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EXPERT REVIEW

Levobupivacaine for Regional Anesthesia and Pain Management

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Abstract: Levobupivacaine is an enantiomer of racemic bupivacaine with a safe pharmacological profile. We present a review of levobupivacaine and its current clinical use in regional anaesthesia and pain management. The pharmacokinetic and pharmacodynamic profile of levobupivacaine is discussed and a qualitative review of studies involving levobupivacaine for regional anaesthesia is presented. Comparisons of levobupivacaine with other local anaesthetic agents as well as studies looking at different doses of levobupivacaine are overviewed.

Keywords: levobupivacaine, anesthesia, local anaesthetics, pain management

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Introduction

Reports of significant mortality and morbidity after regional anaesthesia utilising the local anaesthetic agent bupivacaine in the late 1970s[1] led to the development of enantiomers of racemic bupivacaine with safer pharmacological profiles. The levorotatory or S(−) stereoisomers known as levobupivacaine and ropivacaine have been available since the late 1990s,[2] and have been associated with less central nervous system and cardiovascular toxicity than their dextrorotatory or R(+) counterpart dextrobupivicaine.[3] This review appraises the pharmacological profile of levobupivacaine and its current clinical use in regional anaesthesia and pain management.

Structure

The three commonly used long-acting local anaesthetic solutions bupivacaine, levobupivacaine and ropivacaine are all structurally related (Table 1). Bupivacaine is a racemic mixture of S(−) and R(+) enantiomers; levobupivacaine is the S(−) (or levo) enantiomer of bupivacaine, and ropivicaine is an S(−) enantiomer that resembles bupivacaine structurally. Bupivacaine is an amino-amide local anaesthetic that belongs to the n-alkyl-substituted pipecoloxylidide family. Its molecular structure contains a chiral centre on a piperidine ring, with a butyl group on the amine portion of the pipecoloxylidide.[4] It is this 4-carbon-chain butyl group that confers its high lipid solubility. Levobupivacaine, having the same molecular structure as bupivacaine, is also highly lipid-soluble, whilst ropivacaine possesses a propyl group on the amine portion of pipecoloxylidide, and this 3-carbon side-chain substitution causes the molecule to be much less lipophilic than that of bupivacaine or levobupivacaine.[5] The pharmacokinetic differences of levobupivaciane, bupivacaine and ropivocaine are well described[6–9] and summarised in Table 1.

Pharmacodynamics

Mechanism of action

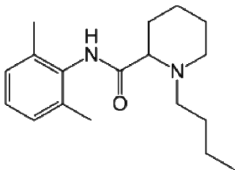
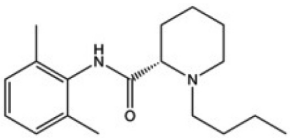
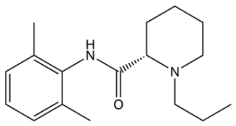
Levobupivacaine, like other local anaesthetic agents, is thought to exert its effects on neuronal membranes by reversibly binding sodium ion channels, thereby preventing voltage-dependent increases in sodium ion conductance, ultimately inhibiting the initiation and propagation of action potentials in neuronal cells.[9] Levobupivacaine has been likened to other local anaesthetic agents in being able to block small-diameter neuronal fibres more readily than large fibres, explaining the blocking of nociception before other sensory modalities. However, the situation remains complex, as the absolute sensitivity of nerve cells to local anaesthetic agents is not merely related to the diameter of the nerves, but also to the degree of myelination and differences in the population of sodium channels.

Levobupivacaine has a pKa of 8.09 (equal to that of bupivacaine) and a volume of distribution of 67 litres. It is >97% plasma protein bound at concentrations between 0.1 and 1 mcg/mL.[9] Its high plasma protein binding and high lipid solubility seem to explain its prolonged duration of action, whilst its pKa (higher than that of lignocaine) explains its slower onset of action, as less of the drug will be unionised at physiological pH. High lipid solubility has also been correlated with the potency of local anaesthetics.

Adverse reactions

Levobupivacaine was developed following concerns of serious central nervous system (CNS) and cardiovascular adverse reactions (including mortality) after inadvertent systemic spread of racemic bupivacaine.[10–12] Central nervous system manifestations range from paraesthesia and mild tremors to seizures and generalised CNS depression,[13,14] whilst cardiovascular reactions include negative inotropy, conduction disturbance (QRS complex widening and dysrhythmias), and death caused by pump failure and/or malignant dysrhythmias.[15–17] It is thought that the cardiotoxic effects of bupivacaine arise as a result of both direct cardiac action (eg, blocking of sodium and potassium channels) and indirect stimulation of the CNS.[18–20] In studying the toxicity of bupivacaine, the significance of chirality became evident.[20] The disparate properties of enantiomers of a chiral compound, though previously known, required the advances in the manufacturing of single enantiomers to allow exploitation of these differences. A ranking of toxicity is thus achievable based on chirality, with an isolated heart model showing that the two pure enantiomers (ropivacaine and levobupivacaine) have less myocardial depressant properties than racemic bupivacaine, with the pure R(+) bupivacaine enantiomer being the most cardiotoxic.[21]

Table 1. Comparison of the pharmacokinetic differences of levobupivaciane, bupivacaine and ropivocaine.

	Bupivicaine	Levobupivacaine	Ropivocaine
Structure			
Type of local anaesthetic	Amino amide	Amino amide	Amino amide
Structure	Racemic mixture of S-and R-enantiomers	Pure S-enantiomer of bupivacaine	Pure S-enantiomer
Systematic International Union of Pure and Applied Chemistry (IUPAC) name	(*RS*)-1-butyl-*N*-(2,6-dimethylphenyl) piperidine-2-carboxamide	(*S*)-1-butyl-*N*-(2,6-dimethylphenyl) piperidine-2-carboxamide	(*S*)-*N*-(2,6-dimethylphenyl)-1-propylpiperidine-2-carboxamide
Formula	$C_{18}H_{28}N_2O$	$C_{18}H_{28}N_2O$	$C_{17}H_{26}N_2O$
Molecular mass	288.43 g/mol	288.43 g/mol	274.4 g/mol
Metabolism	Hepatic by N-de-alkylation, primarily to pipcolyoxylidine. N-desbutyl bupivacaine and 4 hydroxy bupicavaine are also formed	Extensively metabolised, with no unchanged levobupivacaine detected in the urine or faeces. Cytochromes CYP3A4 and CYP1A2 mediate the metabolism of levobupivacaine to desbutyl levobupivacaine and 3-hydroxy levobupivacaine. The 3-hydroxy levobupivacaine appears to undergo further transformation to glucuronide and sulphate conjugates	Hepatic by aromatic hydroxylation mediated by cytochrome P4501A to 3-hydroxy ropivacaine. Approximately 37% excreted in the urine as conjugated 3-hydroxy ropivacaine. Urinary excretion of hydroxy N-dealkylated metabolites accounts for less than 3% of dose. Anaesthetic activity in animal models less than that of ropivacaine
Elimination half-life (adults)	1.15 ± 0.41 hours	1.27 ± 0.37 hours	1.6–6 hours
Excretion	Renal (4%–10%) excreted as pipcoloxylidine; 16% excreted unchanged	Renal (70%), faecal (24%)	Renal (86%)
Clearance	0.47 L/min	0.32 L/min	0.82 L/min
PKa	8.1	8.1	8.1
Volume of distribution	0.41–1 L/kg	0.54 L/kg	0.52–0.66 L/kg

Animal studies have also suggested that levobupivacaine has a higher safety margin than racemic bupivacaine,[20,22–24] with approximately 30% to 40% less systemic toxicity than bupivacaine on a mg:mg basis.[15,23] One study demonstrated the mean fatal dose (± standard deviation) of intravenous levobupivacaine in sheep (277 ± 51 mg) to be significantly greater than that of racemic bupivacaine (156 ± 31 mg).[24] However, there are limited human studies investigating the adverse reactions to intravenous administration of levobupivacaine. One randomized double-blind crossover study[25] involved the administration of 10 mg/min of either levobupivacaine hydrochloride or (racemic) bupivacaine hydrochloride intravenously into healthy male volunteers (n = 14), to a mean dose of 56.1 mg and 47.9 mg respectively. Subjects were monitored for CNS and cardiovascular symptoms. There were no significant differences in the mean and median threshold doses for either drug with regard to their subjective CNS tolerability. While there were no statistically significant differences between PR interval and QT interval (QT_c) prolongation, levobupivacaine was associated with

less of a negative inotropic effect than bupivacaine, with significantly smaller reductions in mean stroke index (–5.1 vs. –11.9 mL/m^2; $P = 0.001$), acceleration index (–0.09 vs. –0.20; $P = 0.011$), and ejection fraction (–2.5% vs. –4.3%; $P = 0.024$). On the other hand, when a similarly structured randomized double-blinded crossover study[26] was performed comparing IV administration of levobupivaciane and ropivacaine in healthy volunteers (n = 13), CNS and cardiovascular effects were similar, suggesting a similar toxicity profile of these two pure enantiomeric drugs. Concerns regarding the vasoactive effects of these three long-acting local anaesthetic drugs on maternal-fetal circulation and the degree of placental transfer have not been conclusively resolved, with no clear benefit of one drug over the other in obstetric situations. A study comparing these three local anaesthetic agents administered as a two-step intravenous infusion in 30 near-term pregnant ewes[27] showed that maternal blood pressure, central venous and intra-amniotic pressures, acid-base status and uterine blood flow were unaffected, with no significant differences in maternal serum, fetal serum, fetal tissue concentrations, and tissue:serum concentration ratios.

Relative potencies

There is a hypothesis that lipid solubility is the primary determinant of intrinsic anaesthetic potency. Theoretically, the more lipophilic a molecule is, the easier it enters neuronal axon membranes, thus requiring fewer molecules to achieve the desired effect. Consistent with this, levobupivacaine and racemic bupivacaine (which have similar lipid solubility) have been demonstrated to be 50% more potent than ropivacaine (which has lower lipid solubility) in inhibiting tetrodoxin-resistant sodium channels.[28] The situation is more complex than this, however, with evidence that despite having similar intracellular concentrations (and thus overcoming lipophilicity as an issue), a difference in the potency of phasic block can still be demonstrated.[29]

In humans, it is more difficult to compare relative potencies, as often the doses used in a clinical setting are at the top of the dose-response curves. Instead, the "minimum local anaesthetic concentration" (MLAC) is most often used as an alternative, which is defined as the median effective analgesic concentration in the first stage of labour, and was developed to determine equipotent analgesic concentrations of local anaesthetics, to compare motor effects and to evaluate the relative toxicity during labour.[30] The term MLAD (median local anaesthetic dose) or ED50 has been employed for a similar concept applied to intrathecal administration of local anaesthetic.

In a randomized, double-blind, sequential allocation study (n = 60), the efficacy of 20 mL of epidural levobupivacaine or bupivacaine was measured using a visual analogue pain score. The MLAC of levobupivacaine was 0.083% w/v and the MLAC of bupivacaine was 0.081% w/v. The mean potency ratio of levobupivacaine:bupivacaine was 0.98.[31] In another study looking at the MLAD of intrathecal bupivacaine, levobupivacaine and ropivacaine in an obstetric population (n = 89), the relative analgesic mean potency ratios were found to be 0.65 for ropivacaine:bupivacaine, 0.80 for ropivacaine:levobupivacaine, and 0.81 for levobupivacaine:bupivacaine.[32] However, MLAC/MLAD studies are not uniform, and can sometimes have contrasting results. While there are multiple studies that have reported ropivacaine to be about 20 to 30% less potent than levobupivacaine,[32–36] there are also studies that show no significant differences between the two drugs.[37,38] When comparing levobupivacaine with bupivacaine and ropivacaine, however, it is important to realize that the commercial preparation of levobupivaciane labels the percentage solution by weight of the active base only, whilst the other two local anaesthetic agents record percentage solution according to the hydrochloride salt.[39] This means that the concentration of levobupivacaine as the hydrochloride salt should be 13% higher than that reported by the commercial preparation of the base form—ie, 5 mg/mL (0.5%) levobupivacaine base is actually 5.63 mg/mL (0.563%) levobupivacaine hydrochloride.[40] Whilst the sensory MLAC potency ratio of levobupivacaine to bupivacaine is 0.98, if a correction is made for molar concentrations this falls to 0.87 (neither value being different from unity).[31] Additionally, whilst levobupivacaine has been shown to have slightly lower motor-blocking capacity than bupivacaine with a levobupivacaine:bupivacaine potency ratio for epidural motor blockade of 0.87 (95% CI, 0.77–0.98),[41] this may be entirely explained by differences in molarity.

Despite the confusion, clinical studies suggest that a linear trend of potency exists between the three local anaesthetics and should be considered as bupivacaine > levobupivacaine > ropivacaine.

Pharmacokinetics

Absorption

Human studies have demonstrated that although the volume of distribution of levobupivacaine at steady state was significantly lower than that of dextrobupivacaine, its decreased toxicity was likely attributed to its increased protein-binding affinity, resulting in a smaller fraction of unbound drug, which causes a higher clearance and shorter elimination half-life.[42] Levobupivacaine has a non-linear binding pattern, binding to both albumin (a low-affinity, high-capacity binding site) and α_1-acid glycoprotein (a high-affinity, low-capacity binding site) in plasma.[43] At lower concentrations it is mainly bound to albumin; however, in higher concentrations there is a much greater affinity for α_1-acid glycoprotein.[44] In vitro studies estimate levobupivacaine 0.1–1.0 µg/mL to be >97% bound to plasma proteins,[9] whilst a study following IV administration to healthy volunteers indicated a steady-state volume of distribution of 54 L.[45]

Drug absorption and systemic disposition are affected by the route of administration and the vascularity of the tissue at the site of administration.[9] Following IV administration of levobupivacaine at 10 mg/min to a mean dose of 56.1 mg, the mean maximum plasma concentration at the end of the infusion or shortly thereafter was 2.62 µg/mL.[25] The rate of systemic absorption of levobupivacaine is increased when administered into tissue sites with high vascularity.[46] When administered as a scalp block, levobupivacaine was rapidly absorbed, requiring only a mean of 12 minutes to reach maximal plasma concentration. It has also been noted that when the same dose of levobupivacaine was administered for a brachial plexus block, the mean duration to reach peak plasma concentration was 33% shorter when administered to both deep and superficial tissue than to superficial tissue alone.[47]

The absorption of levobupivacaine following epidural administration is biphasic,[45,48] with one study showing the means of fraction absorbed and the half-life of the fast absorption process were 0.22 and 5.2 (minutes) respectively, whilst the values for the slow absorption process were 0.84 and 386 (minutes) respectively.[45] Compared to younger patients, there have been reports of decreased fraction absorbed and shorter absorption half-life of levobupivacaine in older patients; however, studies so far have failed to produce statistically significant results.[48] Nonetheless, the possibility of changes in pharmacokinetics with increasing age remains. Studies evaluating the absorption kinetics of levobupivacaine are presented in Table 2.[49–53]

Metabolism and elimination

Following the IV administration of 30 mg racemic bupivacaine to healthy volunteers, the S(–) enantiomer

Table 2. Absorption pharmacokinetics of levobupivacaine.

Route of administration [n=]	Concentration; dose or vol	C_{max} (mcg/mL)	t_{max} (min)	AUC mcg/mL/hr
Thoracic paravertebral block[49]	2.5 mg/mL; 19 mL	0.53	15*	
Cervical brachial plexus block[47]				
Superficial	5 mg/mL; 0.35 mL/kg	0.58	30*	21.0
Combined deep + superficial	5 mg/mL; 0.35 mL/kg	0.52	20*	21.1
Axillary brachial plexus block[50]				
Normal renal function	5 mg/mL; 50 mL	1.2*	55*	11*
End stage renal disease	5 mg/mL; 50 mL	1.6*	48*	13*
Scalp block[51]	5 mg/mL; 2.5 mg/kg	1.58	12	
Paediatrics				
Caudal block[52]	2.5 mg/mL; 2.5 mg/kg	1.38	37	
Ilio-inguinal block[53]	5 mg/mL; 2 mg/kg	1.85	28	2.4

Note: *Median value. Mean values unless otherwise stated.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximal concentration; t_{max}, time to maximal concentration.

(ie, levobupivacaine) showed the following mean values: clearance time 0.317 L/min, steady-state volume of distribution 54 L, and terminal half-life 157 minutes.[45] Metabolism of levobupivacaine occurs almost exclusively in the liver.[54–56] by N-dealkylation, primarily to pipcolyloxylidine. N-desbutyl bupivacaine and 4 hydroxy bupivacaine are also formed.[57] This extensive process occurs through the liver cytochrome p450 enzyme system, and mainly involves the CYP3A4 and the CYP1A2 isoforms.[9,58] It is therefore unsurprising that the mean total body clearance was noted to be slower (0.492 L/min) in a population of liver transplant patients following intercostal blockade.[59] Once metabolised, it is excreted in urine (71% within 48 hours) and faeces (24%).[9]

While it has been proposed that there could be potential interactions between levobupivacaine and cytochrome p450 inhibitors (eg, ketoconzaole acting on CYP3A4 and methylxanthines acting on CYP1A2), there have not been any clinical studies performed to confirm this.[9] Furthermore, studies have indicated that the main metabolites formed (ie, pipcolyloxylidine, N-desbutyl bupivacaine and 4 hydroxy bupivacaine) only constitute up to 5% of the dose administered, and therefore drug interactions caused purely by inhibition of certain cytochrome p450 isomers seem unlikely.[58,60–62]

Efficacy

To determine the efficacy of levobupivacaine in clinical practice, a restricted qualitative review of studies involving levobupivacaine for regional anaesthesia was performed. This review was based on English-language studies conducted on adult subjects which compared levobupivacaine with other local anaesthetic agents; studies looking at different doses of levobupivacaine; and studies related to the use of additives with levobupivacaine. Specifically, this review did not include studies focusing on derivation of potency, regional technique, comparisons with non-regional techniques (including the use of saline as control), comparisons amongst different regional techniques, or studies where the conclusions were not clear from the abstract. The findings of this review are summarised in Tables 1–7 and focus on direction in change and main findings regarding analgesia, sensory and motor block. One of the problems with the literature is that the differences related to the use of levobupivacaine base as opposed to the hydrochloric salt were not clearly taken into account in most of these studies. As a result, caution must be taken with interpreting small differences in alleged "equipotent" dosing of levobupivacaine, bupivacaine and ropivacaine, which may be explained by differences in molarity. This is particularly true of comparisons between levobupivacaine and bupivacaine where the absence of appropriate molarity comparisons increases the apparent potency of levobupivacaine. It is prudent to bear in mind that in general, comparisons are between levobupivacaine base against ropivacaine or bupivacaine hydrochloride.

Levobupivacaine in Spinal Anaesthesia/Analgesia—Obstetric

Anaesthesia

Intrathecal levobupivacaine has been compared with ropivacaine in several obstetric studies for Caesarean section. When 6.6 mg of levobupivacaine was compared with a purported "equipotent" dose of 10 mg ropivacaine (both with sufentanil at 3.3 mcg), analgesic supplementation was still required with the ropivacaine cohort.[63] On the other hand, an intrathecal dose of 8 mg levobupivacaine was just as efficacious as 12 mg ropivacaine (both with 2.5 mcg sufentanil added).[64] The differences may be explained by dosing closer to ED95 rather than ED50.

Studies looking at the same mg dose of levobupivacaine and bupivacaine (with opioids) for Caesarean section consistently show a discrepancy with regards to motor block; either less overall motor block[63,65] or shorter duration of motor block.[64,65] However, in one of these studies,[64] there were also more failures of anaesthesia with levobupivacaine and shorter duration of analgesia with levobupivacaine, lending support for slight non-equivalence, with bupivacaine being more potent.

Analgesia

The use of levobupivacaine has been studied as an intrathecal dose for use in early labour. There seems to be similar efficacy with ropivacaine when both are used at 2.5 mg or 3.0 mg,[35,66] which is surprising, given the reported discrepancies in MLAD/ED50.[32,35] However, the ED95 (albeit with sufentanil 1.5 mcg) of both agents has been reported as being very similar (5.0 mg for levobupivacaine and 4.8 mg for ropivacaine,[67] which may explain the similarities in efficacy. Of course, the

Table 3. Spinal anaesthesia/analgesia for obstetrics.

	Regimen	Differences	Similarities
Studies for anaesthesia			
Levobupivacaine vs. ropivacaine			
Coppejans et al[63]	6.6 mg levobupivacaine vs. 10 mg ropivacaine (vs. 6.6 mg bupivacaine) (All with 3.3 mcg sufentanil)	Less epidural supplementation required with levobupivacaine than ropivacaine	Sensory and motor block
Gautier et al[64]	8 mg levobupivacaine vs. 12 mg ropivacaine (vs. 8 mg bupivacaine) (All with 2.5 mcg sufentanil)		Proportion of parturients with effective anaesthesia
Levobupivacaine vs. bupivacaine			
Coppejans et al[63]	6.6 mg levobupivacaine vs. 6.6 mg bupivacaine (vs. 10 mg ropivacaine) (All with 3.3 mcg sufentanil)	Less motor block with levobupivacaine (+ ropivacaine) than bupivacaine	Sensory and motor block
Gautier et al[64]	8 mg levobupivacaine vs. 8 mg bupivacaine (vs. 12 mg ropivacaine) (All with 2.5 mcg sufentanil)	Inferior success rate; shorter duration of analgesia; shorter motor block with levobupivacaine (+ ropivacaine) than bupivacaine	Proportion with effective anaesthesia
Bremerich et al[65]	10 mg levobupivacaine vs. 10 mg bupivacaine (All with sufentanil 5 mcg, fentanyl 10 mcg or fentanyl 20 mcg)	Shorter motor block; less pronounced motor block with levobupivacaine	Onset of sensory block; maximum sensory block; duration of analgesia
Studies for analgesia			
Levobupivacaine vs. ropivacaine			
Sia et al[35]	Levobupivacaine 1 mg,1.5 mg, 2 mg, 2.5 mg, 3 mg vs. ropivacaine 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg		No difference in duration analgesia $>$ 2.5 mg
Lim et al[66]	Levobupivacaine 2.5 mg vs. ropivacaine 2.5 mg (vs. bupivacaine 2.5 mg)		Duration analgesia; incidence of motor block
Levobupivacaine vs. bupivacaine			
Lim et al[66]	Levobupivacaine 2.5 mg vs. bupivacaine 2.5 mg (vs. ropivacaine 2.5 mg)	Shorter analgesia; less motor block with levobupivacaine than bupivacaine	
Vercauteren[68]	Levobupivacaine 2.5 mg vs. bupivacaine 2.5 mg (Both with sufentanil 1.5 mcg and adrenaline 2.5 mcg)	Less motor block; less subjective impairment in perineal squeezing with levobupivacaine	Time to first painless contraction; duration of spinal analgesia; total LA required

Table 4. Spinal anaesthesia in non-obstetric use.

Study for anaesthesia	Type of surgery	Regimen	Differences	Similarities
Levobupivacaine as sole local anaesthetic agent				
Kazak et al[69]	Perianal	Levobupivacaine 1.5 mg vs. 6 mg (Both hyperbaric)	Sensory block + time to first analgesia shorter with low dose; no motor block with low dose	Anaesthesia for perianal surgery
De Santiago et al[70]	Knee arthroscopy	Levobupivacaine 3 mg vs. 4 mg vs. 5 mg (All with fentanyl 10 mcg)	Inadequate analgesia with 3 mg; ambulation quicker with 4 mg than 5 mg	Time to surgical block; highest level of sensory block; surgical anaesthesia
Onur et al[71]	Knee arthroscopy	Levobupivacaine 7.5 mg vs. 10 mg vs. 12.5 mg vs. 15 mg	Readiness for surgery longest; duration of sensory and motor block shortest; first micturition + unassisted ambulation shortest with 7.5 mg group	Incidence of failed blocks; first analgesic use
Sen et al[72]	Urological	Hyperbaric levobupivacaine 13.5 mg vs. Isobaric levobupivacaine 13.5 mg	Onset of T10 sensory block; maximum sensory block; time to motor block; duration of motor block all shorter with hyperbaric	Duration of analgesia; extent of maximal block
Girgin et al[82]	Inguinal hernia	Levobupivacaine 5 mg + fentanyl 25 mcg vs. levobupivacaine 7.5 mg	Time to 2-segment regression; ambulation; urination; discharge all shorter with fentanyl group	Highest sensory block
Cuvas et al[83]	Transurethral resections	Levobupivacaine 11 mg + fentanyl 15 mcg vs. levobupivacaine 12.5 mg	Motor block less; highest sensory block lower with fentanyl group	
Levobupivacaine vs. ropivacaine				
Cappelleri et al[73]	Knee arthroscopy	Levobupivacaine 5 mg vs. ropivacaine 7.5 mg (vs. levobupivacaine 7.5 mg) (All hyperbaric)		Incidence of unilateral block; time to discharge (levobupivacaine 5 mg and ropivacaine 7.5 mg only)
Breebaart et al[74]	Knee arthroscopy	Levobupivacaine 10 mg vs. ropivacaine 15 mg (vs. lignocaine 60 mg)		Duration of motor block
Mantouvalou et al[75]	Lower abdominal	Levobupivacaine 15 mg vs. ropivacaine 15 mg (vs. bupivacaine 15 mg)	Duration of motor and sensory block longer with levobupivacaine (+ bupivacaine) than ropivacaine	
Levobupivacaine vs. bupivacaine				
Fattorini et al[76]	Orthopaedic	Levobupivacaine 15 mg vs. bupivacaine 15 mg		Potencies; postoperative pain
Glaser et al[77]	Hip replacement	Levobupivacaine 17.5 mg vs. bupivacaine 17.5 mg		Onset and duration of sensory and motor block
Mantouvalou et al[75]	Lower abdominal	Levobupivacaine 15 mg vs. bupivacaine 15 mg (vs. ropivacaine 15 mg)	Less vasoactive drug required with levobupivacaine (+ ropivacaine) than bupivacaine	Onset of motor block; duration of sensory and motor block

Hakan Erbay et al[78]	Transurethral	Levobupivacaine 7.5 mg vs. bupivacaine 7.5 mg (Both hyperbaric and with fentanyl 25 mcg)	Time to maximum block longer; duration of motor block shorter; duration of sensory block longer; time to analgesia longer with levobupivacaine	Time to T10 onset; maximum sensory block; time to 2-segment regression
Erdil et al[79]	TURP	Levobupivacaine 7.5 mg vs. bupivacaine 7.5 mg (Both with fentanyl 15 mcg)	Time to maximum motor block longer; time to T10 block longer; time to peak sensory block longer; peak sensory block lower with levobupivacaine	
Vanna et al[80]	Transurethral endoscopic	Levobupivacaine 12.5 mg vs. hyperbaric bupivacaine 12.5 mg		Time to surgical block; duration of sensory block; time to 2-segment regression; time to onset/offset of motor block; verbal pain score
Levobupivacaine vs. lignocaine				
Breebaart et al[74]	Knee arthroscopy	Levobupivacaine 10 mg vs. lignocaine 60 mg (vs. ropivacaine 15 mg)	Duration of sensory block longer with levobupivacaine (+ ropivacaine) than lignocaine; time to voiding and hospital discharge slower with levobupivacaine (+ ropivacaine) than lignocaine	Duration of motor block
De Santiago[81]	Laparoscopic sterilisation	Levobupivacaine 3 mg vs. lignocaine 10 mg (Both with fentanyl 10 mcg)	Regression of spinal anaesthesia longer with levobupivacaine	Anaesthesia onset time; time to ambulate; time for home discharge

Table 5. Epidural anaesthesia/analgesia for obstetrics.

	Regimen	Differences	Similarities
Studies for anaesthesia			
Levobupivacaine as sole local anaesthetic agent			
Malhotra et al[84]	0.5% levobupivacaine 20 mL + fentanyl 75 mcg vs. 0.5% levobupivacaine 20 mL + saline	More nausea/vomiting in fentanyl group	Onset time; supplemental anaesthesia
Levobupivacaine vs. ropivacaine			
Sng et al[85]	0.5% Levobupivacaine 15–20 mL vs. 0.75% ropivacaine 15–20 mL (vs. 2% lignocaine + adrenaline + fentanyl 15–20 mL)		Time to loss T4 sensation to ice; supplemental anaesthesia
Levobupivacaine vs. bupivacaine			
Bader et al[86]	0.5% levobupivacaine 30 mL vs. 0.5% bupivacaine 30 mL		Level sensory block; motor block; muscle relaxation
Ngamprasertwong et al[87]	0.5% levobupivacaine vs. 0.5% bupivacaine		Volume of LA required; time to block; duration of sensory block; time to regression of sensory block; time to onset/ offset of motor block; pain score
Faccenda et al[88]	0.5% levobupivacaine 25 mL vs. 0.5% bupivacaine 25 mL	Motor block longer with levobupivacaine but less intense	Time to block; segmental spread; duration of block
Levobupivacaine vs. lignocaine mixtures			
Balaji et al[89]	0.5% levobupivacaine 20 mL vs. 2% lignocaine + adrenaline 100 mcg + fentanyl 100 mcg 20 mL	Slower onset of block to touch at T7; and more anaesthetic supplement required with levobupivacaine	
Allam et al[90]	0.5% levobupivacaine 20 mL vs. 1.8% lignocaine + adrenaline 100 mcg + 0.76% bicarbonate 20 mL	Slower onset of block to touch T5; block to ice at T4 with levobupivacaine	
Sng et al[85]	0.5% levobupivacaine 15–20 mL vs. 2% lignocaine + adrenaline + fentanyl 15–20 mL (vs. 0.75% ropivacaine 15–20 mL)		Time to loss of T4 sensation to ice; supplemental anaesthesia
Studies for analgesia			
Levobupivacaine as sole local anaesthetic agent			
Tixier et al[91]	0.0568% levobupivacaine vs. 0.1136% levobupivacaine (Both with sufentanil 0.45 mcg/mL) Bolus +/– top ups, then PCEA	Inferior analgesia with lower concentrations	
Wallet et al[92]	0.0625% levobupivacaine + 2 mcg/mL clonidine vs. 0.0625% levobupivacaine (Both with sufentanil 0.25 mcg/mL) Bolus +/– top ups, then PCEA	Better analgesia; reduction in hourly levobupivacaine and sufentanil dose; earlier onset of analgesia; lower maternal blood pressure with clonidine group	

Levobupivacaine vs. ropivacaine			
Camorcia et al[93]	0.0625% levobupivacaine 20 mL vs. 0.1% ropivacaine 20 mL (vs. 0.0625% bupivacaine 20 mL) (All with sufentanil 0.5 mcg/mL)		Time to first painless contraction; proportion able to walk unaided; duration of analgesia (levobupivacaine and ropivacaine)
Atienzar et al[94]	0.125% levobupivacaine vs. 0.2% ropivacaine (vs. 0.125% bupivacaine) (All with fentanyl 1 mcg/mL) Infusion +/– bolus	VAS greater with levobupivacaine	
Sah et al[95]	0.125% levobupivacaine vs. 0.2% ropivacaine (vs. 0.125% bupivacaine) (Bolus with 100 mcg fentanyl, then infusion of 0.1% of respective LA solution with fentanyl 2 mcg/mL)		VAS; bromage scores
Supandji et al[96]	0.2% levobupivacaine 10 mL vs. 0.2% ropivacaine 10 mL		VAS; highest sensory block; duration of analgesia; degree of motor block; blood pressure
Purdie et al[97]	0.1% levobupivacaine vs. 0.1% ropivacaine (Both with fentanyl 2 mcg/mL) Bolus +/– top ups, then PCEA		Onset time; duration; quality of analgesia; motor block; LA consumption
Beilin et al[98]	0.0625% levobupivacaine vs. 0.0625% ropivacaine (vs. 0.0625% bupivacaine) (All with fentanyl 2 mcg/mL) Bolus then infusion	Less motor block on left side with levobupivacaine	Total LA used; number of top ups; proportion of adequate analgesia after initial bolus
Levobupivacaine vs. bupivacaine			
Sah et al[95]	0.125% levobupivacaine vs. 0.125% bupivacaine (vs. 0.2% ropivacaine) Bolus with 100 mcg fentanyl, then infusion of 0.1% of respective LA solution with fentanyl 2 mcg/mL	Second stage longer with levobupivacaine (+ ropivacaine) compared to bupivacaine	VAS; Bromage scores
Burke et al[99]	0.25% levobupivacaine vs. 0.25% bupivacaine Bolus, then top ups >5 minutes apart (max 2 mg/kg over 4 hours)	More failed pain relief with levobupivacaine	Time to analgesia; duration of pain relief; quality of analgesia
Camorcia et al[93]	0.0625% levobupivacaine 20 mL vs. 0.1% ropivacaine 20 mL (vs. 0.0625% bupivacaine 20 mL) (All with sufentanil 0.5 mcg/mL)	Duration of analgesia longer with levobupivacaine (+ ropivacaine) compared to bupivacaine	Time to first painless contraction; proportion able to walk unaided
Atienzar et al[94]	0.125% levobupivacaine vs. 0.2% ropivacaine (vs. 0.125% bupivacaine) (All with fentanyl 1 mcg/mL) Infusion +/– bolus	VAS greater; motor block less with levobupivacaine	Dose of supplemental analgesia used; sensory block
Beilin et al[98]	0.0625% levobupivacaine vs. 0.0625% bupivacaine (vs. 0.0625% ropivacaine) (All with fentanyl 2 mcg/mL) Bolus then infusion	Less motor block (left and right); less pruritus with levobupivacaine (+ ropivacaine) compared with bupivacaine	Total LA used; number of top-ups; proportion of adequate analgesia after initial bolus

Table 6. Epidural anaesthesia/analgesia for non-obstetric use.

Study for anaesthesia	Type of surgery	Regimen	Differences when using levobupivacaine	Similarities
Levobupivacaine vs. ropivacaine				
Peduto et al[100]	Lower limb	0.5% levobupivacaine 15 mL vs. 0.75% ropivacaine 15 mL		Onset time of sensory bock; duration of motor and sensory block; regression of sensory block; rescue analgesia
Koch et al[102]	Hip surgery	0.5% levobupivacaine bolus, then 0.125% PCEA vs. 0.75% ropivacaine bolus, then 0.2% PCEA (vs. 0.5% bupivacaine bolus, then 0.125% PCEA)	Higher intraoperative anaesthesia	Volume of drug for block; onset/ offset of sensory and motor block
Casati et al[101]	Orthopaedic	0.5% levobupivacaine bolus, then 0.125% PCEA vs. 0.5% ropivacaine bolus, then 0.2% PCEA (vs. 0.5% bupivacaine bolus, then 0.125% PCEA)	More motor block with levobupivacaine (+ bupivacaine) compared with ropivacaine	Volume/dose of LA required; onset time; duration of sensory block
Levobupivacaine vs. bupivacaine				
Casimiro et al[103]	Lower limb	0.5% levobupivacaine 1.2 mL/dermatome vs. 0.5% bupivacaine 1.2 mL/dermatome (Both with fentanyl 100 mcg)	Less motor block with levobupivacaine	Sensory block duration, duration of motor block
Koch et al[102]	Hip surgery	0.5% levobupivacaine bolus, then 0.125% PCEA vs. 0.5% bupivacaine bolus, then 0.125% PCEA (vs. 0.75% ropivacaine bolus, then 0.2% PCEA)		Volume of drug for block, onset/ offset of sensory and motor block
Casati et al[101]	Orthopaedic	0.5% levobupivacaine bolus, then 0.125% PCEA vs. 0.5% bupivacaine bolus, then 0.125% PCEA (vs. 0.5% ropivacaine bolus, then 0.2% PCEA)		Volume/dose of LA required, onset time, duration sensory block
Kopacz et al[104]	Lower abdominal	0.75% levobupivacaine 20 mL ± 7 mL 0.75% bupivacaine 20 mL ± 7 mL	Longer time to complete regression sensory block with levobupivacaine Less motor block with levobupivacaine at 30 minutes	Onset sensory block, peak block height, eventual percentage with motor block
Study for analgesia	**Type of surgery**	**Regimen**	**Differences**	**Similarities**
Levobupivacaine as sole local anaesthetic agent				
Murdoch et al[105]	Orthopaedic	0.0625% vs. 0.125% vs. 0.25% levobupivacaine	VAS lower with 0.25%	Maximal motor block when comparing 0.125% and 0.25%
De Cosmo et al[106]	Thoracotomy	0.0625% levobupivacaine 5 mL/hr vs. 0.125% levobupivacaine 5 mL/hr (Both with sufentanil 1 mcg/mL)	Better analgesia with 0.125%	
Mendola et al[107]	Thoracotomy	0.15% vs. 0.25% vs. 0.5% levobupivacaine at 10 mg/hr (All with sufentanil 2.6 mcg/mL)		Analgesia

Danelli et al[108]	Hip joint replacement	0.125% vs. 0.75% levobupivacaine at 10 mg/hr		Analgesia at rest and movement; motor block
Demedde et al[109]	Lower abdominal surgery	0.15% levobupivacaine 10 mL/hr vs. 0.5% levobupivacaine 3 mL/hr vs. levobupivacaine 0.75% 2 mL/hr	Upper sensory block higher; more hypotension; more nausea in lowest concentration	Analgesia quality
Kopacz et al[111]	Major abdominal	0.25% levobupivacaine + 50 mcg/mL morphine vs. 0.25% levobupivacaine vs. 50 mcg/mL morphine Constant infusion ± bolus and increase in rate	Longer time to supplemental analgesia; lower VAS at rest and activity with opioid combination	
Kopacz et al[111]	Major orthopaedic	0.125% levobupivacaine + 4 mcg/mL fentanyl vs. 0.125% levobupivacaine 4 mcg/mL fentanyl PCEA	Longer time to PCEA use; lower dynamic VAS with opioid combination	
Kopacz et al[112]	Lumbar spine	0.5% levobupivacaine + 5% adrenaline 15 mL vs. 0.5% levobupivacaine + 2.5% adrenaline 15 mL vs. 0.5% levobupivacaine 15 mL	Serum levobupivacaine lower with any adrenaline solution	Onset/duration of sensory block
Levobupivacaine vs. ropivacaine				
De Cosmo et al[113]	Lung	0.125% levobupivacaine 5 mL/hr vs. 0.2% ropivacaine 5 mL/hr (Both with sufentanil 5 mcg/hr)		Static and dynamic analgesia
Koch et al[102]	Hip	0.125% levobupivacaine PCEA after 0.5% levobupivacaine bolus vs. 0.2% ropivaciane PCEA after 0.75% ropivacaine bolus (0.125% bupivacaine PCEA after 0.5% bupivacaine bolus)		Time to first bolus; number of bolus; VAS
Casati et al[101]	Orthopaedic	0.125% levobupivacaine PCEA after 0.5% levobupivacaine bolus vs. 0.2% ropivacaine PCEA after 0.5% ropivacaine bolus (vs. 0.125% bupivacaine PCEA after 0.5% bupivacaine bolus)		Degree of pain relief; LA consumption; need for rescue analgesia
Sitsen et al[115]	Knee replacement	0.125% levobupivacaine vs. 0.2% ropivacaine vs. 0.125% ropivacaine (All with sufentanil 1 mcg/mL)	Higher LA consumption in 0.2% ropivacaine group only	Analgesic quality; motor block; sufentanil consumption
Levobupivacaine vs. bupivacaine				
Koch et al[102]	Hip	0.125% levobupivacaine PCEA after 0.5% levobupivacaine bolus vs. 0.125% bupivacaine PCEA after 0.5% bupivacaine bolus (vs. 0.2% ropivaciane PCEA after 0.75% ropivacaine bolus)		Degree of pain relief; LA consumption; need for rescue analgesia

Table 7. Peripheral nerve blocks for anaesthesia/analgesia.

	Type of block	Regimen	Differences	Similarities
Study for anaesthesia				
Levobupivacaine as sole local anaesthetic agent				
Zhao et al[117]	Axillary BPB	0.1% levobupivacaine 36 mL vs. 0.1% levobupivacaine 72 mL vs. 0.25% levobupivacaine 36 mL		Rate of complete sensory block; onset and duration of sensory block
Casati et al[118]	Sciatic block	0.5% levobupivacaine 20 mL vs. 0.75% levobupivacaine 20 mL (vs. 0.75% ropivacaine 20 mL) (All with femoral nerve block using 2% mepivacaine 15 mL)	Onset time slower; regression of motor block earlier with 0.5% levobupivaciane	
Urbanek et al[119]	3-in-1 block	0.25% levobupivacaine 20 mL vs. 0.5% levobupivacaine 20 mL (vs. 0.5% bupivacaine 20 mL)	Complete sensory block less; duration of block shorter with 0.25% levobupicaine (than 0.5% levobupivacaine and 0.5% bupivacaine)	Sensory onset time; quality of block
Mannion et al[120]	Psoas compartment block	Perinerual clonidine 1 mcg/kg vs. Intravenous clonidine 1 mcg/kg vs. Intravenous saline (All with 0.4 mL/kg of 0.5% levobupivacaine)	First supplementary analgesia later with intravenous clonidine	24-hr cumulative analgesia consumption
Duma et al[121]	Axillary BPB	0.5% levobupivacaine 40 mL + perineural clonidine 150 mcg vs. 0.5% levobupivacaine 40 mL + perineural saline (vs. 0.5% bupivacaine 40 mL + perineural clonidine 150 mcg) (vs. 0.5% bupivacaine 40 mL + perineural saline)		Duration of sensory or motor block
Esmaoglu et al[122]	Axillary BPB	0.5% levobupivacaine 40 mL + dexmedetomidine 100 mcg (1 mL) vs. 0.5% levobupivacaine 40 mL + saline 1 mL	Sensory and motor block onset time shorter; duration of sensory and motor block longer; lower BP and HR with dexmedetomidine	
Levobupivacaine vs. ropivacaine				
Messina et al[123]	Superficial cervical plexus block	0.5% levobupivacaine 1 mg/kg vs. 0.75% ropivacaine 1.5 mcg/kg	Onset time shorter; rescue midazolem more with levobupivacaine	
Palmisani et al[124]	Ankle blocks	0.75% levobupivacaine 12 mL vs. 1.0% ropivacaine 12 mL	Onset time longer; success rate lower with levobupivacaine	Post-op pain

Gonzalez-Suarez et al[125]	Axillary BPB	0.33% levobupivacaine 30 mL vs. 0.5% ropivacaine 30 mL	Onset time for motor block longer; sensory block longer with levobupivacaine	Time to be ready for surgery
Piangatelli et al[126]	Infraclavicular BPB	0.5% levobupivacaine 30 mL vs. 0.75% ropivacaine 30 mL vs.	Onset time for motor block shorter; sensory block longer with levobupivacaine	
De Leeuw et al[127]	Psoas compartment + sciatic nerve blocks	0.3% levobupivacaine total 50 mL vs. 0.45% ropivacaine total 50 mL (vs. 0.3% bupivacaine total 50 mL) (All with adrenaline 5 mcg/mL)	Motor impairment less with levobupivacaine than ropivacaine (+ bupivacaine) at 4 hours; higher pain intensity with levobupivacaine than ropivacaine at 4 hours.	
Piangatelli et al[128]	Psoas compartment + sciatic nerve blocks	0.5% levobupivacaine total 40 mL vs. 0.75% ropivacaine total 40 mL	Onset and offset of motor block shorter; time between resolution of motor and resolution of sensory block longer with levobupivacaine	
Foumier et al[129]	Sciatic nerve block	0.5% levobupivacaine 20 mL vs. 0.5% ropivacaine 20 mL	Time to first analgesia longer; less post-operative analgesia required with levobupivacaine	Onset of sensory block; success rate
Casati et al[130]	Interscalene BPB	0.5% levobupivacaine 30 mL vs. 0.5% ropivacaine 30 mL (Followed by patient-controlled interscalene analgesia using 0.125% levobupivaciane or 0.2% ropivacaine respectively)	Motor block at start of infusion greater with levobupivacaine	Onset time of surgical block; rescue intraoperative analgesia required
Casati et al[131]	Sciatic nerve block	0.5% levobupivacaine 20 mL vs. 0.5% ropivacaine 20 mL (After femoral block with 2% mepivacaine 15 mL)		Onset time; failure rate; recovery of sensory and motor function; duration of analgesia
Baskan et al[133]	Axillary BPB	0.5% levobupivacaine 45 mL vs. 0.5% ropivacaine 45 mL (vs. 0.5% bupivacaine 45 mL)	Less complete sensory anaesthesia with levobupivacaine than ropivacaine (+ bupivacaine) at 45 minutes; less complete motor block at elbow with levobupivaciane (+ bupivacaine) than ropivacaine at 45 minutes	Duration of block

(*Continued*)

Table 7. (*Continued*)

	Type of block	Regimen	Differences	Similarities
Study for anaesthesia				
Levobupivacaine vs. bupivacaine				
Baskan et al[133]	Interscalene BPB posterior approach	0.25% levobupivaciane 40 mL vs. 0.25% bupivacaine 40 mL		Onset time of sensory block; time to complete sensory and motor block
Urbanek et al[119]	3-in-1 block	0.5% levobupivacaine 20 mL vs. 0.5% bupivacaine 20 mL (vs. 0.25% levobupivacaine 20 mL)		Onset time of sensory block; analgesia quality
Casati et al[134]	Sciatic nerve block	0.5% levobupivacaine 20 mL vs. 0.5% bupivacaine 20 mL		Onset time of block; duration of motor and sensory block; time to first analgesia
Branco et al[135]	Inferior alveolar nerve block	0.5% levobupivacaine vs. 0.5% bupivacain (Both with adrenaline 5 mcg/mL)		Success; onset and duration of lipand pulpal anaesthesia
Liisanantti et al[132]	Axillary BPB	0.5% levobupivacaine 45 mL vs. 0.5% bupivacaine 45 mL (vs. 0.5% ropivacaine 45 mL)	Less complete anaesthesia with levobupivaciane than bupivacaine (+ ropivacaine)	Duration of block
De Leeuw[127]	Psoas compartment + sciatic nerve block	0.3% levobupivacaine total 50 mL vs. 0.3% bupivacaine total 50 mL (vs. 0.45% ropivacaine total 50 mL) (All with adrenaline 5 mcg/mL)	Less motor impairment with levobupivacaine than bupivacaine at 4,12,48 hrs	
Study for analgesia				
Levobupivacaine vs. ropivacaine				
Foumier et al[129]	Patient-controlled interscalene analgesia	0.25% levobupivacaine vs. 0.25% ropivacaine vs. 0.4% ropivacaine (All after interscalene block with 1.5% mepivacaine 30 mL)	Total volume; rescue ketoprofen lower with levobupivacaine 0.25% + 0.4% ropivacaine than 0.25% ropivacaine	Analgesia quality
Heid et al[138]	Patient-controlled femoral analgesia	0.125% levobupivacaine vs. 0.2% ropivacaine		Volumes used
Casati et al[130]	Patient-controlled interscalene analgesia	0.125% levobupivacaine vs. 0.2% ropivacaine (After block with 0.5% levobupivaciane 30 mL or 0.5% ropivaciane 30 mL respectively)	Volume; total drug used less with levobupivacaine	Analgesia
Levobupivacaine vs. other agents				
Casati et al[139]	Patient-controlled popliteal sciatic nerve block	0.2% levobupivaciane after 30 mL 0.5% levobupivacaine vs. 0.125% levobupivacaine after 30 mL 0.5% levobupivacaine vs. 0.2% ropivacaine after 30 mL 0.5% ropivacaine	Recovery of motor function at 24 hours slower with levobupivacaine 0.2%	Intraoperative efficacy; volume of anaesthesia utilised

doses of anaesthetic agent in the latter study looking at ED95 were much higher than those used to establish equivalence with the studies of Sia et al[35] and Lim et al,[66] but the strict definition of efficacy established in the ED95 study may explain the difference.

When intrathecal levobupivacaine has been compared to an equivalent amount of bupivacaine (both 2.5 mg) for labour analgesia, motor block seems to be less prominent in the levobupivacaine group.[66,68] This may come at a cost of shorter duration of analgesia with levobupivacaine,[66] though this was not apparent in the study by Vercauteren et al,[68] perhaps because they used sufentanil 0.75 mcg/mL together with adrenaline 1.25 mcg/mL in both groups.

Levobupivacaine in Spinal Anaesthesia—Non-Obstetric

Intrathecal levobupivacaine has been used to establish surgical anaesthesia in a range of non-obstetric settings. For perianal surgery, a remarkably low dose of hyperbaric levobupivacaine at 1.5 mg (to achieve a "perianal block" only to S4) was just as successful as a conventional dose of hyperbaric levobupivacaine at 6 mg (for a saddle block), but was associated with earlier time to ambulate, void and readiness for discharge.[69] A low dose of hypobaric 4 mg levobupivacaine with 10 mcg fentanyl for knee arthroscopy was associated with quicker ambulation and higher percentage able to bypass the post-anaesthesia recovery unit when compared with 5 mg with 10 mcg fentanyl,[70] though 3 mg resulted in an unacceptably high failure rate. The advantage of using >7.5 mg of plain levobupivacaine (without any opioid) has been questioned, as there was no difference in time to discharge or first analgesic use or failure rate, even though it shortened the time for readiness to surgery.[71] One study has examined the effect of baricity on levobupivacaine, comparing hyperbaric to isobaric 13.5 mg levobupivacaine at 3 mL for urological surgery[72]: it was found that hyperbaric solutions reduced time to onset of surgical block, time to maximum block, time to regression to L1, time to motor block and duration of motor block, without compromising analgesic effects.

In comparison to ropivacaine at ostensibly equipotent doses in the context of knee arthroscopy, 5 mg hyperbaric levobupivacaine for unilateral block led to similar surgical anaesthesia results and time to discharge as 7.5 mg hyperbaric ropivacaine[73]; isobaric levobupivacaine at 10 mg has also been shown to be similar to isobaric ropivacaine 15 mg.[74] Consistent with the above studies, equivalent mg dosing of isobaric levobupivacaine and ropivacaine for lower abdominal surgery found levobupivacaine to be more potent, with longer duration of motor and sensory block.[75]

When isobaric levobupivacaine has been compared to isobaric bupivacaine, several orthopaedic studies suggest clinical equivalence[76,77] at 15 mg and 17.5 mg. Levobupivacaine may be more haemodynamically stable requiring less ephedrine and atropine than bupivacaine when used at 15 mg for lower abdominal surgery.[75] When used for transurethral surgery (together with fentanyl), levobupivacaine 7.5 mg was found to have longer time for onset of maximum motor block than bupivacaine 7.5 mg,[78,79] whilst having a longer duration of sensory block.[78] However, in one of these studies,[79] the peak sensory block took longer to achieve and was lower in height (and thus associated with less hypotension and nausea) than bupivacaine, presumably because of the use of plain rather than heavy anaesthetic agents. Interestingly, when plain levobupivacaine was compared with hyperbaric bupivacaine at higher doses (12.5 mg each) for transurethral surgery, there was no difference in motor or sensory block.[80]

Studies comparing levobupivacaine and lignocaine for intrathecal anaesthesia are difficult to compare given their vastly different pharmacodynamics. Nevertheless, it is of interest that the motor block resolution with 10 mg of intrathecal levobupivacaine was just as quick as 60 mg intrathecal lignocaine for knee arthroscopy, despite having a more prolonged sensory block and time to voiding.[74] Also, 3 mg of intrathecal levobupivacaine with 10 mcg fentanyl diluted to 3 mL produced similar results (such as onset time of anaesthesia, time to ambulate postoperatively and time for home discharge) as 10 mg lignocaine with 10 mcg fentanyl diluted to 3 mL for laparoscopic sterilization.[81] A statistically significant shorter regression of anaesthesia was demonstrated with lignocaine than levobupivacaine in this study, but this is unlikely to be clinically significant (93 minutes vs. 105 minutes).

The effects of opioids on intrathecal levobupivacaine include a sparing effect. The addition of 25 mcg of fentanyl allowed a reduction of levobupivacaine

Table 8. Ocular blocks for anaesthesia.

Study for anaesthesia	Type of block	Regimen	Differences	Similarities
Levobupivacaine vs. ropivacaine				
Di Donato et al[140]	Peribulbar block	0.5% levobupivacaine 6 mL vs. 0.75% ropivacaine 6 mL (Both with hyaluronidase)	Onset of sensory and motor block shorter; duration of sensory and motor block longer; akinesia score better with levobupivacaine	
Borazan et al[141]	Peribulbar block	0.75% levobupivacaine 5 mL vs. 1% ropivacaine 5 mL (vs. 1:1 mixture of 0.5% bupivacaine + 2% lignocaine, 5 mL)	Akinesia score better at 4 and 6 minutes; pain score lower at 4 hrs post-op with levobupivacaine (+ bupivacaine mixture) than ropivacaine	
Levobupivacaine vs. bupivacaine				
Aksu et al[142]	Retrobulbar	0.5% levobupivacaine 5 mL vs. 0.5% bupivacaine 5 mL (vs. 2% lignocaine 5 mL)	Pain on injection less with levobupivacaine than bupivacaine; intraoperative pain less in levobupivacaine group than bupivacaine (+ lignocaine)	
McLure et al[143]	Peribulbar	0.75% levobupivacaine vs. 0.75% bupivacaine		Volume used; time to satisfactory block; perioperative pain score
Birt et al[144]	Peribulbar	0.75% levobupivacaine 5 mL vs. 0.75% bupivacaine 5 mL (Both with hyaluronidase)		Time to satisfactory anaesthesia and akinesia
Levobupivacaine (+/– mixtures) vs. other				
Aksu et al[142]	Retrobulbar	0.5% levobupivacaine 5 mL vs. 2% lignocaine 5 mL (vs. 0.5% bupivacaine 5 mL)	Duration of motor and sensory block longer with levobupivacaine (+ bupivacaine) than lignocaine; intraoperative pain less in levobupivacaine than lignocaine (+ bupivacaine)	
McLure et al[145]	Sub-Tenon's	0.75% levobupivacaine 4 mL vs. 2% lignocaine 4 mL (Both with hyaluronidase)	Onset of block slower with levobupivacaine	Rescue analgesia; ocular akinesia; supplemental injections
Borazan et al[141]	Peribulbar	0.75% levobupivacaine 5 mL vs. 1:1 mix 0.5%bupivacaine and 2% lignocaine 5 mL (vs. 1% ropivacaine 5 mL)		Verbal pain score; ocular movement score
Raman et al[146]	Sub-Tenon's	1:1 mix 0.5% levobupivacaine + 2% lignocaine 4 mL vs. 4% articane 4 mL	Onset of akinesia slower; inferior akinesia with levobupivaciane mix	Patient and surgeon rating of analgesia

Table 9. Use in local infiltration, topical and intra-articular use.

Study for anaesthesia/analgesia	Type of block	Regimen	Differences	Similarities
Levobupivacaine vs. ropivacaine				
Papagiannopoulou et al[152]	Local infiltration for laparoscopic cholecystectomy	0.5% levobupivacaine 20 mL vs. 1% ropivacaine 20 mL (vs. normal saline 20 mL)	Analgesia longer; consumption of analgesia less with levobupivacaine	
Kakagia et al[153]	Local infiltration for abdominoplasty	0.15% levobupivacaine 100 mL vs. 0.375% ropivacaine 100 mL	Pain lower at 4 and 24 hours with levobupivacaine	Pain at 2 hours
Borazan et al[151]	Topical for cataract surgery	0.75% levobupivacaine vs. 1% ropivacaine (vs. 2% lignocaine)		VAS score
Levobupivacaine vs. bupivacaine				
Bay-Nielsen et al[154]	Local infiltration for inguinal herniorrhaphy	0.25% levobupivacaine 50 mL vs. 0.25% bupivacaine 50 mL		VAS score; post-op analgesia use
Kingsnorth et al[155]	Local infiltration for inguinal herniorrhaphy	0.25% levobupivacaine 50 mL vs. 0.25% bupivacaine 50 mL		Area under curve of VAS over time
Levobupivacaine vs. other				
Jacobson et al[147]	Local infiltration plus intra-articular for knee arthroscopy	0.25% levobupivacaine 20 mL vs. 0.5% levobupivacaine 20 mL vs. 1% lignocaine + 5 mcg/mL adrenaline 20 mL	Analgesia less for 24 hours with 0.5% levobupivacaine compared to other groups; requirement for analgesia more with 0.25% levobupivacaine than other groups	
Rood et al[149]	Local infiltration for impacted 3rd molars	0.75% levobupivacaine vs. 2% lignocaine + 12.5 mcg/mL adrenaline (vs. Placebo)	Analgesia less; VAS lower; time to request analgesia longer with levobupivacaine than other groups	
Demiraran et al[150]	Local infiltration for nasal surgery	0.25% levobupivacaine 5 or 10 mL vs. 2% lignocaine + 12.5 mcg/mL adrenaline 5 or 10 mL	Pain lower with levobupivacaine at 30 min, 1, 2, 8, 12 hours; less analgesic supplementation	
Borazan et al[151]	Topical for cataract surgery	0.75% levobupivacaine vs. 2% lignocaine (vs. 1% ropivacaine)	Pain score lower during surgery, end of surgery, 1st hour post-op with levobupivacine (+ ropivacaine) than lignocaine	
Crincoli et al[148]	Local infiltration for impacted 3rd molars	0.75% levobupivacaine vs. 3% mepivacaine	Pain later; time of first drug consumption later; VAS lower at 1 and 2 hours post-op with levobupivacaine	Onset of anaesthesia

from 7.5 mg to 5.0 to achieve the same block height relevant for inguinal hernia surgery, but with shorter regression of block, time to ambulate, time to micturate and time to discharge.[82] Similarly, the addition of 15 mcg of fentanyl to levobupivacaine for transurethral surgery allowed a reduction in levobupivacaine from 12.5 mg to 11 mg, which resulted in shorter time of motor block and a lower sensory block height.[83]

Levobupivacaine in Epidural Anaesthesia/Analgesia—Obstetric

Anaesthesia

There appears to be no benefit to the addition of opioids when topping up a low-dose epidural infusion for Caesarean section, if opioids have been running in the low-dose mixture already.[84] Doing so was found to increase the incidence of nausea and vomiting without altering onset time of anaesthesia or rate of analgesic supplementation.

For the creation of surgical anaesthesia appropriate for Caesarean section, levobupivacaine has been compared to ropivacaine,[85] bupivacaine[86–88] and with lignocaine mixtures.[89,90] Levobupivacaine 0.5% was found to be similar in onset and quality of analgesia when compared to ropivacaine 0.75%.[87] Levobupivacaine seems to behave similarly to bupivacaine at equivalent mg doses[86–88]; however, lower-limb motor block appeared to be longer, though less intense with levobupivacaine in one study.[88] The increase in duration of motor block with levobupivacaine is surprising given that the epidural MLAC for motor block show that levobupivacaine is slightly less potent than bupivacaine.[33,41]

When levobupivacaine 0.5% was compared to 1.8%–2% lignocaine mixtures, levobupivacaine performed less well, either requiring more analgesia supplement,[89] or taking longer to achieve appropriate blockade.[90] On the other hand, this finding was not borne out in the study by Sia et al,[35] who found similar results between levobupivacaine 0.5% and 2% mixtures. However, this may have been because of the higher amounts of local anaesthetic used in the infusions for labour analgesia before "topping up" for Caesarean section.

Analgesia

Low concentrations of levobupivacaine (around 0.05%) with sufentanil have been used for labour analgesia, but have been found to be less effective for analgesia than higher concentrations (around 0.1% or higher) also with sufentanil.[91] The effect of clonidine (at 2 mcg/mL) on 0.0625% levobupivacaine combined with sufentanil 0.25 mcg/mL using a patient-controlled epidural analgesia technique was an improvement in analgesia, but with a reduction in blood pressure, albeit still in the normal range.[92]

The studies comparing levobupivacaine and ropivacaine for labour analgesia have been confusing. No difference was found when comparing supposedly equipotent concentrations of these agents with sufentanil 0.5 mcg/mL (levobupivacaine 0.0625% against 0.1% ropivacaine).[93] However, when Atienzar et al[94] studied "equipotent" doses of 0.125% levobupivacaine against 0.2% ropivacaine (both with fentanyl 1 mcg/mL), worse pain scores were recorded with levobupivacaine. When a bolus of these same concentrations (ie, 0.125% levobupivacaine and 0.2% ropivacaine) was given and then continued at a rate of 10 mL/hr, both at "non-equipotent" concentrations of 0.1%, analgesia was not different.[95] This, when considered with the study by Atienzar et al,[94] implies that the continuous infusion of equivalent concentrations of levobupivacaine and ropivacaine is important for maintaining equivalent analgesia. Interestingly, two studies show equivalence between levobupivacaine and ropivacaine when used at the same mg dose.[96,97] Additionally, in an admittedly underpowered study to thoroughly examine levobupivacaine, comparison with ropivacaine showed no difference in adequate analgesia, though motor block was less with levobupivacaine.[98]

Whilst one study examining levobupivacaine and bupivacaine at equivalent doses for labour analgesia appears to show similar efficacy for analgesia (with fentanyl),[95] other studies suggest inferior analgesia[93,94,99] and less motor block[94,98] with levobupivacaine.

Levobupivacaine in Epidural Anaesthesia/Analgesia—Non-Obstetric

Anaesthesia

Successful surgical anaesthesia has been achieved using levobupivacaine at a median dose of about 15 mL at 0.5% concentration for lower limb procedures. This seems equivalent to the corresponding volume of ropivacaine 0.75%[100] or bupivacaine 0.5%[101] in

terms of onset and offset of sensory and motor block. Nevertheless, differences have been observed at these doses. In a study involving hip surgery, 0.5% levobupivacaine followed by a PCEA infusion using 0.125% levobupivacaine was associated with requiring more intraoperative anaesthesia than ropivacaine 0.75% followed by a 0.2% solution for PCEA or bupivacaine 0.5% bolus followed by 0.125% solution for PCEA.[102] Also, 0.5% levobupivacaine at 1.2 mL/dermatome had less motor block than bupivacaine 0.5% at the same volume (both given with fentanyl).[103]

These doses are based on an assumption of potency ratio of 1.5:1 for levobupivacaine with regards to ropivacaine, and near equipotency between levobupivacaine and bupivacaine, which has been established by the obstetric literature. At higher concentrations, this ratio may not be optimal. For example, in lower abdominal surgery, epidural anaesthesia using 0.75% levobupivacaine was associated with a more prolonged sensory block and a delayed onset of motor block[104] than 0.75% bupivacaine. Despite this, time to onset of surgical anaesthesia and peak block height were similar.

This potency ratio has also been recently challenged in a recent study by Casati et al[101] who demonstrated equivalent time to onset of surgical anaesthesia conditions and time to recovery of pinprick with similar total mg amounts of levobupivacaine, ropivacaine and bupivacaine, all at 0.5%, suggesting equipotent sensory block potential. However, motor block was greater with bupivacaine and levobupivacaine than ropivacaine immediately after block completion, implying a discrepancy between potencies with regards to motor and sensory block.

Analgesia

In studies looking at dosing of levobupivacaine for analgesia, higher concentrations are associated with better analgesia. Murdoch et al[105] reported superior analgesia with levobupivacaine 0.25% solution run at 6 mL/hr for orthopaedic procedures compared to a 0.125% solution, without an increase in motor block. The superiority of analgesia with higher concentrations is true even when opioids are added to the solution. A weak solution of 0.0625% together with sufentanil 1 mg/mL run at 5 mL/hr (ie, 3.125 mg/hr of levobupivacaine) for thoracotomy pain was found to be less efficacious than a 0.125% levobupivacaine solution together with sufentanil 1 mg/mL run at 5 mL/hr (6.25 mg/hr of levobupivacaine).[106] However, when the dosing was altered to a constant mg/hr regime (ie, running a higher volume for a lower concentration of levobupivacaine),[107–109] no difference in analgesia quality was observed. On the other hand, a higher volume has been associated with a higher upper sensory block height, hypotension and nausea.[109]

When opioids are added to epidural solutions of levobupivacaine, analgesic supplementation is delayed, and lower pain scores at rest and activity are achieved.[110,111] The effect of epinephrine on epidural analgesia for spine surgery was to reduce serum concentrations, but with no difference in sensory block.[112]

In analgesic studies, levobupivacaine 0.125% was found to be similar or equivalent to ropivacaine 0.2%,[101,102,113] but inferior to ropivacaine 0.165%,[114] implying a necessity to ensure equipotency when comparing different local anaesthetic agents. However, the relative potency of ropivacaine to levobupivacaine in the non-obstetric scenario has not been fully characterised. In fact, one study found no difference in analgesia quality with ropivacaine 0.125% and levobupivacaine 0.125% when using a PCEA technique.[115]

In comparing levobupivacaine with racemic bupivacaine, 0.125% levobupivacaine may require more total drug amount than the same concentration of bupivacaine.[102]

Levobupivacaine for Peripheral Nerve Blocks

Anaesthesia

Even though the MLAC for levobupivacaine has been demonstrated to be different depending on the block performed,[116] for ease of comparison, studies will be grouped based on the local anaesthetic agents used.

In studies comparing the effects of different concentrations of levobupivacaine, an ultra-low dose of levobupivacaine (36 mg in 36 mL) for axillary block was unexpectedly found to be just as efficacious as a higher dose (72 mg in 36 mL).[117] This is in contrast to other studies showing slower onset time, shorter regression of motor block in sciatic nerve block,[118] and less complete sensory block and shorter duration with 3-in-1 blocks[119] with lower concentrations.

In terms of adjuvants to levobupivacaine for peripheral blocks, intravenous clonidine prolonged postoperative analgesia in psoas compartment block, whilst perineural infusion of clonidine did not.[120] This may

be because of non-responder behaviour of clonidine with perineural blocks.[121] Dexmedetomidine given perineurally, however, shortened onset of sensory and motor block whilst prolonging the duration of sensory and motor block as well. However, it was also associated with more hypotension and bradycardia.[122]

When comparing levobupivacaine with ropivacaine, studies comparing near-equipotent or equipotent concentrations show the need for more rescue sedation[123], delayed sensory onset[123,124], longer duration of sensory block[125], delayed onset of motor block[125,126], less motor block[127], and slightly shorter motor block duration[128] when using levobupivacaine in a variety of blocks. Studies comparing equivalent mg doses of levobupivacaine and ropivacaine, on the other hand, also show a variety of responses including superior post-op analgesia,[129] no difference[130,131] or less complete sensory and motor block with levobupivacaine.[132] These disparate results may indicate different responses depending on the location of the block performed and the regimen utilised.

Levobupivacaine has been compared with bupivacaine and found to behave similarly in terms of sensory and motor block in most studies.[119,133–135] Nevertheless, these findings are not consistent, with motor block shown to be less with levobupivacaine in some studies[127,132] and sensory block also shown to be less complete.[132]

There has only been one small study examining the potential use of levobupivacaine for intravenous anaesthesia of the upper limb.[136] In eight volunteers, 40 mL of 0.125% levobupivacaine was compared against 40 mL of 0.5% lignocaine. Unsurprisingly, levobupivacaine was found to have slower onset of block and longer duration of block.

Analgesia

There are a number of studies examining peripheral nerve block infusions using a patient-controlled analgesic technique involving perineural levobupivacaine.[130,137–139] Three of these studies demonstrated a greater potency of levobupivacaine compared to ropivacaine. In one of these studies, the volume of 0.25% levobupivacaine utilised for patient-controlled interscalene analgesia was similar to that of 0.4% ropivacaine but not 0.25% ropivacaine[137]; in another study, there was no difference in the volumes utilised for patient-controlled femoral catheters when using 0.125% levobupivacaine or 0.2% ropivacaine[138]; and yet another study suggested that 0.125% levobupivacaine might be even more potent than 0.2% ropivacaine in patient-controlled interscalene analgesia, given the reduction in volume utilised in the levobupivacaine group.[130] The only other study comparing levobupivacaine and other local anaesthetics in peripheral nerve block infusion is difficult to interpret, given that the infusion regimes at different concentrations were administered after an equivalent mg dose of each agent had been given as a bolus.[139]

Levobupivacaine for Ocular Blocks

When comparing allegedly equipotent doses of levobupivacaine and ropivacaine for peribulbar blocks (0.5% levobupivacaine vs. 0.75% ropivacaine[140] or 0.75% levobupivacaine vs. 1% ropivacaine,[141]) levobupivacaine appeared to have better akinesia and longer duration of block. In contrast, "equipotent" doses of levobupivacaine and bupivacaine (either at 0.5% each[142] or 0.75% each[143,144]) produced very similar results, although less pain on injection was noted with levobupivacaine used for retrobulbar block.[142]

Levobupivacaine has also been compared with lignocaine; unsurprisingly, levobupivacaine was found to have a longer duration of motor and sensory block (using 0.5% solution[142]) and a slightly slower onset of block (using 0.75% solution[145]) than lignocaine 2%. On the other hand, when levobupivacaine 0.75% was compared to a mixture of 2% lignocaine and 0.5% bupivacaine, there was no difference in verbal pain score or ocular movement scores over time.[141] A lignocaine 2% plus levobupivacaine 0.5% mix has been compared with 4% articaine in sub-Tenon's anaesthesia and found to have a slower onset and inferior akinesia than the articaine block[146]; however, the differences in potencies do not allow valid comparisons.

Levobupivacaine for Local Infiltration, Topical and Intra-Articular Use

For intra-articular use, 0.5% levobupivacaine has been shown to be more efficacious than 0.25% levobupivacaine or 1% lignocaine with 5 mcg/mL of epinephrine.[147] Comparisons between levobupivacaine and other short acting agents (*viz* mepivacaine[148] and lignocaine[149–151] for local infiltration after removal of

impacted 3rd molars,[148,149] nasal surgery[150] or ocular topical use,[151] consistently show superior analgesia when using levobupivacaine.

In comparisons between levobupivacaine and ropivacaine for local infiltration, levobupivacaine appears to perform better, even at less than "equipotent" concentrations. Longer duration of analgesia and less consumption of analgesic agents were demonstrated with 0.5% levobupivacaine compared to 1% ropivacaine for laparoscopic cholecystectomy,[152] and 0.15% levobupivacaine was associated with less pain at 4 and 24 hours than 0.375% ropivacaine.[153] Nevertheless, when used for ocular topical blocks, no difference was found between 0.75% levobupivacaine and 1% ropivacaine.[151]

In contrast, traditionally quoted "equipotent" concentrations of levobupivacaine appear to be equivalent to bupivacaine.[144,155]

Place in Therapy

Studies in a variety of clinical settings and methods of administration have generally shown that levobupivacaine, ropivacaine and bupivacaine have similar anaesthetic and analgesic effects at equipotent doses. It was noted, however, that intrathecal levobupivacaine tended to have a longer time to onset of adequate motor blockade. There are contrasting reports of the duration and efficacy of sensory and motor blockade following levobupivacaine compared to bupivacaine, with some studies reporting that both drugs behaved similarly, whilst others reported decreased sensory/motor blockade with levobupivacaine. Levobupivacaine was also shown to provide better anaesthesia/analgesia than ropivacaine when used for local infiltration.

Whilst providing comparable anaesthetic and analgesic properties to the more commonly used bupivacaine, levobupivacaine has been shown to be associated with less cardiovascular and CNS toxicity, and a greater safety margin in both animal studies and healthy human volunteers. These properties suggest that levobupivacaine would be a useful alternative to bupivacaine in clinical scenarios where toxicity is perceived to be a higher risk, such as use of higher doses or concentrations (eg, peripheral limb blocks), administration into highly vascular areas (eg, scalp blocks), or in patient populations perceived to potentially be more susceptible to toxicity (eg, paediatric or geriatric populations).

Conclusion

In conclusion, levobupivacaine is a long-acting amino-amide local anaesthetic that is closely related to bupivacaine in structure, and has similar anaesthetic and analgesic properties. In clinical scenarios and patient populations where toxicity is potentially a higher risk, levobupivacaine should be considered as an alternative to racemic bupivacaine due to its safer side-effect profile.

Disclosures

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References

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology*. 1979;51:285–7.
2. Burlacu CL, Buggy DJ. Update on local anesthetics: focus on Levobupivacaine. *Ther Clin Risk Manag*. 2008;4:381–92.
3. Alberg G. Toxicological and local anesthetic effects of optically active isomers of two local anesthetic compounds. *Acta Pharmacol Toxicol Scand*. 1972;31:273–86.
4. Lund PC, Cwik JC, Vallesteros F. Bupivacaine—a new long-acting local anesthetic agent. A preliminary clinical and laboratory report. *Anesth Analg*. 1970;49:103–4.
5. Casati A, Putzu M. Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? *Best Pract Res Clin Anaesthesiol*. 2005;19: 247–68.
6. Levobupivaciane. From http://www.orgyn.com/resources/genrx/D003445.asp. Accessed June 2011.
7. Sasada M, Smith S. Drugs in Anaesthesia and Intensive Care. *Oxford University Press Inc*. New York; 1997:52.
8. Naropin. From http://www.naropin-us.com/. Accessed June 2011.
9. Chirocaine product information [Internet]. Abbott, c2006 [updated 2009 Jan 01]. From https://www.mimsonline.com.au. Accesses June 2011.
10. Crandell JT, Kotelco DM. Cardiotoxicity of local anaesthetics during late pregnancy. *Anesth Analg*. 1985;64:204.
11. Strichartz GR, Berde CB. Local anaesthetics. In: Miller RD, editor, Anaesthesia, 4th ed, New York: Churchill Livingstone, 1994s.
12. Santos AC, Pedersen H. Current controversies in obstetric anaesthesia. *Anesth Analg*. 1994;78:753–60.
13. Greensmith JR, Murray WB. Complications of regional anesthesia. *Curr Opin Anaesthesiol*. 2006;19:531–7.

14. Groban L. Central nervous system and cardiac effects from long-acting amide local anesthetic toxicity in the intact animal model. *Regional Anesthesia and Pain Medicine*. 2003;28:3–11.
15. Chang DH, Ladd LA, Copeland S, Iglesias MA, Plummer JL, Mather LE. Direct cardiac effects of intracoronary bupivacaine, levobupivacaine and Ropivacaine in the sheep. *Br J Pharmacol*. 2001;132:649–58.
16. Nath S, Häggmark S, Johansson G, Reiz S. Differential depressant and electrophysiologic cardiotoxicity of local anesthetics: An experimental study with special reference to lidocaine and bupivacaine. *Anesth Analg*. 1986; 65:1263–1270.
17. Morrison SG, Dominguez JJ, Frascarolo P, Reiz S. A comparison of the electrocardiographic cardiotoxic effects of racemic bupivacaine, levobupivacaine, and ropivacaine in anesthetized swine. *Anesth Analg*. 2000;90:1308–14.
18. Rutten AJ, Nancarrow C, Mather LE, et al. Hemodynamic and central nervous system effects of intravenous bolus doses of lignocaine, bupivacaine and ropivacaine in sheep. *Anesth Analg*. 1989;69:291–9.
19. Butterworth JF, Brownlow RC, Leith JP, et al. Bupivacaine inhibits cyclic-3′5- adenosine monophosphate production. A possible contributing factor to cardiovascular toxicity. *Anesthesiol*. 1993;79:88–95.
20. McLeod GA, Burke D. Levobupivacaine. *Anaesthesia*. 2001;56:331–41.
21. Heavner JE. Cardiac toxicity of local anesthetics in the intact isolated heart model: a review. *Reg Anesth Pain Med*. 2002;27:545–5.
22. Huang YF, Pryor ME, Mather LE, et al. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. *Anesth Analg*. 1998;86:797–804.
23. Ohmura S, Kawada M, Ohta T, Yamamoto K, Kobayashi T. Systemic toxicity and resuscitation in bupivacaine-, levobupivacaine-, or ropivacaine-infused rats. *Anesth Analg*. 2001;93:7430–8.
24. Chang DH, Ladd LA, Wilson KA, et al. Tolerability of large-dose intravenous levobupivacaine in sheep. *Anesth Analg*. 2000;91:671–9.
25. Bardsley H, Gristwood R, Baker H, Watson N, Walter N. A comparison of the cardiovascular effects of Levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol*. 1998;46:245–59.
26. Stewart J, Kellett N, Castro D. The central nervous system and cardiovascular effects on levobupivacaine and Ropivacaine in healthy volunteers. *Anesth Analg*. 2003;97:412–6.
27. Santos AC, Karpel B, Nobel G. The placental transfer and fetal effects of levobupivacaine, racemic bupivacaine and ropivacaine. *Anesthesiol*. 1999;90:1698–703.
28. Brau ME, Branitzki P, Olschewski A, Vogel W, Hempelmann G. Block of neuronal tetrodotoxin-resistant Na+ currents by stereoisomers of piperidine local anesthetics. *Anesth Analg*. 2000;91:1499–505.
29. Kanai Y, Katsuki H, Takasaki M. Comparisons of the anesthetic potency and intracellular concentrations of S(−) and R(+) bupivacaine and ropivacaine in crayfish giant axon in vitro. *Anesth Analg*. 2000;90:415–20.
30. Graf BM, Zausig Y, Zink W. Current status and clinical relevance of studies of minimum local-anaesthetic concentration (MLAC). *Curr Opin Anaesthesiol*. 2005;18:241–5.
31. Lyons G, Columb M, Wilson RC, Johnson RV. Epidural pain relief in labor: potencies of levobupivacaine and racemic bupivacaine. *Br J Anaesth*. 1998; 81:899–901.
32. Camorcia M, Capogna G, Columb MO. Minimum local analgesic doses of ropivacaine, levobupivacaine, and bupivacaine for intrathecal labor analgesia. *Anesthesiol*. 2005;102:646–50.
33. Lacassie HJ, Habib AS, Lacassie HP, Columb MO. Motor blocking minimum local anesthetic concentrations of bupivacaine, levobupivacaine and ropivacaine in labor. *Reg Anesth Pain Med*. 2007;32:323–9.
34. Camorcia M, Capogna G, Beritta C, Columb MO. The relative potencies for motor block after intrathecal ropivacaine, levobupivacaine and bupivacaine. *Anesth Analg*. 2007;104:904–7.
35. Sia AT, Goy RW, Lim Y, Ocampo C. A comparison of median effective doses of intrathecal levobupivacaine and ropivacaine for labor analgesia. *Anesthesiology*. 2005;102:651–6.
36. Parpaglioni R, Frigo MG, Lemma A, Sebastiani M, Barbati G, Celleno D. Minimum local anaesthetic dose (MLAD) of intrathecal levobupivacaine and ropivacaine for Caesarean section. *Anaesthesia*. 2006;61:110–5.
36. Benhamou D, Ghosh C, Mercier FJ. A randomized sequential allocation study to determine the minimum effective analgesic concentration of levobupivacaine and ropivacaine in patients receiving epidural analgesia for labor. *Anesthesiology*. 2003;99:1383–6.
38. Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJ, Goralski KH. Relative analgesic potencies of levobupivacaine and ropivacaine for epidural analgesia in labor. *Anesthesiology*. 2003;99:1354–135.
39. Regionally and locally administered analgesic drugs. In: Macintyre P, Scott D, Schug S, Visser EJ, Walker S, editors. Acute Pain Management Scientific Evidence. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. 2010:123–5.
40. Rosenberg PA, Schug SA. Levobupivacaine base and levobupivacaine hydrochloride. *Br J Anaesth*. 2005;94:544.
41. Lacassie HJ, Columb MO. The relative motor blocking potencies of bupivacaine and levobupivvacaine in labor. *Anesth Analg*. 2003;97:1509–13.
42. Burm AG, van der Meer AD, van Kleef JW, Zeijlmans PW, Groen K. Pharmacokinetics of the enatiomers of bupivacaine following intravenous administration of the racemate. *Br J Clin Pharmacol*. 1994;38:125–9.
43. Denson D, Coyle D, Thompson G, Myers J. Alpha 1-acid glycoprotein and albumin in human serum bupivacaine binding. *Clin Pharmacol Ther*. 1984;35:409–15.
44. Mazoit JX, Cao LS, Samii K. Binding of bupivacaine to human serum proteins, isolated albumin and isolated alpha-1-acid glycoprotein. Differences between the two enantiomers are partly due to cooperativity. *J Pharmacol Exp Ther*. 1996;276:109–15.
45. Simon MJ, Veering BT, Stienstra R, van Kleef JW, Williams SG, McGuire GM, et al. The systemic absorption and disposition of levobupivacaine 0.5% after epidural administration in surgical patients: a stable-isotope study. *Eur J Anaesthesiol*. 2004;6:460–70.
46. Vickers MD, Morgan M, Spencer PS, Read MS. Drugs in Anaesthetic and Intensive Care Practice. 8th ed. Oxford: Butterworth Heinemann; 1999.
47. Pintaric TS, Kozelj G, Stanovnik L, Casati A, Hocevar M, Jankovic JN. Pharmacokinetics of levobupivacaine 0.5% after superficial or combined (deep and superficial) cervical plexus block in patients undergoing minimally invasive parathyroidectomy. *J Clin Anesth*. 2008;20:333–7.
48. Simon MJ, Veering BT, Stienstra R, van Kleef JW, Burm AG. Effect of age on the clinical profile and systemic absorption and disposition of levobupivacaine after epidural administration. *Br J Anaesth*. 2004;93: 512–20.
49. Burlacu CL, Moriarty DC, Buggy DJ. Pharmacokinetics of levobupivacaine, fentanyl and clonidine after administration in thoracic paravertebral analgesia. *Reg Anesth Pain Med*. 2007;32:136–45.
50. Crews JC, Weller RS, Moss J. Levobupivacaine for axillary brachial plexus block: a pharmacokinetic and clinical comparison in patients with normal renal function or renal disease. *Anesth Analg*. 2002;95:219–23.
51. Costello TG, Cormack JR, Mather LE, LaFerlita B, Murphy MA, Harris K. Plasma levobupivacaine concentrations following scalp block in patients undergoing awake craniotomy. *Br J Anaesth*. 2005;94:848–51.
52. Cortinez LI, Fuentes R, Solari S, Ostermann P, Vega M, Munoz HR. Pharmacokinetics of levobupivacaine (2.5 mg/kg) after caudal administration in children younger than 3 years. *Anesth Analg*. 2008;107:1182–4.
53. Ala-Kokko TI, Raiha E, Karinen J, Kiviluoma K, Alahuhta S. Pharmacokinetic of 0.5% levobupivacaine following ilioinguinal-iliohypogastric nerve blockade in children. *Acta Anaesthesiol Scand*. 2005;49:397–400.
54. Rutten AJ, Mather LE, McLean CF. Cardiovascular effects and regional clearances of intravenous bupivacaine in sheep: enantiomeric analysis. *Br J Anaesth*. 1991;67:247–256.
55. Nancarrow C, Mather LE, Runciman WB, Upton RN, Plummer JL. The influence of acidosis on the distribution of lidocaine and bupivacaine into the myocardium and brain of the sheep. *Anesth Analg*. 1987;66: 925–35.
56. Irestedt L, Andreen M, Belfrage I, Fagerstrom T. The elimination of bupivacaine (marcaine) after short intravenous infusion in the dog: with special reference to the role played by the liver and lungs. *Acta Anaesthesiol Stand*. 1978;22:413–22.
57. Sasada M, Smith S. Drugs in Anaesthesia and Intensive Care. 3rd ed. Oxford: Oxford University Press; 2003.

58. Gantenbein M, Attolini L, Bruguerolle B, Villard PH, Puyoou F, Durand A, et al. Oxidative metabolism of bupivacaine into pipecolylxylidine in humans is mainly catalyzed by CYP3A. *Drug Metab Dispos*. 2000;28:383–5.
59. Mather LE, McCall P, McNicol L. Bupivacaine enantiomer pharmacokinetics after intercostal neural blockade in liver transplantation patients. *Anesth Analg*. 1995;80:328–35.
60. Pihlajamaki K, Kanto J, Lindberg R, Karanko M, Kiilholma P. Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women. *Br J Anaesth*. 1990;64:556–62.
61. Pere P, Tuominen M, Rosenberg PH. Cumulation of bupivacaine, desbutylbupivacaine and 4-hydroxybupivacaine during and after continuous interscalene brachial plexus block. *Acta Anaesthesiol Scand*. 1991;35:647–50.
62. Rosenberg PH, Pere P, Hekali R, Tuominen M. Plasma concentrations of bupivacaine and two of its metabolites during continuous interscalene brachial plexus block. *Br J Anaesth*. 1991;66:25–30.
63. Coppejans HC, Vercauteren MP. Low-dose combined spinal-epidural anesthesia for cesarean delivery: a comparison of three plain local anesthetics. *Acta Anaesthesiologica Belgica*. 2006;57:39–43.
64. Gautier P, De Kock M, Huberty L, Demir T, Izydorczic M, Vanderick B. Comparison of the effects of intrathecal ropivacaine, levobupivacaine, and bupivacaine for Caesarean section. *British Journal of Anaesthesia*. 2003;91:684–9.
65. Bremerich DH, Fetsch N, Zwissler BC, Meininger D, Gogarten W, Byhahn C. Comparison of intrathecal bupivacaine and levobupivacaine combined with opioids for Caesarean section. *Current Medical Research and Opinion*. 2007;23:3047–54.
66. Lim Y, Ocampo CE, Sia AT. A comparison of duration of analgesia of intrathecal 2.5 mg of bupivacaine, ropivacaine, and levobupivacaine in combined spinal epidural analgesia for patients in labor. *Anesthesia and Analgesia*. 2004;98:235–9.
67. Van de Velde M, Dreelinck R, Dubois J, et al. Determination of the full dose-response relation of intrathecal bupivacaine, levobupivacaine, and ropivacaine, combined with sufentanil, for labor analgesia. *Anesthesiology*. 2007;106:149–56.
68. Vercauteren MP, Hans G, De Decker K, Adriaensen HA. Levobupivacaine combined with sufentanil and epinephrine for intrathecal labor analgesia: a comparison with racemic bupivacaine. *Anesthesia and Analgesia*. 2001;93: 996–1000.
69. Kazak Z, Ekmekci P, Kazbek K. Hyperbaric levobupivacaine in anal surgery: Spinal perianal and spinal saddle blocks. *Anaesthesist*. 2010;59:709–13.
70. De Santiago J, Santos-Yglesias J, Giron J, Jimenez A, Errando CL. Low-dose, low-concentration levobupivacaine plus fentanyl selective spinal anesthesia for knee arthroscopy: a dose finding study. *Anesthesia and Analgesia*. 2011;112:477–80.
71. Onur O, Sibel AM, Mustafa A, Mehmet Y. Comparison of the effects of intrathecal different dosage of levobupivacaine in elective day-case arthroscopy of the knee. *Middle East Journal of Anesthesiology*. 2010;20:703–8.
72. Sen H, Purtuloglu T, Sizlan A, et al. Comparison of intrathecal hyperbaric and isobaric levobupivacaine in urological surgery. *Minerva Anestesiologica*. 2010;76:24–8.
73. Cappelleri G, Aldegheri G, Danelli G, et al. Spinal anesthesia with hyperbaric levobupivacaine and ropivacaine for outpatient knee arthroscopy: a prospective, randomized, double-blind study. *Anesthesia and Analgesia*. 2005;101:77–82.
74. Breebaart MB, Vercauteren MP, Hoffmann VL, Adriaensen HA. Urinary bladder scanning after day-case arthroscopy under spinal anaesthesia: comparison between lidocaine, ropivacaine, and levobupivacaine. *British Journal of Anaesthesia*. 2003;90:309–13.
75. Mantouvalou M, Ralli S, Arnaoutoglou H, Tziris G, Papadopoulos G. Spinal anesthesia: comparison of plain ropivacaine, bupivacaine and levobupivacaine for lower abdominal surgery. *Acta Anaesthesiologica Belgica*. 2008;59:65–71.
76. Fattorini F, Ricci Z, Rocco A, Romano R, Pascarella MA, Pinto G. Levobupivacaine versus racemic bupivacaine for spinal anaesthesia in orthopaedic major surgery. *Minerva Anestesiologica*. 2006;72:637–44.
77. Glaser C, Marhofer P, Zimpfer G, et al. Levobupivacaine versus racemic bupivacaine for spinal anesthesia. *Anesthesia and Analgesia*. 2002;94: 194–8.
78. Hakan Erbay R, Ermumcu O, Hanci V, Atalay H. A comparison of spinal anesthesia with low-dose hyperbaric levobupivacaine and hyperbaric bupivacaine for transurethral surgery: a randomized controlled trial. *Minerva Anestesiologica*. 2010;76:992–1001.
79. Erdil F, Bulut S, Demirbilek S, Gedik E, Gulhas N, Ersoy MO. The effects of intrathecal levobupivacaine and bupivacaine in the elderly. *Anaesthesia*. 2009;64:942–6.
80. Vanna O, Chumsang L, Thongmee S. Levobupivacaine and bupivacaine in spinal anesthesia for transurethral endoscopic surgery. *Journal of the Medical Association of Thailand*. 2006;89:1133–9.
81. De Santiago J, Santos-Yglesias J, Giron J, Montes de Oca F, Jimenez A, Diaz P. Low-dose 3 mg levobupivacaine plus 10 microg fentanyl selective spinal anesthesia for gynecological outpatient laparoscopy. *Anesthesia and Analgesia*. 2009;109:1456–61.
82. Girgin NK, Gurbet A, Turker G, et al. The combination of low-dose levobupivacaine and fentanyl for spinal anaesthesia in ambulatory inguinal herniorrhaphy. *Journal of International Medical Research*. 2008;36:1287–92.
83. Cuvas O, Basar H, Yeygel A, Turkyilmaz E, Sunay MM. Spinal anesthesia for transurethral resection operations: levobupivacaine with or without fentanyl. *Middle East Journal of Anesthesiology*. 2010;20:547–2.
84. Malhotra S, Yentis SM. Extending low-dose epidural analgesia in labour for emergency Caesarean section—a comparison of levobupivacaine with or without fentanyl. *Anaesthesia*. 2007;62:667–71.
85. Sng BL, Pay LL, Sia AT. Comparison of 2% lignocaine with adrenaline and fentanyl, 0.75% ropivacaine and 0.5% levobupivacaine for extension of epidural analgesia for urgent caesarean section after low dose epidural infusion during labour. *Anaesthesia and Intensive Care*. 2008;36: 659–4.
86. Bader AM, Tsen LC, Camann WR, Nephew E, Datta S. Clinical effects and maternal and fetal plasma concentrations of 0.5% epidural levobupivacaine versus bupivacaine for cesarean delivery. *Anesthesiology*. 1999;90:1596–601.
87. Ngamprasertwong P, Udomtecha D, Charuluxananan S, Rodanant O, Srihatajati C, Baogham S. Levobupivacaine versus racemic bupivacaine for extradural anesthesia for cesarean delivery. *Journal of the Medical Association of Thailand*. 2005;88:1563–8.
88. Faccenda KA, Simpson AM, Henderson DJ, Smith D, McGrady EM, Morrison LM. A comparison of levobupivacaine 0.5% and racemic bupivacaine 0.5% for extradural anesthesia for caesarean section. *Regional Anesthesia and Pain Medicine*. 2003;28:394–400.
89. Balaji P, Dhillon P, Russell IF. Low-dose epidural top up for emergency caesarean delivery: a randomised comparison of levobupivacaine versus lidocaine/epinephrine/fentanyl. *International Journal of Obstetric Anesthesia*. 2009;18:335–41.
90. Allam J, Malhotra S, Hemingway C, Yentis SM. Epidural lidocaine-bicarbonate-adrenaline vs. levobupivacaine for emergency Caesarean section: a randomised controlled trial. *Anaesthesia*. 2008;63:243–9.
91. Tixier S, Bonnin M, Bolandard F, et al. Continuous patient-controlled epidural infusion of levobupivacaine plus sufentanil in labouring primiparous women: effects of concentration. *Anaesthesia*. 2010;65:573–80.
92. Wallet F, Clement HJ, Bouret C, et al. Effects of a continuous low-dose clonidine epidural regimen on pain, satisfaction and adverse events during labour: a randomized, double-blind, placebo-controlled trial. *European Journal of Anaesthesiology*. 2010;27:441–7.
93. Camorcia M, Capogna G. Epidural levobupivacaine, ropivacaine and bupivacaine in combination with sufentanil in early labour: a randomized trial. *European Journal of Anaesthesiology*. 2003;20:636–9.
94. Atienzar MC, Palanca JM, Torres F, Borras R. Gil S, Esteve I. A randomized comparison of levobupivacaine, bupivacaine and ropivacaine with fentanyl, for labor analgesia. *International Journal of Obstetric Anesthesia*. 2008;17:106–1.
95. Sah N, Vallejo M, Phelps A, Finegold H, Mandell G, Ramanathan S. Efficacy of ropivacaine, bupivacaine, and levobupivacaine for labor epidural analgesia. *Journal of Clinical Anesthesia*. 2007;19:214–7.
96. Supandji M, Sia AT, Ocampo CE. 0.2% Ropivacaine and levobupivacaine provide equally effective epidural labour analgesia. *Canadian Journal of Anaesthesia*. 2004;51:918–22.

97. Purdie NL, McGrady EM. Comparison of patient-controlled epidural bolus administration of 0.1% ropivacaine and 0.1% levobupivacaine, both with 0.0002% fentanyl, for analgesia during labour. *Anaesthesia*. 2004;59:133–7.
98. Beilin Y, Guinn NR, Bernstein HH, Zahn J, Hossain S, Bodian CA. Local anesthetics and mode of delivery: bupivacaine versus ropivacaine versus levobupivacaine. *Anesthesia and Analgesia*. 2007;105:756–63.
99. Burke D, Henderson DJ, Simpson AM, et al. Comparison of 0.25% S(−)-bupivacaine with 0.25% RS-bupivacaine for epidural analgesia in labour. *British Journal of Anaesthesia*. 1999;83:750–5.
100. Peduto VA, Baroncini S, Montanini S, et al. A prospective, randomized, double-blind comparison of epidural levobupivacaine 0.5% with epidural ropivacaine 0.75% for lower limb procedures. *European Journal of Anaesthesiology*. 2003;20:979–83.
101. Casati A, Santorsola R, Aldegheri G, et al. Intraoperative epidural anesthesia and postoperative analgesia with levobupivacaine for major orthopedic surgery: a double-blind, randomized comparison of racemic bupivacaine and ropivacaine. *Journal of Clinical Anesthesia*. 2003;15:126–31.
102. Koch T, Fichtner A, Schwemmer U, et al. Levobupivacaine for epidural anaesthesia and postoperative analgesia in hip surgery: a multi-center efficacy and safety equivalence study with bupivacaine and ropivacaine. *Anaesthesist*. 2008;57:475–82.
103. Casimiro C, Rodrigo J, Mendiola MA, Rey F, Barrios A, Gilsanz F. Levobupivacaine plus fentanyl versus racemic bupivacaine plus fentanyl in epidural anaesthesia for lower limb surgery. *Minerva Anestesiologica*. 2008;74:381–91.
104. Kopacz DJ, Allen HW, Thompson GE. A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. *Anesthesia and Analgesia*. 2000;90:642–8.
105. Murdoch JA, Dickson UK, Wilson PA, Berman JS, Gad-Elrab RR, Scott NB. The efficacy and safety of three concentrations of levobupivacaine administered as a continuous epidural infusion in patients undergoing orthopedic surgery. *Anesthesia and Analgesia*. 2002;94:438–44.
106. De Cosmo G, Congedo E, Mascia A, Adducci E, Lai C, Aceto P. Epidural infusion of levobupivacaine and sufentanil following thoracotomy. *Anaesthesia*. 2007;62:994–9.
107. Mendola C, Ferrante D, Oldani E, et al. Thoracic epidural analgesia in post-thoracotomy patients: comparison of three different concentrations of levobupivacaine and sufentanil. *British Journal of Anaesthesia*. 2009;102:418–23.
108. Danelli G, Venuti FS, Zasa M, et al. Continuous lumbar epidural infusion of levobupivacaine: effects of small-or large-volume regimen of infusion. *Acta Anaesthesiologica Scandinavica*. 2009;53:483–8.
109. Dernedde M, Stadler M, Bardiau F, Boogaerts J. Comparison of different concentrations of levobupivacaine for post-operative epidural analgesia. *Acta Anaesthesiologica Scandinavica*. 2003;47:884–90.
110. Crews JC, Hord AH, Denson DD, Schatzman C. A comparison of the analgesic efficacy of 0.25% levobupivacaine combined with 0.005% morphine, 0.25% levobupivacaine alone, or 0.005% morphine alone for the management of postoperative pain in patients undergoing major abdominal surgery. *Anesthesia and Analgesia*. 1999;89:1504–9.
111. Kopacz DJ, Sharrock NE, Allen HW. A comparison of levobupivacaine 0.125%, fentanyl 4 microg/mL, or their combination for patient-controlled epidural analgesia after major orthopedic surgery. *Anesthesia and Analgesia*. 1999;89:1497–503.
112. Kopacz DJ, Helman JD, Nussbaum CE, Hsiang JN, Nora PC, Allen HW. A comparison of epidural levobupivacaine 0.5% with or without epinephrine for lumbar spine surgery. *Anesthesia and Analgesia*. 2001;93:755–60.
113. De Cosmo G, Congedo E, Lai C, et al. Ropivacaine vs. levobupivacaine combined with sufentanil for epidural analgesia after lung surgery. *European Journal of Anaesthesiology*. 2008;25:1020–5.
114. Smet I, Vlaminck E, Vercauteren M. Randomized controlled trial of patient-controlled epidural analgesia after orthopaedic surgery with sufentanil and ropivacaine 0.165% or levobupivacaine 0.125%. *British Journal of Anaesthesia*. 2008;100:99–103.
115. Sitsen E, Van Poorten F, Van Alphen W, Rose L, Dahan A, Stienstra R. Postoperative epidural analgesia after total knee arthroplasty with sufentanil 1 microg/mL combined with ropivacaine 0.2%, ropivacaine 0.125%, or levobupivacaine 0.125%: a randomized, double-blind comparison. *Regional Anesthesia and Pain Medicine*. 2007;32:475–80.
116. McLeod GA, Dale J, Robinson D, et al. Determination of the EC50 of levobupivacaine for femoral and sciatic perineural infusion after total knee arthroplasty. *British Journal of Anaesthesia*. 2009;102:528–33.
117. Zhao X, Wang YW, Chen H, et al. Efficacy of low dose levobupivacaine (0.1%) for axillary plexus block using multiple nerve stimulation. *Anaesthesia and Intensive Care*. 2008;36:850–4.
118. Casati A, Vinciguerra F, Santorsola R, Aldegheri G, Putzu M, Fanelli G. Sciatic nerve block with 0.5% levobupivacaine, 0.75% levobupivacaine or 0.75% ropivacaine: a double-blind, randomized comparison. *European Journal of Anaesthesiology*. 2005;22:452–6.
119. Urbanek B, Duma A, Kimberger O, et al. Onset time, quality of blockade, and duration of three-in-one blocks with levobupivacaine and bupivacaine. *Anesthesia and Analgesia*. 2003;97:888–92.
120. Mannion S, Hayes I, Loughnane F, Murphy DB, Shorten GD. Intravenous but not perineural clonidine prolongs postoperative analgesia after psoas compartment block with 0.5% levobupivacaine for hip fracture surgery. *Anesthesia and Analgesia*. 2005;100:873–8.
121. Duma A, Urbanek B, Sitzwohl C, Kreiger A, Zimpfer M, Kapral S. Clonidine as an adjuvant to local anaesthetic axillary brachial plexus block: a randomized, controlled study. *British Journal of Anaesthesia*. 2005;94:112–6.
122. Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. *Anesthesia and Analgesia*. 2010;111:1548–51.
123. Messina M, Magrin S, Bignami E, et al. Prospective randomized, blind comparison of ropivacaine and levobupivacaine for superficial plexus anesthesia in carotid endoarterectomy. *Minerva Anestesiologica*. 2009;75:7–12.
124. Palmisani S, Arcioni R, Di Benedetto P, De Blasi RA, Mercieri M, Ronconi P. Ropivacaine and levobupivacaine for bilateral selective ankle block in patients undergoing hallux valgus repair. *Acta Anaesthesiologica Scandinavica*. 2008;52:841–4.
125. Gonzalez-Suarez S, Pacheco M, Roige J, Puig MM. Comparative study of ropivacaine 0.5% and levobupivacaine 0.33% in axillary brachial plexus block. *Regional Anesthesia and Pain Medicine*. 2009;34:414–9.
126. Piangatelli C, De Angelis C, Pecora L, Recanatini F, Cerchiara P, Testasecca D. Levobupivacaine and ropivacaine in the infraclavicular brachial plexus block. *Minerva Anestesiologica*. 2006;72:217–21.
127. De Leeuw MA. Dertinger JA, Hulshoff L, et al. The efficacy of levobupivacaine, ropivacaine, and bupivacaine for combined psoas compartment-sciatic nerve block in patients undergoing total hip arthroplasty. *Pain Practice*. 2008;8:241–7.
128. Piangatelli C, De Angelis C, Pecora L, Recanatini F, Testasecca D. Levobupivacaine versus ropivacaine in psoas compartment block and sciatic nerve block in orthopedic surgery of the lower extremity. *Minerva Anestesiologica*. 2004;70:801–7.
129. Fournier R, Faust A, Chassot O, Gamulin Z. Levobupivacaine 0.5% provides longer analgesia after sciatic nerve block using the Labat approach than the same dose of ropivacaine in foot and ankle surgery. *Anesthesia and Analgesia*. 2010;110:1486–9.
130. Casati A, Borghi B, Fanelli G, et al. Interscalene brachial plexus anesthesia and analgesia for open shoulder surgery: a randomized, double-blinded comparison between levobupivacaine and ropivacaine. *Anesthesia and Analgesia*. 2003;96:253–9.
131. Casati A, Borghi B, Fanelli G, et al. A double-blinded, randomized comparison of either 0.5% levobupivacaine or 0.5% ropivacaine for sciatic nerve block. *Anesthesia and Analgesia*. 2002;94:987–90.
132. Liisanantti O, Luukkonen J, Rosenberg PH. High-dose bupivacaine, levobupivacaine and ropivacaine in axillary brachial plexus block. *Acta Anaesthesiologica Scandinavica*. 2004;48:601–6.

133. Baskan S, Taspinar V, Ozdogan L, et al. Comparison of 0.25% levobupivacaine and 0.25% bupivacaine for posterior approach interscalene brachial plexus block. *Journal of Anesthesia*. 2010;24:38–42.
134. Casati A, Chelly JE, Cerchierini E, et al. Clinical properties of levobupivacaine or racemic bupivacaine for sciatic nerve block. *Journal of Clinical Anesthesia*. 2002;14:111–4.
135. Branco FP, Ranali J, Ambrosano GM, Volpato MC. A double-blind comparison of 0.5% bupivacaine with 1:200,000 epinephrine and 0.5% levobupivacaine with 1:200,000 epinephrine for the inferior alveolar nerve block. Oral Surgery *Oral Medicine Oral Pathology Oral Radiology and Endodontics*. 2006;101:442–7.
136. Atanassoff PG, Aouad R, Hartmannsgruber MW, Halaszynski T. Levobupivacaine 0.125% and lidocaine 0.5% for intravenous regional anesthesia in volunteers. *Anesthesiology*. 2002;97:325–8.
137. Borghi B, Facchini F, Agnoletti V, et al. Pain relief and motor function during continuous interscalene analgesia after open shoulder surgery: a prospective, randomized, double-blind comparison between levobupivacaine 0.25%, and ropivacaine 0.25% or 0.4%. *European Journal of Anaesthesiology*. 2006;23:1005–9.
138. Heid F, Muller N, Piepho T, et al. Postoperative analgesic efficacy of peripheral levobupivacaine and ropivacaine: a prospective, randomized double-blind trial in patients after total knee arthroplasty. *Anesthesia and Analgesia*. 2008;106:1559–61.
139. Casati A, Vinciguerra F, Cappelleri G, et al. Levobupivacaine 0.2% or 0.125% for continuous sciatic nerve block: a prospective, randomized, double-blind comparison with 0.2% ropivacaine. *Anesthesia and Analgesia*. 2004;99:919–23.
140. Di Donato A, Fontana C, Lancia F, Celleno D. Efficacy and comparison of 0.5% levobupivacaine with 0.75% ropivacaine for peribulbar anaesthesia in cataract surgery. *European Journal of Anaesthesiology*. 2006;23:487–90.
141. Borazan M, Karalezli A, Oto S, Algan C, Aydin Akova Y. Comparison of a bupivacaine 0.5% and lidocaine 2% mixture with levobupivacaine 0.75% and ropivacaine 1% in peribulbar anaesthesia for cataract surgery with phacoemulsification. *Acta Ophthalmologica Scandinavica*. 2007;85:844–7.
142. Aksu R, Bicer C, Ozkiris A, Akin A, Bayram A, Boyaci A. Comparison of 0.5% levobupivacaine, 0.5% bupivacaine, and 2% lidocaine for retrobulbar anesthesia in vitreoretinal surgery. *European Journal of Ophthalmology*. 2009;19:280–4.
143. McLure HA, Rubin AP. Comparison of 0.75% levobupivacaine with 0.75% racemic bupivacaine for peribulbar anaesthesia. *Anaesthesia*. 1998;53: 1160–4.
144. Birt DJ, Cummings GC. The efficacy and safety of 0.75% levobupivacaine vs. 0.75% bupivacaine for peribulbar anaesthesia. *Eye*. 2003;17:200–6.
145. McLure HA, Kumar CM, Ahmed S, Patel A. A comparison of lidocaine 2% with levobupivacaine 0.75% for sub-Tenon's block. *European Journal of Anaesthesiology*. 2005;22:500–3.
146. Raman SV, Barry JS, Murjaneh S, et al. Comparison of 4% articaine and 0.5% levobupivacaine/2% lidocaine mixture for sub-Tenon's anaesthesia in phacoemulsification cataract surgery: a randomised controlled trial. *British Journal of Ophthalmology*. 2008;92:496–9.
147. Jacobson E, Assareh H, Cannerfelt R, Anderson RE, Jabsson JG. The postoperative analgesic effects of intra-articular levobupivacaine in elective day-case arthroscopy of the knee: a prospective, randomized, double-blind clinical study. *Knee Surgery, Sports Traumatology, Arthroscopy*. 2006;14:120–4.
148. Crincoli V, Di Bisceglie MB, Massaro M, Giuliani R, Favia G, Brienza N. Postoperative pain relief after surgical removal of impacted third molars: a single-blind, randomized, controlled study to compare levobupivacaine and mepivacaine. *Journal of Orofacial Pain*. 2009;23:325–9.
149. Rood JP, Coulthard P, Snowdon AT, Gennery BA. Safety and efficacy of levobupivacaine for postoperative pain relief after the surgical removal of impacted third molars: a comparison with lignocaine and adrenaline. *British Journal of Oral and Maxillofacial Surgery*. 2002;40:491–6.
150. Demiraran Y, Ozturk O, Guclu E, Iskender A, Ergin MH, Tokmak A. Vasoconstriction and analgesic efficacy of locally infiltrated levobupivacaine for nasal surgery. *Anesthesia and Analgesia*. 2008;106:1008–11.
151. Borazan M, Karalezli A, Akova YA, Algan C, Oto S. Comparative clinical trial of topical anaesthetic agents for cataract surgery with phacoemulsification: lidocaine 2% drops, levobupivacaine 0.75% drops, and ropivacaine 1% drops. *Eye*. 2008;22:425–9.
152. Papagiannopoulou P, Argiriadou H, Georgiou M, Papaziogas B, Sfyra E, Kanakoudis F. Preincisional local infiltration of levobupivacaine vs. ropivacaine for pain control after laparoscopic cholecystectomy. *Surgical Endoscopy*. 2003;17:1961–4.
153. Kakagia DD, Fotiadis S, Tripsiannis G, Tsoutsos D. Postoperative analgesic effect of locally infiltrated levobupivacaine in fleur-de-Lys abdominoplasty. *Aesthetic Plastic Surgery*. 2007;31:128–32.
154. Bay-Nielsen M, Klarskov B, Bech K, Andersen J, Kehlet H. Levobupivacaine vs. bupivacaine as infiltration anaesthesia in inguinal herniorrhaphy. *British Journal of Anaesthesia*. 1999;82:280–2.
155. Kingsnorth AN, Cummings CG, Bennett DH. Local anaesthesia in elective inguinal hernia repair: a randomised, double-blind study comparing the efficacy of levobupivacaine with racemic bupivacaine. *European Journal of Surgery*. 2002;168:391–6.