	0	0	102	0	No
40	2.5	6	3	3	130	0	No
41	15.0	7	3	3	158	0	No
42	2.5	4	3	3	113	0	No
43	15.0	5	3	3	127	0	No
44	15.0	5	3	3	110	0	No
45	12.5	7	0	0	125	0	No
46	12.5	6	3	3	119	0	No
47	15.0	8	3	3	131	0	No
48	5.0	7	3	3	124	0	No
49	2.5	4	3	3	124	0	No

APPENDIX B2 LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

No	GROUP: 1=levobupivacaine, 2=levobupivacaine with fentanyl	Age (year)	Body weight (Kg)	Height (year)	ASA	Operation: 1=TURP, 2=TURBT	Baseline HR (bpm)	HR at 5 min (bpm)	HR at 10 min (bpm)
1	1	75	62	165	2	1	71	71	66
2	1	71	55	167	2	2	63	61	63
3	1	73	56	165	2	2	65	60	62
4	1	73	56	166	2	2	102	95	90
5	1	55	55	166	2	1	72	77	74
6	1	62	55	165	2	1	72	62	68
7	1	74	51	166	2	2	73	79	74
8	1	54	64	170	1	1	70	60	76
9	1	69	71	165	2	1	75	76	74
10	1	71	58	157	1	1	54	53	51
11	1	67	76	170	2	1	59	63	64
12	1	59	76	157	2	1	72	63	65
13	1	68	78	160	2	1	72	104	94
14	1	71	64	156	2	2	77	79	75
15	1	70	51	166	2	2	73	74	76
16	1	66	70	167	1	1	74	86	93
17	1	63	60	166	1	1	105	115	105
18	1	66	57	160	1	1	78	94	89
19	1	73	73	170	2	1	72	76	73
20	1	66	61	165	2	1	66	62	64
21	1	71	62	171	1	1	63	61	61
22	1	68	55	150	1	1	70	71	73
23	1	71	70	165	2	2	69	80	77
24	1	70	52	154	2	2	71	78	74
25	1	66	70	153	3	1	65	80	73

APPENDIX B2 LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

No	GROUP: 1=levobupivacaine, 2=levobupivacaine with fentanyl	Age (year)	Body weight (Kg)	Height (year)	ASA	Operation: 1=TURP, 2=TURBT	Baseline HR (bpm)	HR at 5 min (bpm)	HR at 10 min (bpm)
26	2	75	69	163	1	1	79	70	65
27	2	64	46	160	2	1	71	73	80
28	2	75	63	160	2	2	63	59	53
29	2	70	59	165	3	1	74	79	70
30	2	75	62	156	1	1	56	57	57
31	2	74	55	168	1	1	79	74	66
32	2	73	60	160	2	2	100	106	110
33	2	72	73	163	1	1	71	81	83
34	2	69	79	177	1	2	65	70	80
35	2	69	66	153	2	2	81	80	79
36	2	68	63	161	2	1	62	63	68
37	2	71	80	165	2	1	89	86	73
38	2	57	52	174	2	1	90	90	89
39	2	70	73	172	2	2	66	97	75
40	2	69	63	157	2	1	80	72	76
41	2	60	67	175	2	1	70	70	75
42	2	73	73	161	2	1	61	60	64
43	2	70	66	168	2	1	64	71	71
44	2	72	59	169	1	1	73	72	72
45	2	66	79	175	2	1	75	85	86
46	2	70	58	160	2	1	80	75	82
47	2	72	55	153	2	2	82	78	81
48	2	61	66	171	1	2	77	82	84
49	2	70	77	175	1	2	57	70	62
50	2	65	70	165	1	2	56	56	60

APPENDIX B2 LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

No	Baseline systolic BP (mm Hg)	Systolic BP at 5 min (mm Hg)	Systolic BP at 10 min (mmHg)	Baseline mean BP (mmHg)	Mean BP at 5 min (mmHg)	Mean BP at 10 min (mm Hg)
1	151	135	130	105	84	89
2	135	142	148	92	104	106
3	136	140	120	94	78	85
4	176	181	170	116	116	114
5	120	136	133	85	105	107
6	174	175	162	119	122	114
7	140	144	122	94	102	101
8	130	124	140	109	125	117
9	144	150	145	118	110	102
10	175	135	140	121	110	103
11	162	147	142	131	115	112
12	159	140	107	120	76	78
13	147	82	91	103	69	70
14	160	167	149	123	120	116
15	201	190	186	126	128	120
16	148	150	150	113	112	115
17	145	146	136	104	101	101
18	126	140	120	95	90	94
19	145	141	140	97	97	99
20	144	130	126	106	81	84
21	150	127	125	111	85	91
22	124	108	115	89	88	88
23	144	150	136	118	110	105
24	158	152	131	115	98	80
25	158	100	118	121	94	87

APPENDIX B2 LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

No	Baseline systolic BP (mm Hg)	Systolic BP at 5 min (mm Hg)	Systolic BP at 10 min (mmHg)	Baseline mean BP (mmHg)	Mean BP at 5 min (mmHg)	Mean BP at 10 min (mm Hg)
26	134	123	116	88	104	88
27	154	143	133	119	105	84
28	147	148	141	121	89	90
29	178	180	186	128	129	134
30	111	114	115	99	87	80
31	148	134	127	115	92	88
32	123	114	124	100	75	104
33	185	156	147	147	111	122
34	157	142	143	120	117	110
35	154	101	108	124	76	90
36	121	121	125	100	84	103
37	154	132	93	124	100	71
38	127	125	125	87	94	89
39	147	137	110	88	96	85
40	150	151	150	116	110	110
41	147	138	133	112	110	105
42	151	148	146	107	108	106
43	175	167	150	127	115	110
44	150	151	143	101	109	109
45	152	140	146	105	97	111
46	160	156	148	102	113	107
47	185	143	134	120	99	90
48	153	162	162	100	120	117
49	144	137	136	124	111	100
50	124	116	105	101	85	82

APPENDIX B2 LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

No	Time to achieve sensory block of T10	Highest level of sensory block (thoracic level)	Motor block at the start of operation (Bromage score)	Motor block at the end of operation (Bromage score)	Time interval from intrathecal injection to the end of surgery (min)
1	2.5	5	3	3	60
2	5.0	6	3	3	43
3	5.0	10	2	3	26
4	15.0	10	3	3	43
5	15.0	9	3	3	29
6	15.0	10	2	2	54
7	5.0	5	3	3	44
8	2.5	6	3	3	53
9	5.0	10	3	3	30
10	15.0	10	2	3	47
11	5.0	9	3	3	28
12	5.0	3	3	3	70
13	7.5	4	3	3	100
14	5.0	9	3	3	63
15	10.0	6	3	3	32
16	7.5	8	3	3	73
17	15.0	10	2	3	67
18	5.0	4	3	3	78
19	15.0	5	3	3	73
20	5.0	7	3	3	76
21	5.0	6	3	3	56
22	5.0	6	3	3	124
23	7.5	10	3	3	23
24	5.0	5	3	3	31
25	12.5	6	3	3	37

APPENDIX B2 LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

No	Time to achieve sensory block of T10	Highest level of sensory block (thoracic level)	Motor block at the start of operation (Bromage score)	Motor block at the end of operation (Bromage score)	Time interval from intrathecal injection to the end of surgery (min)
26	2.5	5	3	3	75
27	5.0	6	2	3	55
28	5.0	6	3	3	25
29	10.0	8	3	3	97
30	7.5	6	3	3	105
31	10.0	6	3	3	124
32	5.0	7	3	3	24
33	10.0	10	2	2	116
34	7.5	7	2	3	25
35	2.5	8	3	3	21
36	10.0	8	3	3	95
37	5.0	4	3	3	87
38	10.0	8	2	0	61
39	5.0	6	3	3	33
40	5.0	7	2	3	58
41	10.0	6	2	2	59
42	12.5	10	3	3	55
43	5.0	8	3	3	97
44	10.0	8	3	3	72
45	10.0	9	3	3	60
46	10.0	7	3	3	58
47	7.5	6	3	3	22
48	5.0	7	3	3	40
49	10.0	9	3	3	23
50	5.0	6	0	2	30

APPENDIX B2 LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

No	Lowest mean BP (mm Hg)	Side-effect: 0=no, 2=shivering	Maximunm motor block (Bromage score)	Hypotension
1	72	0	3	No
2	92	0	3	No
3	72	0	3	No
4	99	0	3	No
5	94	0	3	No
6	102	0	2	No
7	89	0	3	No
8	71	0	3	No
9	99	0	3	No
10	92	0	3	No
11	107	0	3	No
12	72	2	3	No
13	50	2	3	Yes
14	102	0	3	No
15	105	0	3	No
16	100	0	3	No
17	98	0	3	No
18	88	0	3	No
19	91	0	3	No
20	73	0	3	No
21	72	0	3	No
22	76	0	3	No
23	90	0	3	No
24	76	0	3	No
25	76	2	3	No

APPENDIX B2 LEVOBUPIVACAINE AND FENTANYL FOR SPINAL ANAESTHESIA: A RANDOMIZED TRIAL

No	Lowest mean BP (mm Hg)	Side-effect: 0=no, 2=shivering	Maximunm motor block (Bromage score)	Hypotension
26	88	0	3	No
27	70	0	3	No
28	88	0	3	No
29	77	0	3	No
30	75	0	3	No
31	85	0	3	No
32	75	0	3	No
33	104	0	2	No
34	106	0	3	No
35	76	0	3	No
36	77	0	3	No
37	74	0	3	Yes
38	83	0	2	No
39	63	0	3	Yes
40	88	0	3	No
41	98	0	2	No
42	93	0	3	No
43	85	0	3	No
44	91	0	3	No
45	84	0	3	No
46	104	0	3	No
47	79	0	3	Yes
48	86	0	3	No
49	97	0	3	No
50	82	0	2	No

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Group: 1=ropivacaine, 2=bupivacaine	Age (year)	Sex: 1=male, 0=female	Height (cm)	ASA
1	1	54	1	158	1
2	1	74	1	163	2
3	1	61	0	170	1
4	1	75	1	180	2
5	1	72	1	165	3
6	1	75	1	158	3
7	1	53	1	175	2
8	1	78	1	161	1
9	1	69	1	165	2
10	1	74	1	168	2
11	1	70	1	166	2
12	1	64	1	157	2
13	1	54	1	159	1
14	1	74	1	165	2
15	1	66	1	168	1
16	1	73	0	149	1
17	2	70	1	155	1

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Group: 1=ropivacaine, 2=bupivacaine	Age (year)	Sex: 1=male, 0=female	Height (cm)	ASA
18	2	74	1	163	3
19	2	72	1	173	3
20	2	62	1	164	1
21	2	69	1	171	1
22	2	75	1	170	2
23	2	73	0	149	1
24	2	71	1	159	1
25	2	75	1	159	2
26	2	64	1	160	2
27	2	70	1	165	3
28	2	52	1	173	1
29	2	72	1	152	2
30	2	75	1	156	3
31	2	70	1	163	1
32	2	74	0	146	1
33	2	71	1	170	1

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Baseline HR (bpm)	HR at 5 min (bpm)	HR at 10 min (bpm)	HR at 15 min (bpm)	Baseline systolic BP (mm Hg)	Systolic BP at 5 min (mm Hg)	Systolic BP at 10 min (mm Hg)	Systolic BP at 15 min (mm Hg)
1	97	121	124	109	148	152	121	126
2	105	107	110	112	160	149	139	154
3	91	66	68	72	168	150	148	148
4	53	55	54	52	178	146	143	147
5	52	58	51	51	171	140	114	142
6	85	88	89	88	147	161	155	140
7	90	87	83	95	171	159	162	164
8	79	67	78	71	164	159	152	157
9	86	78	81	84	154	163	167	166
10	60	66	67	60	140	143	140	137
11	92	99	100	107	167	143	150	150
12	86	79	88	90	140	128	132	137
13	77	98	99	96	136	142	141	159
14	67	86	76	69	147	107	102	92
15	94	88	65	73	153	122	104	117
16	61	60	59	60	128	129	116	122
17	92	95	81	79	122	96	114	105

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Baseline HR (bpm)	HR at 5 min (bpm)	HR at 10 min (bpm)	HR at 15 min (bpm)	Baseline systolic BP (mm Hg)	Systolic BP at 5 min (mm Hg)	Systolic BP at 10 min (mm Hg)	Systolic BP at 15 min (mm Hg)
18	82	77	77	84	116	136	138	144
19	61	66	61	60	160	159	158	155
20	76	80	85	76	151	175	164	163
21	95	88	92	98	131	140	139	141
22	70	76	72	68	170	138	119	134
23	64	63	60	60	153	148	144	137
24	68	78	88	74	141	140	131	125
25	81	98	98	94	148	170	115	145
26	100	107	107	107	147	164	149	155
27	107	102	103	100	182	185	185	190
28	67	66	64	62	132	118	123	115
29	75	72	75	75	169	157	149	152
30	78	78	79	61	118	151	130	149
31	54	59	63	61	137	140	109	127
32	80	74	75	73	147	135	130	134
33	87	98	100	102	148	147	169	162

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Time to achieve sensory block of T10	Highest level of sensory block	Highest level of motor block (Bromage score)	Sensory block at 2.5 min	Sensory block at 5 min	Sensory block at 7.5 min	Sensory block at 10 min	Sensory block at 12.5 min
1	2.5	5	3	8	5	5	5	5
2	12.5	6	3	18	11	11	11	10
3	7.5	5	3	11	11	10	8	8
4	7.5	5	0	18	12	7	7	6
5	5.0	4	3	12	10	5	5	4
6	5.0	8	3	18	8	8	8	8
7	10.0	6	3	13	12	11	8	7
8	5.0	6	3	14	10	7	7	7
9	7.5	6	3	13	11	10	10	10
10	2.5	4	3	10	10	6	6	5
11	2.5	4	3	8	8	6	4	4
12	10.0	8	3	13	12	11	10	10
13	10.0	5	3	16	12	12	10	8
14	2.5	4	3	10	7	5	4	4
15	2.5	4	3	7	5	5	5	4
16	5.0	5	3	12	9	9	9	7
17	5.0	5	3	11	8	8	5	5

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Time to achieve sensory block of T10	Highest level of sensory block	Highest level of motor block (Bromage score)	Sensory block at 2.5 min	Sensory block at 5 min	Sensory block at 7.5 min	Sensory block at 10 min	Sensory block at 12.5 min
18	7.5	5	3	12	11	10	8	7
19	7.5	9	3	18	11	10	10	10
20	7.5	7	3	12	11	10	8	8
21	5.0	6	3	12	8	8	7	6
22	2.5	3	3	8	5	4	3	3
23	5.0	6	3	12	10	8	7	7
24	5.0	4	3	11	7	6	5	5
25	2.5	4	3	10	8	5	5	4
26	5.0	5	3	11	10	7	7	6
27	7.5	5	3	12	11	9	5	5
28	5.0	5	3	11	7	7	7	5
29	5.0	6	3	11	9	7	7	7
30	7.5	6	3	12	11	7	7	6
31	10.0	3	3	13	11	11	10	6
32	2.5	3	3	5	5	5	4	4
33	5.0	5	3	11	10	8	8	7

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Sensory block at 15 min	Senory block at 105 min	Sensory block at 120 min	Sensory block at 135 min	Sensory block at 150 min	Sensory block at 165 min	Sensory block at 180 min	Sensory block at 195 min
1	5	6	10	16	18	18	18	18
2	10	10	10	10	10	10	10	10
3	8	6	6	6	6	7	10	11
4	5	6	7	7	12	12	12	14
5	4	5	5	5	5	6	6	6
6	8	8	8	8	8	9	10	11
7	6	9	9	10	12	18	18	18
8	6	9	9	10	10	10	11	12
9	10	7	7	10	10	18	18	18
10	5	5	6	7	7	8	8	9
11	4	6	7	8	8	9	11	11
12	10	12	13	14	15	15	18	18
13	8	11	18	18	18	18	18	18
14	4	6	10	10	13	14	18	18
15	4	4	4	4	4	5	8	10
16	6	7	9	10	10	11	11	12
17	5	7	8	9	9	9	9	10

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Sensory block at 15 min	Senory block at 105 min	Sensory block at 120 min	Sensory block at 135 min	Sensory block at 150 min	Sensory block at 165 min	Sensory block at 180 min	Sensory block at 195 min
18	6	5	6	7	9	9	9	9
19	10	10	10	10	11	11	12	12
20	8	11	11	12	12	12	12	13
21	6	9	10	11	11	12	13	13
22	3	8	8	8	9	9	13	18
23	7	7	7	7	8	8	10	11
24	4	5	6	8	9	9	11	12
25	4	5	9	9	9	11	12	13
26	5	8	10	10	10	11	12	14
27	5	6	6	8	10	11	13	13
28	5	5	6	7	9	9	10	10
29	7	6	6	6	6	8	10	12
30	6	7	9	10	10	10	10	11
31	3	8	8	8	10	13	13	13
32	3	6	6	6	6	7	8	10
33	5	6	6	6	6	7	8	9

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Motor block at 2.5 min	Motor block at 5 min	Motor block at 7.5 min	Motor block at 10 min	Motor block at 12.5 min	Motor block at 15 min	Motor block at 105 min	Motor block at 120 min
1	1	1	1	2	2	2	0	0
2	0	2	3	3	3	3	2	2
3	1	3	3	3	3	3	3	2
4	0	0	0	0	0	0	0	0
5	3	3	3	3	3	3	0	0
6	0	0	0	1	3	3	3	3
7	0	0	0	2	3	3	0	0
8	0	1	1	2	2	2	3	3
9	0	0	0	0	0	0	1	0
10	0	2	3	3	3	3	3	0
11	0	0	2	2	3	3	2	1
12	3	3	3	3	3	3	3	3
13	0	0	1	1	1	2	0	0
14	2	2	3	3	3	3	1	0
15	3	3	3	3	3	3	3	3
16	2	2	3	3	3	3	2	1
17	3	3	3	3	3	3	3	3

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Motor block at 2.5 min	Motor block at 5 min	Motor block at 7.5 min	Motor block at 10 min	Motor block at 12.5 min	Motor block at 15 min	Motor block at 105 min	Motor block at 120 min
18	0	3	3	3	3	3	3	3
19	0	2	3	3	3	3	1	1
20	1	2	3	3	3	3	3	3
21	1	3	3	3	3	3	3	3
22	0	2	2	2	3	3	1	0
23	3	3	3	3	3	3	3	3
24	0	3	3	3	3	3	3	2
25	2	2	3	3	3	3	3	3
26	1	2	3	3	3	3	3	3
27	0	1	3	3	3	3	2	2
28	0	0	3	3	3	3	3	3
29	0	2	2	2	2	2	3	3
30	0	0	2	2	3	3	3	3
31	0	0	0	3	3	3	3	3
32	3	3	3	3	3	3	3	3
33	0	0	2	2	2	3	3	3

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Motor block at 135 min	Motor block at 150 min	Motor block at 165 min	Motor block at 180 min	Motor block at 195 min	Onset time of motor block (min)
1	0	0	0	0	0	2.5
2	2	1	1	1	1	5.0
3	2	2	1	0	0	2.5
4	0	0	0	0	0	105.0
5	0	0	0	0	0	2.5
6	2	2	1	0	0	10.0
7	0	0	0	0	0	10.0
8	3	3	3	2	2	5.0
9	0	0	0	0	0	27.0
10	0	0	0	0	0	5.0
11	0	0	0	0	0	7.5
12	0	0	0	0	0	2.5
13	0	0	0	0	0	7.5
14	0	0	0	0	0	2.5
15	2	0	0	0	0	2.5
16	0	0	0	0	0	2.5
17	3	3	3	2	2	2.5

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Motor block at 135 min	Motor block at 150 min	Motor block at 165 min	Motor block at 180 min	Motor block at 195 min	Onset time of motor block (min)
18	3	3	3	3	2	5.0
19	0	0	0	0	0	5.0
20	3	3	3	1	0	2.5
21	3	2	2	1	0	2.5
22	0	0	0	0	0	5.0
23	3	3	2	1	0	2.5
24	1	0	0	0	0	5.0
25	3	2	1	0	0	2.5
26	3	3	2	2	1	2.5
27	0	0	0	0	0	5.0
28	3	3	3	3	3	7.5
29	3	3	3	3	3	5.0
30	3	3	3	3	2	7.5
31	3	3	3	3	3	10.0
32	3	3	2	2	0	2.5
33	3	3	3	2	3	7.5

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Duration of opertion (min)	Hypotension : 1=yes, 0=no	Time to regression of sensory block to T10 (min)	Duration of complete motor block (min)	Duration of motor block (min)
1	9	0	126	34	66
2	38	0	245	60	215
3	20	0	182	112	175
4	100	0	145	0	0
5	62	0	250	82	90
6	58	0	182	122	167
7	43	0	147	60	102
8	43	0	168	168	288
9	12	0	156	99	118
10	71	0	241	108	120
11	50	0	173	93	135
12	16	0	96	126	135
13	13	0	100	70	85
14	29	1	140	80	110
15	72	0	221	131	146
16	8	0	160	91	132
17	83	0	218	173	233

APPENDIX B3 RANDOMIZED DOUBLE-BLIND COMPARISON OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL FOR SPINAL ANAESTHESIA FOR UROLOGICAL SURGERY

No	Duration of opertion (min)	Hypotension : 1=yes, 0=no	Time to regression of sensory block to T10 (min)	Duration of complete motor block (min)	Duration of motor block (min)
18	50	0	220	185	235
19	74	0	145	92	125
20	19	0	95	170	185
21	27	0	128	143	187
22	55	0	169	79	109
23	19	0	189	159	189
24	65	0	174	109	138
25	85	0	160	145	175
26	59	0	164	164	224
27	10	0	154	94	125
28	42	0	231	261	276
29	100	0	195	197	285
30	101	0	195	181	225
31	42	0	154	214	229
32	54	0	200	155	185
33	85	0	265	175	265

APPENDIX B4 SPINAL ROPIVACAINE FOR LOWER LIMB SURGERY: A DOSE RESPONSE STUDY

No.	GROUP (1=2mg, 2=4mg, 3=7mg, 4=10mg, 5=14mg)	Sex: 1=male, 0=female	Age (year)	Height (cm)	Success: 0=Successful case; 1=Unsuccessful case, inadequate level of block at 20 min; 2=Unsuccessful case, epidural supplementation required in the first 50 min	Tourniquet: 1=applied, 0=not applied	Operation: 1=hip or above knee surgery; 2=knee or above ankle surgery; 3=ankle or foot surgery
1	1	0	76	151	1	0	1
2	1	1	75	175	2	1	3
3	1	0	74	155	1	0	1
4	1	0	82	152	1	0	1
5	1	1	61	161	1	1	3
6	1	1	77	172	2	0	1
7	1	0	76	151	2	1	2
8	1	1	68	170	1	0	1
9	1	1	51	167	1	1	3
10	1	1	62	174	2	0	1
11	1	0	57	175	1	1	2
12	1	1	71	164	1	0	1
13	2	0	68	153	2	0	1
14	2	0	69	150	1	0	1
15	2	0	66	150	1	1	2
16	2	0	58	151	1	1	2
17	2	0	72	165	1	0	1
18	2	0	62	152	1	1	3
19	2	1	54	166	1	1	2
20	2	0	77	157	1	0	1
21	2	1	75	160	1	0	2
22	2	1	45	164	1	0	3
23	2	1	57	160	1	1	3
24	2	1	47	170	1	0	1
25	3	1	59	160	1	0	1
26	3	1	75	175	0	0	3
27	3	0	75	169	1	1	3
28	3	1	51	164	0	1	2
29	3	0	81	151	0	0	1
30	3	0	35	166	1	0	1
31	3	0	48	165	1	0	1

APPENDIX B4 SPINAL ROPIVACAINE FOR LOWER LIMB SURGERY: A DOSE RESPONSE STUDY

No.	GROUP (1=2mg, 2=4mg, 3=7mg, 4=10mg, 5=14mg)	Sex: 1=male, 0=female	Age (year)	Height (cm)	Success: 0=Successful case; 1=Unsuccessful case, inadequate level of block at 20 min; 2=Unsuccessful case, epidural supplementation required in the first 50 min	Tourniquet: 1=applied, 0=not applied	Operation: 1=hip or above knee surgery; 2=knee or above ankle surgery; 3=ankle or foot surgery
32	3	1	68	164	1	0	1
33	3	0	76	153	2	0	1
34	3	0	62	153	0	1	3
35	3	1	58	162	0	1	2
36	3	0	41	164	1	0	1
37	4	0	73	150	0	1	2
38	4	0	79	152	0	0	1
39	4	1	59	159	0	0	1
40	4	0	57	156	0	1	2
41	4	1	70	174	0	0	1
42	4	1	61	157	0	1	2
43	4	1	76	169	1	0	1
44	4	1	52	166	0	1	3
45	4	0	71	167	0	0	1
46	4	0	73	163	0	0	1
47	4	1	61	167	0	1	3
48	4	0	78	173	1	0	1
49	5	1	52	165	0	0	1
50	5	1	60	161	0	0	1
51	5	1	62	163	0	1	2
52	5	0	45	165	0	0	1
53	5	1	50	163	0	0	1
54	5	0	87	153	0	0	1
55	5	0	79	154	0	1	2
56	5	0	68	152	0	1	2
57	5	1	78	150	0	0	1
58	5	0	62	153	0	1	2
59	5	0	63	150	0	0	1
60	5	1	79	169	0	0	3

APPENDIX B4 **SPINAL ROPIVACAINE FOR LOWER LIMB SURGERY: A DOSE RESPONSE STUDY**

No.	Motor block at 2.5 min	Motor block at 5 min	Motor block at 7.5 min	Motor block at 10 min	Motor block at 12.5 min	Motor block at 15 min	Motor block at 17.5 min	Motor block at 20 min
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
6	0	0	0	0	0	1	1	1
7	0	0	1	1	1	1	1	1
8	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0
26	0	0	0	1	1	1	2	2
27	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0
29	1	3	3	3	3	3	3	3
30	0	0	0	0	0	0	0	0
31	0	0	1	1	1	1	1	1

APPENDIX B4 SPINAL ROPIVACAINE FOR LOWER LIMB SURGERY: A DOSE RESPONSE STUDY

No.	Motor block at 2.5 min	Motor block at 5 min	Motor block at 7.5 min	Motor block at 10 min	Motor block at 12.5 min	Motor block at 15 min	Motor block at 17.5 min	Motor block at 20 min
32	0	0	0	0	0	0	0	0
33	0	0	1	1	1	1	1	1
34	0	0	1	1	1	1	1	1
35	0	0	0	0	0	1	1	1
36	0	0	0	0	0	0	0	0
37	0	1	1	3	3	3	3	3
38	1	2	2	2	2	2	3	3
39	0	0	0	0	0	0	0	0
40	0	0	1	2	2	2	2	2
41	0	0	1	1	2	2	2	2
42	0	0	2	2	3	3	3	3
43	0	0	0	0	1	3	3	3
44	0	0	0	0	0	0	2	3
45	0	1	2	2	2	2	2	2
46	1	2	2	2	3	3	3	3
47	0	1	3	3	3	3	3	3
48	0	0	1	3	3	3	3	3
49	2	2	2	2	2	2	3	3
50	1	3	3	3	3	3	3	3
51	0	2	2	3	3	3	3	3
52	0	0	1	1	2	2	3	3
53	2	2	3	3	3	3	3	3
54	2	2	2	2	3	3	3	3
55	1	1	2	3	3	3	3	3
56	0	2	2	3	3	3	3	3
57	0	0	0	1	1	2	3	3
58	0	1	1	2	2	2	3	3
59	2	2	3	3	3	3	3	3
60	0	2	3	3	3	3	3	3

APPENDIX B4 **SPINAL ROPIVACAINE FOR LOWER LIMB SURGERY: A DOSE RESPONSE STUDY**

No.	Sensory block at 2.5 min	Sensory block at 5 min	Sensory block at 7.5 min	Sensory block at 10 min	Sensory block at 12.5 min	Sensory block at 15 min	Sensory block at 17.5 min	Sensory block at 20 min
1	18	18	18	18	18	18	18	18
2	13	13	13	13	12	12	12	12
3	15	15	15	15	14	14	14	14
4	15	15	15	15	15	15	15	15
5	16	16	16	16	16	16	16	16
6	14	12	12	12	10	10	10	10
7	10	10	10	10	10	10	10	10
8	18	16	16	16	16	16	16	16
9	16	16	16	15	15	15	15	15
10	18	18	13	12	10	10	8	8
11	18	16	16	15	15	15	15	15
12	18	18	18	18	18	18	18	18
13	15	15	15	15	12	12	12	12
14	15	15	15	14	14	14	14	14
15	18	18	16	16	15	15	15	15
16	18	16	15	15	14	14	14	14
17	18	18	18	16	15	15	14	13
18	18	15	15	15	14	14	13	13
19	18	18	18	16	16	15	15	15
20	18	18	18	16	16	16	16	15
21	16	16	15	14	14	14	14	14
22	18	18	15	14	14	14	14	14
23	16	16	16	16	15	15	15	15
24	18	16	16	15	15	11	11	11
25	18	18	18	18	18	16	15	15
26	10	10	10	10	10	10	10	10
27	16	15	15	14	14	14	14	14
28	15	13	13	13	13	13	13	12
29	11	11	11	11	10	10	10	10
30	18	18	16	16	16	16	15	15
31	18	18	15	14	14	14	14	13

APPENDIX B4 **SPINAL ROPIVACAINE FOR LOWER LIMB SURGERY: A DOSE RESPONSE STUDY**

No.	Sensory block at 2.5 min	Sensory block at 5 min	Sensory block at 7.5 min	Sensory block at 10 min	Sensory block at 12.5 min	Sensory block at 15 min	Sensory block at 17.5 min	Sensory block at 20 min
32	15	14	13	13	13	13	13	13
33	16	10	10	10	10	9	9	9
34	16	15	15	13	13	13	12	12
35	16	13	13	12	12	10	9	9
36	16	16	16	15	14	14	14	14
37	4	4	4	3	3	3	3	3
38	12	11	6	4	2	2	2	2
39	11	11	11	9	8	7	7	7
40	18	13	11	9	8	8	7	7
41	13	12	10	9	8	8	8	7
42	12	6	4	4	3	3	3	3
43	18	18	15	15	14	14	13	13
44	18	18	16	16	15	14	10	7
45	18	10	5	5	5	4	4	4
46	15	14	10	10	8	8	7	7
47	11	11	10	7	4	4	4	4
48	16	15	14	14	14	14	13	13
49	6	4	3	3	3	3	2	2
50	9	9	7	7	7	7	7	7
51	8	6	6	4	3	3	2	2
52	8	7	7	7	7	7	7	6
53	13	13	13	13	12	12	12	12
54	11	10	10	10	9	9	9	9
55	11	11	11	11	11	10	10	10
56	15	11	10	7	7	6	4	4
57	18	15	14	12	11	8	5	5
58	16	15	11	9	8	8	8	7
59	11	8	5	5	4	4	3	3
60	12	11	10	8	8	7	6	5

APPENDIX B5 **THE MEDIAN EFFECTIVE DOSE OF BUPIVACAINE, LEVOBUPIVACAINE, AND ROPIVACAINE AFTER INTRATHECAL INJECTION IN LOWER LIMB SURGERY**

No	Age (year)	Height (cm)	Sex: 1=male, 0=female	Group: 1=bupivacaine, 2=levobupivacaine, 3=ropivacaine	Dose (mg)	Result: 1=success, 0=failure
1	75	161	1	1	8	1
2	64	154	0	1	7	1
3	76	149	0	1	6	1
4	68	167	1	1	5	0
5	75	155	0	1	6	1
6	62	170	1	1	5	1
7	44	178	1	1	4	0
8	79	168	1	1	5	0
9	51	168	0	1	6	0
10	66	164	1	1	7	1
11	73	153	0	1	6	0
12	40	170	1	1	7	1
13	71	167	1	1	6	1
14	68	153	0	1	5	0
15	73	154	0	1	6	1
16	63	166	1	1	5	0
17	50	166	1	1	6	0
18	84	153	0	1	7	1
19	20	173	1	1	6	1

APPENDIX B5 **THE MEDIAN EFFECTIVE DOSE OF BUPIVACAINE, LEVOBUPIVACAINE, AND ROPIVACAINE AFTER INTRATHECAL INJECTION IN LOWER LIMB SURGERY**

No	Age (year)	Height (cm)	Sex: 1=male, 0=female	Group: 1=bupivacaine, 2=levobupivacaine, 3=ropivacaine	Dose (mg)	Result: 1=success, 0=failure
20	54	168	1	1	5	1
21	32	178	1	1	4	0
22	77	152	0	1	5	1
23	71	167	0	1	4	0
24	38	170	1	1	5	0
25	68	152	0	1	6	1
26	80	164	1	2	8	1
27	57	173	1	2	7	0
28	73	151	0	2	8	1
29	71	156	0	2	7	1
30	74	151	0	2	6	1
31	54	156	0	2	5	1
32	67	157	0	2	4	0
33	69	167	1	2	5	0
34	73	149	0	2	6	1
35	84	167	1	2	5	1
36	65	158	0	2	4	0
37	55	163	0	2	5	0
38	59	156	0	2	6	1

APPENDIX B5 **THE MEDIAN EFFECTIVE DOSE OF BUPIVACAINE, LEVOBUPIVACAINE, AND ROPIVACAINE AFTER INTRATHECAL INJECTION IN LOWER LIMB SURGERY**

No	Age (year)	Height (cm)	Sex: 1=male, 0=female	Group: 1=bupivacaine, 2=levobupivacaine, 3=ropivacaine	Dose (mg)	Result: 1=success, 0=failure
39	61	170	1	2	5	0
40	76	162	0	2	6	1
41	43	172	1	2	5	0
42	62	158	0	2	6	1
43	57	165	0	2	5	0
44	44	168	0	2	6	0
45	68	176	1	2	7	1
46	75	170	1	2	6	1
47	64	154	0	2	5	0
48	69	155	0	2	6	0
49	64	154	1	2	7	1
50	81	163	0	2	6	1
51	70	174	1	3	8	0
52	72	165	0	3	9	1
53	51	152	0	3	8	0
54	44	175	1	3	9	0
55	78	162	1	3	10	0
56	58	165	1	3	11	1
57	75	170	1	3	10	1

APPENDIX B5 **THE MEDIAN EFFECTIVE DOSE OF BUPIVACAINE, LEVOBUPIVACAINE, AND ROPIVACAINE AFTER INTRATHECAL INJECTION IN LOWER LIMB SURGERY**

No	Age (year)	Height (cm)	Sex: 1=male, 0=female	Group: 1=bupivacaine, 2=levobupivacaine, 3=ropivacaine	Dose (mg)	Result: 1=success, 0=failure
58	55	160	1	3	9	1
59	71	148	0	3	8	0
60	82	165	1	3	9	0
61	72	149	0	3	10	1
62	69	178	1	3	9	1
63	54	160	0	3	8	1
64	46	161	0	3	7	0
65	76	156	1	3	8	1
66	57	163	0	3	7	1
67	66	160	0	3	6	0
68	42	165	1	3	7	0
69	40	178	1	3	8	0
70	68	175	1	3	9	1
71	70	164	0	3	8	1
72	30	173	1	3	7	0
73	71	150	0	3	8	1
74	68	146	0	3	7	1
75	68	157	0	3	6	1