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Levobupivacaine

A Review of its Use in Regional Anaesthesia and Pain Management

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Data Selection

Sources: Medical literature published in any language since 1980 on 'levobupivacaine', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search term was 'levobupivacaine'. Searches were last updated 25 March 2010.

Selection: Studies in patients who received levobupivacaine for regional anaesthesia or analgesia. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Levobupivacaine, regional anaesthesia, labour analgesia, postoperative pain management, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Abstract

Levobupivacaine (Chirocaine®) is a long-acting amide local anaesthetic that is effective when administered as an epidural, spinal, peripheral nerve or ocular block, or by topical application or local infiltration. In comparative trials, its clinical effects were not generally significantly different from those of bupivacaine or ropivacaine, although there was some variability in efficacy findings in different clinical populations. Levobupivacaine was generally well tolerated. Levobupivacaine provides effective anaesthesia and analgesia for a wide range of clinical populations and is a useful alternative to bupivacaine.

1. Introduction

Local anaesthetics, administered alone or in combination with opioids or other drugs, block peripheral nerves and are used to prevent pain, to provide motor blockade during surgery, and for pain control during labour or postoperatively.[1-3]

Bupivacaine is a widely used local anaesthetic that is associated with a reduced requirement for repeat administration or top-up doses because of its prolonged action.[1] At low concentrations, bupivacaine produces a greater degree of sensory than motor block (differential sensitivity),[3] which is an advantage in labour and postoperative pain management, where motor paralysis is unwanted. Bupivacaine may be more cardiotoxic than other local anaesthetics and has been associated with deaths when accidentally injected intravenously and with sudden cuff deflation during Bier's block.[4]

Levobupivacaine (Chirocaine®) is the pure S (−)-enantiomer of racemic bupivacaine, developed as an alternative anaesthetic agent to bupivacaine.[5] Levobupivacaine was developed for the purpose of achieving a lower risk of cardiotoxicity than bupivacaine.[6,7] In the EU, it is indicated for minor (local infiltration and peribulbar block) and major (epidural, intrathecal, peripheral nerve block) surgical anaesthesia, and for pain management.[5] This review focuses, from an EU perspective, on the efficacy and tolerability of levobupivacaine when used for anaesthesia or analgesia and provides an overview of its pharmacological properties.

2. Pharmacodynamic Properties

2.1 Mechanism of Action

Levobupivacaine is an amide local anaesthetic, with a mechanism of action and pharmacodynamic properties that are similar to those of bupivacaine.[2,3] Local anaesthetics exert their anaesthetic and analgesic effects through reversible blockade of neuronal sodium channels.[2,3] As myelinated nerves can be blocked by exposure to local anaesthetic at the nodes of Ranvier, they are more readily blocked than unmyelinated nerves; similarly, small nerves are more easily blocked than large nerves.[3]

Levobupivacaine is lipid soluble, highly protein bound and has a dissociation constant (pKa) of 8.1, similar to that of bupivacaine (8.1) and ropivacaine (8.2), but higher than that of lidocaine (7.7).[3] These pharmacological characteristics determine its speed of onset of action, potency and duration of action.[3] For drugs with a high pKa (pH at which a solution is in equilibrium of half neutral base and half active ionized state), physiological conditions favour the ionized state, which is more slowly absorbed into the axoplasm than the neutral base, leading to a slow onset of action. Highly lipid-soluble drugs are more potent than low lipid-soluble drugs, as they are more readily absorbed through the neuronal membrane, while highly protein-bound drugs have a longer duration of effect, as they remain bound to nerve membrane longer than low protein-bound drugs.[3]

Levobupivacaine is a high potency, long-acting local anaesthetic with a relatively slow onset of action.[3] As with other local anaesthetics, levobupivacaine inhibits impulse transmission and conduction in cardiovascular and other tissues,[1] effects that are important to the development of adverse reactions (section 5).

2.2 Relative Potency

Clinical studies in various patient populations suggest that levobupivacaine is less potent than bupivacaine and more potent than ropivacaine (table I).[8-20] These studies evaluated the minimum local analgesic concentration (MLAC) or the median effective dose (ED_{50}) of levobupivacaine and the comparator agents; MLAC and ED_{50} are estimates of the minimum concentration/dose that provides effective anaesthesia in 50% of patients. In all studies that included bupivacaine, MLAC and ED_{50} values were lower for bupivacaine than for levobupivacaine and ropivacaine. In addition, values were also lower or marginally lower for levobupivacaine than ropivacaine in all but one instance[19] (table I). The apparent higher potency of levobupivacaine over ropivacaine could arise because levobupivacaine (but not ropivacaine) concentrations are reported as the base, which underestimates the concentration by ≈13%.[21] However, in four studies the potency difference was >30%, suggesting that levobupivacaine is in fact more potent than ropivacaine.[11,14,16,20] Compared with local anaesthetic alone, adding an opioid reduced overall local anaesthetic requirements (table I). For example, in one study there was a 4.2-fold reduction in requirements across groups when epidural levobupivacaine, bupivacaine or ropivacaine were combined with sufentanil 0.75 μg/mL.[18]

2.3 Cardiovascular and CNS Effects

Animal studies suggest that bupivacaine is more likely to induce seizures and is more cardiotoxic than levobupivacaine and ropivacaine,[6] but it is unclear how findings in animals translate to the clinical setting. Like bupivacaine and ropivacaine, levobupivacaine prolongs cardiac conduction by blocking sodium channels in a dose-dependent manner, thereby increasing PR interval and QRS duration.[6] It also blocks potassium channels, contributing to corrected QT interval (QT_c) prolongation.[6]

Randomized, double-blind, crossover[22,23] and parallel groups[24] studies in healthy male volunteers compared cardiovascular and/or CNS effects of intravenous levobupivacaine with bupivacaine[22,24] and ropivacaine.[23] In a crossover study (n = 14), levobupivacaine 10 mg/min was associated with significantly smaller reductions in mean stroke index (−5.1 vs −11.9 mL/m^2; p = 0.0001), acceleration index (−0.09 vs −0.20 s^2; p = 0.011) and ejection fraction (−2.5% vs −4.3%; p = 0.024) than bupivacaine 10 mg/min.[22] There were no treatment group differences in PR interval or QT_c. There was also no indication that subjective CNS effects were different between treatment groups.[22] In a parallel groups study (n = 22), in a subgroup who received doses of >75 mg (numbers in analysis not reported), levobupivacaine was associated with a lower mean increase in QT_c than bupivacaine (3 vs 24 ms; p = 0.022).[24] In a second crossover study (n = 13), there were no significant differences between levobupivacaine and ropivacaine in haemodynamic variables (stroke index, cardiac index, acceleration index, PR interval, QRS duration, QTc and heart rate).[23] There was also no treatment difference in time to CNS symptoms.[23] These findings suggest that in

Table I. Relative potency of epidural or spinal levobupivacaine (LEV), bupivacaine (BUP) and ropivacaine (ROP), alone or combined with fentanyl (FEN) or sufentanil (SUF) in patients during labour[8-12,17-19] or undergoing Caesarean section[13-15,20] or lower limb surgery[16] (n = 60–450). Minimum local analgesic concentration (MLAC) after epidural administration of 10[18] or 20 mL[8-10,17] of local anaesthetic (LA) or median effective dose (ED_{50}) after intrathecal administration of LA[11-16,19,20]

Epidural analgesia		
	MLAC (mg/mL)[a]	**Potency ratio (95% CI)**
LA alone		
Lyons et al.[8]	LEV 0.83; BUP 0.81	LEV : BUP 0.98 (0.67, 1.41)
Polley et al.[9]	ROP 0.89; LEV 0.87	ROP : LEV 0.98 (0.80, 1.20)
Benhamou et al.[10]	LEV 0.77; ROP 0.92	LEV : ROP 1.19 (0.91, 1.48)
LA plus opioid		
Robinson et al.[17]	LEV 0.91; LEV + FEN 0.47 (0.50)[b]	NR
Buyse et al.[18]	LEV 1.79; BUP 1.49; ROP 1.94; LEV + SUF 0.40; BUP + SUF 0.15; ROP + SUF 0.42	ROP : BUP 0.77; LEV : BUP 0.83; ROP + SUF : BUP + SUF 0.36; LEV + SUF : BUP + SUF 0.38
Spinal analgesia or anaesthesia		
	ED_{50} (mg)[c]	**Potency ratio (95% CI)**
LA alone		
Sia et al.[11]	LEV 1.07; ROP 1.40	LEV : ROP 1.31 (1.04, 2.01)
Camorcia et al.[12]	LEV 2.94; BUP 2.37; ROP 3.64	LEV : BUP 0.81 (0.69, 0.94); ROP : LEV 0.80 (0.70, 0.92); ROP : BUP 0.65 (0.56, 0.76)
Huysmans et al.[13]	LEV 7.25; BUP 5.42; ROP 7.51	NR
Parpaglioni et al.[14]	LEV 10.58; ROP 14.22	LEV : ROP 1.34 (1.17, 1.40)
Camorcia et al.[15]	LEV 4.83; BUP 3.44; ROP 5.79	LEV : BUP 0.71 (0.51, 0.98); ROP : LEV 0.83 (0.64, 1.09); ROP : BUP 0.59 (0.42, 0.82)
Lee et al.[16]	LEV 5.68; BUP 5.50; ROP 8.41	LEV : BUP 0.97 (0.81, 1.17); ROP : LEV 0.68 (0.55, 0.84); ROP : BUP 0.65 (0.54, 0.80)
LA plus opioid		
Van de Velde et al.[19]	BUP + SUF 1.7; LEV + SUF 2.3; ROP + SUF 2.2	NR
Parpaglioni et al.[20]	LEV 10.65; ROP 14.12; LEV + SUF 4.73; ROP + SUF 6.44	LEV : ROP 1.34 (1.15, 1.41); LEV + SUF : ROP + SUF 1.36 (1.30, 1.43)

a Based on visual analogue scale pain score cutoffs.

b There were two LEV + FEN groups, with FEN doses of 2 μg/mL and 3 μg/mL.

c Dose for effective analgesia,[11,12,19] surgical anaesthesia[13,14,16,20] or lower limb motor block within 5 min of drug administration.[15]

NR = not reported.

humans levobupivacaine has fewer cardiac effects than bupivacaine, but that it is not significantly different from ropivacaine in cardiac effects.[22-24] Levobupivacaine was not significantly different from bupivacaine or ropivacaine in subjective CNS effects or time to CNS symptoms.[22] See section 5 for discussion of the cardiac effects of levobupivacaine in clinical populations.

3. Pharmacokinetic Properties

This section provides an overview of the pharmacokinetics of levobupivacaine. Data are from various sources, including the UK summary of product characteristics[5] and clinical studies in patients who received levobupivacaine as an epidural infusion,[25,26] or peripheral nerve or nerve plexus block.[27-30] Limited data on the pharmacokinetics of levobupivacaine in children[31] and in adults with renal impairment[32] are also briefly reviewed.

3.1 Absorption and Distribution

The absorption of levobupivacaine depends on the route of administration and tissue vascularity at the site of administration.[5] After epidural administration of levobupivacaine 112.5 mg (7.5 mg/mL solution), the mean plasma maximum concentration (C_{max}) was 0.58 μg/mL and

the mean area under the plasma concentration-time curve (AUC) was 3.6 μg • h/mL.[5] In surgical patients, levobupivacaine absorption after epidural administration was biphasic, with rapid absorption of a small quantity of drug into the systemic circulation and slower absorption of the remainder of the drug.[25] The systemic exposure to levobupivacaine was approximately dose proportional following epidural levobupivacaine 75 mg (5 mg/mL solution) and 112.5 mg (7.5 mg/mL solution), and following levobupivacaine doses of 1 and 2 mg/kg, administered during a brachial plexus block.[5]

Epidural levobupivacaine absorption kinetics were affected by age, as the fraction absorbed was decreased and the fast absorption phase (initial phase of biphasic absorption) was shorter in older (aged >70 years) compared with younger (aged 18–44 years) patients.[26] The older patients also had a higher spread of analgesia (by three dermatomes).[26] The clinical relevance of these findings is uncertain, although it is recommended that elderly patients receive reduced doses of levobupivacaine, according to their physical status.[5]

Plasma levobupivacaine absorption data are shown in table II. Consistent with an increased rate of absorption in highly vascular regions, plasma concentrations rose rapidly in patients undergoing scalp block for craniotomy.[29] In five patients who had clinically effective levobupivacaine 5.0 mg/mL posterior lumbar plexus block (30 mL) combined with a sciatic nerve block (20 mL), the median plasma C_{max} was 2.2 μg/mL (range 1.95–3.10 μg/mL) and the concentration rose rapidly (5–10 minutes) after injection.[30]

Although the range of plasma concentrations producing toxic effects is not established, a serum concentration of 2.7 μg/mL 14 minutes after injection was associated with CNS symptoms in a patient with accidental nonlethal intravenous injection.[33]

Levobupivacaine is highly bound to plasma proteins, with *in vitro* binding of >97% with levobupivacaine 0.1–1.0 μg/mL.[5] Following intravenous administration of 50 mL of radiolabelled levobupivacaine 0.48 mg/mL, the steady-state volume of distribution was 56 L, indicating widespread distribution in tissues.[25]

3.2 Metabolism and Elimination

In vitro studies show that levobupivacaine is metabolized by hepatic cytochrome P450 (CYP) enzymes, predominantly by CYP1A2, to form

Table II. Summary of absorption pharmacokinetics of levobupivacaine in surgical patients (pts). Mean values unless stated otherwise

Route of administration (no. of pts)	Concentration; volume or dose	C_{max} (μg/mL)	t_{max} (min)	AUC[a] (μg • h/mL)
Adults				
Epidural block[25] (27)	5 mg/mL; 50 mL	1.0–1.2[b]	6–15[b]	5.9–7.6[b]
Brachial plexus block[32] (11)	5 mg/mL; 50–60 mL	1.2[c]	55[c]	11[c]
Cervical plexus[28]				
superficial (7)	5 mg/mL; 0.35 mg/kg	0.58	30[c]	21.0
deep and superficial (5)	5 mg/mL; 0.35 mg/kg	0.52	20[c]	21.1
Scalp block[29] (10)	5 mg/mL; ≤40 mL[d]	1.6	12	
Thoracic paravertebral block[7] (13)	2.5 mg/mL; 19 mL	0.53	15[c]	
Posterior lumbar plexus and sciatic nerve block[30] (5)	5 mg/mL; 30 + 20 mL[e]	2.2[c]		
Children				
Ilioinguinal-iliohypogastric nerve block[31] (20)	5 mg/mL; 2 mg/kg	1.85	28	2.4

a AUC from time 0 to infinity,[25] to 24 h,[32] to 60 min[28] or to 120 min.[31]

b Range of values across three age groups.

c Median value.

d Mean dose 177 mg.

e 30 mL was injected into the lumbar plexus and 20 mL was injected near the sciatic nerve.

AUC = area under the plasma concentration-time curve; **C_{max}** = maximum concentration; **t_{max}** = time to C_{max}.

3-hydroxylevobupivacaine, and CYP3A4, to form desbutyl-levobupivacaine.[5] Metabolism is extensive, as no unchanged levobupivacaine is detected in the urine or faeces, whereas glucuronic acid and sulphate ester conjugates of 3-hydroxylevobupivacaine are excreted in the urine.[5] In volunteers, after intravenous injection of a single dose of radiolabelled levobupivacaine, 95% of the radioactivity was recovered in the urine (71%) and faeces (24%).[1,5] In patients, after intravenous injection of levobupivacaine 40 mg, the mean terminal elimination half-life ($t_{½\beta}$) was ≈80 minutes.[5] After intravenous infusion, the total plasma clearance of levobupivacaine was 39 L/hour.[5] Levobupivacaine does not undergo racemization *in vivo*.[5]

3.3 Special Populations

There are no relevant data pertaining to the use of levobupivacaine in patients with hepatic impairment.[5] Data are also limited in patients with renal impairment, but there were no significant differences in levobupivacaine AUC, C_{max} and time to C_{max} (t_{max}) values between patients with end-stage renal disease (n = 8) and patients with normal renal function (n = 11) who received axillary block with 50–60 mL of levobupivacaine 5.0 mg/mL.[32] As this was a small study, it would be premature to draw conclusions regarding the safety or otherwise of levobupivacaine in patients with renal disease.[32]

In children aged 2–10 years who received levobupivacaine 5.0 mg/mL (2 mg/kg) as an ilioinguinal-iliohypogastric nerve block, mean C_{max}, AUC and t_{max} values were 1.8 μg/mL, 2.4 μg • h/mL and 28.0 minutes, respectively.[31]

3.4 Drug Interactions

As CYP3A4 and CYP1A2 are involved in the metabolism of levobupivacaine, there is a potential for interactions with inhibitors of these enzymes, such as methylxanthines (CYP1A2 inhibitors), and ketoconazole (a CYP3A4 inhibitor).[5]

Although it is unknown if there are pharmacokinetic interactions with antiarrhythmic drugs, it is recommended that caution is taken when coadministering levobupivacaine with antiarrhythmics that have local anaesthetic effects, such as class III antiarrhythmics and mexiletine, as toxic effects may be additive.[5]

4. Therapeutic Efficacy

This section reviews findings from clinical trials in adults that evaluated the efficacy of levobupivacaine for surgical anaesthesia (section 4.1) and for the management of labour pain and postoperative analgesia (section 4.2).

Randomized, double-blind or observer-blind trials with ≥30 patients per treatment group are included. Where data are lacking, randomized, open-label trials and trials with <30 patients per treatment group are also discussed. Apart from several multicentre trials,[34-40] the trials were single-centre. The main comparator agents to levobupivacaine were other amide local anaesthetics (bupivacaine, ropivacaine and lidocaine [lignocaine]) and fentanyl or other opioids. Additional treatments, including supplemental anaesthesia or analgesia, are identified when these were important to the treatment effect, differed between groups or were clinical endpoints. The trials are mostly fully published, except for some available as abstracts.[41-43]

The main efficacy endpoints included assessments of sensory and motor block, patient intra- or postoperative pain scores, patient and/or clinician assessments of the quality of anaesthesia and other key clinical outcomes. This article focuses on data for sensory and motor block. Sensory block was assessed at different dermatomal levels by response to pinprick, temperature or light touch, while motor block was assessed by the Bromage or modified Bromage scale (0 = no paralysis to 3 = complete paralysis) for the relevant muscle groups. As the trials used somewhat different criteria to establish presence or absence of sensory and motor block, caution should be taken when comparing data across trials. Generally, trials also included a pain assessment based on a visual analogue scale (VAS) [range 0–10 or 0–100, with 0 representing no pain and 10 or 100 a high level of pain] or a verbal pain rating (range 0–10 with 0 representing a low and 10 a high level of pain). Statistical analyses are in per-protocol populations and patient numbers

Table III. Efficacy of epidural levobupivacaine (LEV) in randomized, double-blind trials in patients (pts) undergoing elective Caesarean section.[34,42-45] Time to onset and duration of sensory and motor block after initiation of epidural LEV, bupivacaine (BUP) or ropivacaine (ROP)

Study	Regimen [no. of pts]	Mean time (min)			
		sensory block onset[a]	sensory block duration[b]	motor block onset[c]	motor block duration[d]
Bader et al.[44]	LEV 5.0 mg/mL (30 mL) [30]	8.2	329	17.2	241
	BUP 5.0 mg/mL (30 mL) [30]	6.4	317	12.5	265
Faccenda et al.[34]	LEV 5.0 mg/mL (25 mL) [31]	10.0[e]	486		242
	BUP 5.0 mg/mL (25 mL) [31]	8.4[e]	463		172
Jung et al.[42][f]	LEV 5.0 mg/mL (20 mL) [31]	18.7	224*	26.8	126
	ROP 5.0 mg/mL (20 mL) [31]	11.8	177	16.5	107
Jung et al.[43][f]	LEV 5.0 mg/mL (20 mL) [30]	15.7	221*†	23.5	113†
	BUP 5.0 mg/mL (20 mL) [30]	11.1	198	10.9‡	188
	ROP 5.0 mg/mL (20 mL) [30]	11.0	174	14.0‡	125†
Ngamprasertwong et al.[45]	LEV 5.0 mg/mL (15 mL) [31]	16.7	244	12.3	126
	BUP 5.0 mg/mL (15 mL) [30]	15.0	281	12.0	130

a Time to sensory block at T4–T6,[34,44] or T6.[42,43,45]

b Time to regression of sensory block to T10.[34,42-45]

c Time to modified Bromage score of 2 or 3[44] or >0.[42,43,45]

d Time to modified Bromage score of 0,[44] <3,[45] or the precise criterion for duration of motor block was not specified.[34,42,43]

e Primary endpoint.

f Reported as an abstract.

* $p < 0.05$ vs ROP; † $p < 0.05$ vs BUP; ‡ $p < 0.05$ vs LEV.

cited refer to the per-protocol population, unless otherwise specified.

4.1 Regional Anaesthesia

This section summarizes trials in adult patients that evaluated the use of levobupivacaine as an epidural (section 4.1.1), spinal or spinal-epidural (section 4.1.2), peripheral nerve or ocular (section 4.1.3) block, or by local infiltration or topical application at the surgical site (section 4.1.4).

4.1.1 Epidural Block

Randomized, double-blind,[34,36,42-48] observer-blind[35] or patient-blind[49] single centre[42-49] or multicentre[34-36] trials compared the efficacy of levobupivacaine epidural anaesthesia with that of bupivacaine[34,35,43-45,48] ropivacaine[36,42,43,47] or lidocaine (in combination with adrenaline plus bicarbonate[46] or fentanyl[47,49]) in patients undergoing elective Caesarean section[34,42-45] (table III), urgent Caesarean section[46,47,49] (figure 1), elective lower abdominal surgery[48] (table IV) or lower limb surgery[35,36] (table V). The local anaesthetics were administered in combination with fentanyl in one of these trials.[35] Additional randomized, double-blind trials compared levobupivacaine alone with levobupivacaine plus fentanyl in urgent Caesarean section[50] (figure 1), or in combination with low- or high-dose adrenaline in patients undergoing elective lumbar spine surgery[51] (table IV).

Where specified, included patients were American Society of Anesthesiology (ASA) physical status I or II[34,35,43-46] or I–III,[36,48,51] and were without major medical conditions.[35,36] Patients undergoing urgent Caesarean section were nulliparous,[46,47,49,50] or multiparous,[46,47,49] had singleton pregnancies at full term[46,47,49,50] and were previously healthy.[50] At inception, patients were receiving effective epidural labour analgesia,[46,47,50] but were excluded if they had received pethidine within 4 hours[46,47,50] or epidural supplementation within 2 hours[47] of Caesarean section.

Where specified, the mean/median age in women undergoing Caesarean section ranged from 27 to 34 years,[34,44-47,49,50] whereas, in

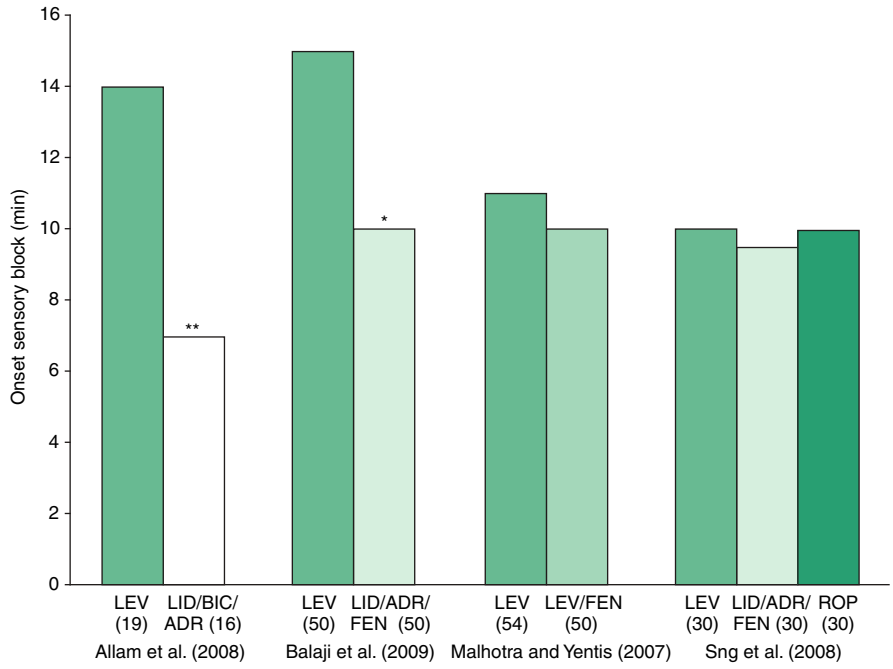

Fig. 1. Efficacy of epidural levobupivacaine (LEV) in randomized, double-blind trials in patients (pts) undergoing urgent Caesarean section. Median times to sensory block to T4,[47,50] T5[46] or T7[49] (primary endpoints[46,47,49,50]). Pts already receiving effective epidural analgesia for labour were randomized to epidural injections of 20 mL of LEV 5.0 mg/mL or lidocaine (LID) 18 mg/mL plus bicarbonate (BIC) 7.6 mg/mL plus adrenaline (ADR) 1 : 200000;[46] 20 mL of LEV 5.0 mg/mL or LID 20 mg/mL plus ADR 100 μg plus fentanyl (FEN) 100μg;[49] 20 mL LEV 5.0 mg/mL or LEV 5.0 mg/mL plus FEN 75 μg;[50] or 15–20 mL of LEV 5.0 mg/mL, LID 20 mg/mL plus ADR 1 : 200 000 plus FEN 50 μg, or ropivacaine (ROP) 7.5 mg/mL.[47] Pt numbers are shown in parentheses (one trial[46] used a sequential analysis technique and was stopped after the first block of 40 pts). * $p < 0.001$, ** $p = 0.00004$ vs LEV.

patients undergoing lower abdominal, lumbar spine or lower limb surgery, the mean age ranged from 43 to 57 years.[35,36,48,51]

Where specified, primary endpoints included the time to sensory block[34,46-50] (adequate for surgery,[34] or to T4,[47,50] T5,[46] T7[49] or T10[48]), the duration of sensory block[35,51] (above the T10 dermatome[51]), or the amount of intraoperative anaesthesia or analgesia supplementation required.[50]

Table IV. Efficacy of epidural levobupivacaine (LEV) in patients (pts) undergoing elective lower abdominal[48] or lumbar spine[51] surgery. Sensory and motor block endpoints in randomized, double-blind trials in pts who received LEV or bupivacaine (BUP),[48] and LEV, LEV plus adrenaline (ADR) 1 : 200 000 (low-dose ADR) or LEV plus ADR 1 : 400 000 (high-dose ADR)[51]

Study	Regimen [no. of pts]	Mean time (min)		
		sensory block onset[a]	sensory block duration[b]	motor block duration[c]
Kopacz et al.[48]	LEV 7.5 mg/mL (20 mL) [28]	14[d]	375	355
	BUP 7.5 mg/mL (20 mL) [28]	14[d]	340	376
Kopacz et al.[51]	LEV 5.0 mg/mL (15 mL) [35]	12	186[d]	204
	LEV 5.0 mg/mL (15 mL) + low-dose ADR [37]	13	202[d]	206
	LEV 5.0 mg/mL (15 mL) + high-dose ADR [36]	13	200[d]	239

a Time to sensory block at T10.

b Time from onset of bilateral sensory block to bilateral regression of sensory block to T10.

c Time to end of motor block (modified Bromage score of 0 in both legs).

d Primary endpoint.

Table V. Efficacy of epidural levobupivacaine (LEV) in patients (pts) undergoing orthopaedic or vascular lower limb surgery.[35,36] Sensory and motor block endpoints and use of supplemental analgesia in randomized, double-blind[36] and observer-blind[35] trials in pts who received LEV plus fentanyl (FEN) 100 μg or bupivacaine (BUP) plus FEN 100 μg;[35] and LEV or ropivacaine (ROP).[36] The analyses were in per-protocol[36] or intent-to-treat[35] populations

Study	Regimen [no. of pts]	Mean[36] or median[35] time (min)			Pts (%)
		sensory block onset[a]	sensory block duration[b]	motor block duration[c]	supplemental analgesia[d]
Casimiro et al.[35]	LEV 5.0 mg/mL (1.2 mL/dermatome) + FEN [49]		170[e]	105	49
	BUP 5.0 mg/mL (1.2 mL/dermatome) + FEN [46]		195[e]	120	54
Peduto et al.[36]	LEV 5.0 mg/mL (15 mL) [30]	29	185	105	4
	ROP 7.5 mg/mL (15 mL) [35]	25	201	95	6

a Time to loss of sensation at T10.

b Duration of sensory block[35] or time to regression of sensory block to T12.[36]

c Duration of motor block (precise method unspecified)[35] or time to modified Bromage score of 0.[36]

d Rescue analgesia during a 12 h follow-up period[35] or supplemental FEN during surgery.[36]

e Primary endpoint.

Patient numbers and details of the randomized treatments are given in tables III–V and in figure 1.

Epidural levobupivacaine provided effective anaesthesia for patients undergoing elective Caesarean section or lower abdominal, lumbar spine or lower limb surgery. Irrespective of the type of surgery, the time to sensory block did not differ significantly between levobupivacaine recipients and recipients of bupivacaine,[34,43-45,48] ropivacaine[36,42,43,47] or lidocaine plus adrenaline plus fentanyl[47] (tables III–V and figure 1). However, levobupivacaine recipients undergoing urgent Caesarean section had a significantly longer time to sensory block than lidocaine plus bicarbonate plus adrenaline recipients[46] and lidocaine plus adrenaline plus fentanyl recipients[49] (figure 1). Furthermore, after taking into account drug preparation times, lidocaine plus adrenaline plus fentanyl still provided a shorter time to sensory block than levobupivacaine (15 vs 18 minutes; $p = 0.05$).[49]

In the majority of trials, the duration of sensory block did not differ between treatment groups[34-36,44,45,48] (table III–V). However, in two trials in patients undergoing elective Caesarean section, the duration of sensory block was significantly longer with levobupivacaine than with ropivacaine[42,43] or bupivacaine[43] (table III), and in a trial in patients undergoing lower abdominal surgery the time to complete regression of sensory block in levobupivacaine recipients was significantly longer than in bupivacaine recipients (551 vs 506 minutes; $p = 0.016$).[48] Furthermore, in a trial in patients undergoing urgent Caesarean section, the duration of sensory block (time for block to recede two segments) was longer in levobupivacaine than in lidocaine plus adrenaline plus fentanyl recipients ($p = 0.001$), whereas there was no significant difference between ropivacaine and lidocaine plus adrenaline plus fentanyl recipients.[47]

In general, there were no significant differences between levobupivacaine recipients and those receiving comparator local anaesthetics in the onset and duration of motor block (table III–V). However, in one trial in patients undergoing elective Caesarean section, levobupivacaine recipients had a longer time to motor block than bupivacaine or ropivacaine recipients, while bupivacaine recipients had a longer duration of motor block than levobupivacaine or ropivacaine recipients[43] (table III). In abdominal surgery, there were no significant between-group differences in measures of rectus abdominis muscle relaxation or in anaesthetist and surgeon ratings of muscle relaxation.[48] In lower limb surgery, a significantly higher proportion of levobupivacaine versus bupivacaine recipients experienced a complete lack of motor block (39% vs 13%; $p = 0.017$).[35]

During elective Caesarean section, patients treated with levobupivacaine had low pain scores that were generally not significantly different from those of bupivacaine or ropivacaine

recipients.[34,42-45] Initial failure to achieve sensory block was uncommon (where specified,[34,44] up to two patients in any treatment group) and no anaesthesia was rated as a failure or unsatisfactory by the anaesthetist or obstetrician.[44,45] There were also no significant between-treatment differences in neonatal outcomes.[34,42-44]

Similarly, in patients undergoing urgent Caesarean section, there were few significant between-treatment differences in other efficacy endpoints, such as requirement for intraoperative epidural supplementation,[46,47] intravenous fentanyl supplementation[47] and neonatal outcomes.[46,47,50] In the trial in women undergoing urgent Caesarean section that compared levobupivacaine alone with levobupivacaine plus fentanyl, coadministering fentanyl 75 μg with levobupivacaine 5.0 mg/mL had no significant impact on time to sensory block (co-primary endpoint)[50] [figure 1], use of supplemental anaesthesia or analgesia (co-primary endpoint), VAS pain scores or neonatal outcomes.[50]

In patients undergoing lumbar spine surgery, when levobupivacaine was administered with adrenaline, there were no differences in anaesthesia endpoints between low-dose and high-dose adrenaline groups.[51] The time to onset of sensory block, the duration of sensory block (time to regression to T10) and the duration of motor block were not significantly different between patients who received levobupivacaine 5 mg/mL with or without adrenaline (table IV). In 85% of all patients, the overall quality of block was rated as 'excellent' or 'good' by investigators, and there was no significant difference between treatments in time to analgesia request.[51]

4.1.2 Spinal and Spinal-Epidural Block

Spinal anaesthesia with levobupivacaine was compared with bupivacaine,[52-57] ropivacaine[52-54,58,59] or lidocaine[58] in randomized, double-blind, single-centre trials in patients undergoing elective Caesarean section;[52,53] inguinal herniorrhaphy or varicoele repair[54] or transurethral endoscopic surgery[55] (table VI); or lower limb surgery[56-59] (table VII).

Where specified, included patients were ASA physical status I,[58] I–II[53,59] or I–III.[54-57] The mean age of Caesarean section patients ranged from 29 to 32 years,[52,53] whereas the mean age of lower abdominal, urological or lower limb surgery patients ranged from 30 to 68 years.[54-59]

The primary endpoint, specified in one trial, was no requirement for rescue epidural lidocaine.[53]

Patient numbers and details of the randomized treatments are provided below (Caesarean section) and in table VI (abdominal/urological surgery) and table VII (lower limb surgery). In the elective Caesarean section trials, patients were randomized to intrathecal levobupivacaine 6.6 mg (n = 31), bupivacaine 6.6 mg (n = 30) or ropivacaine 10 mg (n = 30),[52] and intrathecal levobupivacaine 8 mg (n = 30), bupivacaine 8 mg (n = 30) or ropivacaine 12 mg (n = 30).[53] All patients also received

Table VI. Efficacy of spinal levobupivacaine (LEV) in patients (pts) undergoing inguinal hernia or varicoele repair[54] or transurethral endoscopic surgery.[55] Sensory and motor block endpoints in randomized, double-blind trials in pts who received spinal LEV, bupivacaine (BUP) or ropivacaine (ROP),[54] and spinal LEV or BUP[55]

Study	Regimen [no. of pts]	Mean time (min)			
		Sensory block onset[a]	sensory block duration[b]	motor block onset[c]	motor block duration[d]
Mantouvalou et al.[54]	LEV 5.0 mg/mL (15 mg) [39]	11	230	11	273
	BUP 5.0 mg/mL (15 mg) [39]	13	237	8*†	278
	ROP 7.5 mg/mL (15 mg) + NaCl 0.9% (1 mL) [39]	12	220*†	12	269*†
Vanna et al.[55]	LEV 5.0 mg/mL (2.5 mL) [35]	10	140	8	192
	BUP 5.0 mg/mL (2.5 mL) [35]	7	133	5	154

a Time from intrathecal injection to sensory block at T8[54] or T10.[55]

b Time from intrathecal injection to complete resolution of sensory block,[54] or to regression of sensory block to T12.[55]

c Time from intrathecal injection to a modified Bromage score of 3.[54,55]

d Time from intrathecal injection to a modified Bromage score of 0[54] or <3.[55]

* $p < 0.05$ vs BUP; † $p < 0.05$ vs LEV; ‡ $p < 0.05$ vs ROP.

Table VII. Efficacy of spinal anaesthesia with levobupivacaine (LEV) in patients (pts) undergoing knee arthroscopy,[58,59] hip[56,57] or knee[56] replacement. Sensory and motor block endpoints in randomized, double-blind trials in pts who received LEV, ropivacaine (ROP) or lidocaine (LID),[58] LEV (two doses) or ROP,[59] and LEV or bupivacaine (BUP)[56,57]

Study	Regimen[a] [no. of pts]	Mean[56-58] or median[59] time (min)			
		sensory block onset[b]	sensory block duration[c]	motor block onset[d]	motor block duration[e]
Breebaart et al.[58]	LEV 5.0 mg/mL (10 mg) [30]	8	173*		137
	ROP 7.5 mg/mL (15 mg) [30]	7	167*		142
	LID 20 mg/mL (60 mg) [30]	6	145		127
Cappelleri et al.[59]	LEV 5.0 mg/mL (5 mg) [30]	10			150
	LEV 5.0 mg/mL (7.5 mg) [30]	11			162
	ROP 5.0 mg/mL (7.5 mg) [31]	10			135†
Fattorini et al.[56]	LEV 5.0 mg/mL (3 mL) [29]	12	230	11	256
	BUP 5.0 mg/mL (3 mL) [30]	9	222	8	245
Glaser et al.[57]	LEV 5.0 mg/mL (3.5 mL) [39]	11	228	10	280
	BUP 5.0 mg/mL (3.5 mL) [40]	13	237	9	284

a Intrathecal injection with the pt in the lateral decubitus position[58,59] or sitting.[56,57]

b Onset of sensory block defined as time to sensory block at T12,[58] maximal pinprick score[56] or maximal spread of sensory block,[57] or readiness for surgery defined as time to sensory block at T12 and a modified Bromage score of ≥2.[59]

c Time to regression of sensory block to L2.[56-58]

d Time to maximal definitive modified Bromage score[56] or to a modified Bromage score of 3.[57]

e Time to Bromage/modified Bromage score of 0[57] or ≤1,[58] or motility,[56] or time to end of sensory/motor block.[59]

* $p < 0.05$ vs LID; † $p < 0.05$ vs LEV 7.5 mg.

intrathecal sufentanil 2.5 μg[53] or 3.3 μg,[52] with further epidural administration of 4 mL of lidocaine 20 mg/mL (with additional 2 mL boluses),[52] and 10 mL of lidocaine 20 mg/mL plus adrenaline 1 : 200 000,[53] if required. In patients undergoing lower limb surgery, the intrathecal local anaesthetic injection was given with the patient sitting,[56,57] or in the lateral decubitus position to achieve a stronger block on the operated side.[58,59]

In patients undergoing Caesarean section, levobupivacaine produced an adequate sensory block, although the the trials were discrepant with respect to the comparative requirements for supplemental anaesthesia in levobupivacaine, bupivacaine and ropivacaine recipients.[52,53] In one trial, there was no significant difference between treatment groups in the frequency of epidural anaesthesia supplementation (9%, 10% and 23% in levobupivacaine, bupivacaine and ropivacaine groups, respectively).[52] Two bupivacaine recipients did not reach the T5 sensory block required for surgery.[52] In the second trial, all patients had adequate sensory block, but supplemental epidural anaesthesia (primary endpoint) was required in 20%, 3% and 13% of levobupivacaine, bupivacaine and ropivacaine recipients, respectively ($p = 0.03$ for bupivacaine vs levobupivacaine), indicating that bupivacaine was more effective than levobupivacaine for this endpoint.[53] Levobupivacaine was noninferior to ropivacaine, as the upper limit of the 97.5% confidence interval (CI) for the between-group difference was within a prespecified 20% margin ($p = 0.007$).[53]

Compared with bupivacaine, spinal anaesthesia with levobupivacaine or ropivacaine was associated with a lesser degree of motor block.[52,53] The bupivacaine group had a significantly higher ($p < 0.01$) proportion of patients with a modified Bromage score of 3 at incision and >1 at the end of surgery; in bupivacaine, levobupivacaine and ropivacaine groups, the respective proportions were 70%, 26% and 36% (incision) and 66%, 22% and 30% (end of surgery).[52] Bupivacaine recipients also had a significantly ($p < 0.05$) longer mean duration of motor block (142 vs 121 and 116 minutes in levobupivacaine and ropivacaine groups).[53]

In patients undergoing lower abdominal, urological or lower limb surgery, there was no significant difference between spinal levobupivacaine

recipients and bupivacaine,[54-57] ropivacaine[54,58] or lidocaine[58] recipients in the time to onset of sensory block (tables VI and VII). Similarly, the duration of sensory block did not significantly differ between treatment groups,[55-57] except in patients undergoing lower abdominal surgery (in which the duration of sensory block was significantly shorter with ropivacaine than with levobupivacaine or bupivacaine)[54] [table VI] and in patients undergoing knee arthroscopy (in which the duration of sensory block was significantly shorter with lidocaine than with levobupivacaine or ropivacaine)[58] [table VII].

In patients undergoing lower abdominal surgery, the time to onset of motor block was significantly shorter with bupivacaine than with levobupivacaine or ropivacaine[54] (table VI). However, the time to onset of motor block did not differ significantly between levobupivacaine and bupivacaine recipients in patients undergoing urological[55] or lower limb[56,57] surgery (tables VI and VII).

The duration of motor block did not significantly differ between treatment groups (tables VI and VII),[55-58] apart from in the trial in patients undergoing lower abdominal surgery (in which the duration of motor block was significantly shorter with ropivacaine than with levobupivacaine or bupivacaine)[54] [table VI].

Other endpoints indicated that patients received adequate anaesthesia, irrespective of the local anaesthetic used.[54,55,57,58] In abdominal or urological surgery, there were few patients with insufficient block (none[55] or one patient from each treatment group[54]). No urological surgery patient required intraoperative supplemental analgesics.[55]

In the immediate postoperative period after lower limb surgery, there were no significant treatment group differences in requirements for supplemental analgesia[56-58] or in VAS pain scores.[56,57]

In a trial in patients undergoing knee arthroscopy, there was no significant difference between levobupivacaine and ropivacaine recipients in the time to readiness for surgery (defined as the time to sensory block at T12 and a modified Bromage score of ≥2)[59] [table VII]. The time to complete resolution of the sensory and motor block was significantly shorter in patients receiving ropivacaine 7.5 mg than in those receiving levobupivacaine 7.5 mg, although no significant difference was seen between ropivacaine 7.5 mg and levobupivacaine 5 mg recipients (table VII).[59] In this trial, the local anaesthetic was injected with the patient in the lateral decubitus position and was associated with a strictly unilateral sensory block 30 minutes later in 61%, 50% and 73% of levobupivacaine 5 mg, levobupivacaine 7.5 mg and ropivacaine 7.5 mg recipients, respectively; in the corresponding groups, 83%, 93% and 94% had unilateral motor block.[59]

4.1.3 Peripheral Nerve and Ocular Blocks

Randomized, double-blind, single-centre[60-68] and multicentre[37,38] trials compared levobupivacaine with bupivacaine[60,61] or ropivacaine[37,60,62-64] in axillary brachial plexus,[60] interscalene brachial plexus,[37,61] gluteal[62] and popliteal[63] sciatic nerve, and anterior tibial/peroneal nerve[64] blocks for upper and lower limb surgery (table VIII). Levobupivacaine was also compared with bupivacaine,[65,68] ropivacaine,[66] lidocaine[38,68] or in combination with lidocaine versus articaine[67] in bulbar nerve block[65,66,68] and sub-Tenon block (infiltration of anaesthetic agent into the space between the Tenon capsule and sclera)[38,67] for eye surgery (table IX).

A further randomized, double-blind[69] trial evaluated the efficacy of a psoas compartment block with levobupivacaine 5.0 mg/mL, alone or combined with intravenous or psoas compartment tramadol 1.5 mg/kg in patients undergoing hip or knee arthroplasty.[69]

Where specified, included patients were ASA physical status I–II,[37,62,63] I–III[38,61,65,68,69] or I–IV.[66] The mean/median ages ranged from 38 to 69 years in the upper and lower limb surgery trials,[37,60-64,69] and from 55 to 78 years in the eye surgery trials.[38,65-68]

Where specified, the primary endpoint was the duration of analgesia[62] or the time to onset of block adequate for surgery.[65] In the eye surgery trials, analyses were in the intention-to-treat population, except in a trial that excluded 12 patients who required additional local anaesthetic before surgery to obtain adequate block.[66]

Table VIII. Efficacy of peripheral nerve block with levobupivacaine (LEV) in patients (pts) undergoing upper limb surgery,[60] shoulder surgery[37,61] or hallux valgus repair.[62-64] Surgical block and supplemental anaesthesia/analgesia endpoints in randomized, double-blind trials

Study	Regimen [no. of pts]	Block onset[a] (min)	Analgesia duration[b] (h)	Block duration[c] (h)	IV sedative[d] (% of pts)	IV opioid[e] (% of pts)	Rescue LA[f] (% of pts)	GA[g] (% of pts)
Axillary brachial plexus								
Liisanantti et al.[60]	LEV 5 mg/mL (45 mL) [30]		17	20	60	43	20	7
	BUP 5 mg/mL (45 mL [30]		18	19	73	50	7	3[h]
	ROP 5 mg/mL (45 mL [30]		15	17	27	37	13	3
Interscalene brachial plexus								
Baskan et al.[61]	LEV 2.5 mg/mL (40 mL) [30]	25	7					
	BUP 2.5 mg/mL (40 mL) [30]	22.5	7					
Casati et al.[37]	LEV 5.0 mg/mL (30 mL) [23]	20				35	8[i]	0
	ROP 5.0 mg/mL (30 mL) [24]	20				33	4[i]	0
Gluteal sciatic nerve								
Casati et al.[62]	LEV 5.0 mg/mL (20 mL) [25][j]	30	16[k,l]	13[l]	8[i]	24	8[i]	
	ROP 5.0 mg/mL (20 mL) [25][j]	15	15[k,l]	12[l]	4[i]	20	8[i]	
Popliteal sciatic nerve								
Casati et al.[63]	LEV 5.0 mg/mL (30 mL bolus) → 1.25 mg/mL [20][j,m]	32			60			
	LEV 5.0 mg/mL (30 mL bolus) → 2.0 mg/mL [20][j,m]	34			60			
	ROP 5.0 mg/mL (30 mL bolus) → 2.0 mg/mL [20][j,m]	28			50			
Tibial and peroneal nerves								
Palmisani et al.[64]	LEV 7.5 mg/mL (12 mL) [40][n]	20	12				25	0
	ROP 10 mg/mL (12 mL) [40][n]	10**	11				10*	0

a Mean time to complete sensory block C5–C6,[61] median time to C4–C7 sensory and shoulder/arm motor,[37] sensory[64] or sensory/motor[62] block, or mean time to tibial/peroneal nerve block.[63]

b Mean time to postoperative analgesic use,[60] complete recovery of sensation,[61] end of postoperative analgesia,[64] or median time to administration of ketoprofen.[62]

c Mean time to resolution of sensory/motor block[60] or median time to ankle movement.[62]

d Pt required intraoperative IV propofol[62] or propofol or midazolam.[60]

e Pt required intraoperative IV fentanyl[37,62] or IV fentanyl or tramadol.[60]

f Supplementary LA required,[64] with randomized LA[60] or lidocaine 20 mg/mL.[37,62]

g Pt required GA to complete surgery.

h A pt who required unexpectedly long surgery (200 min).

i Pts were withdrawn from study due to unsuccessful block.

j Sciatic nerve block was performed after a femoral nerve block.

k Primary endpoint.

l Data were estimated from a figure.

m Pts received a bolus dose followed by continuous popliteal sciatic nerve infusion.

n Total trial sample was 40 pts but bilateral ankle blocks were administered with each pt receiving each randomized treatment.

BUP = bupivacaine; **GA** = general anaesthesia; **IV** = intravenous; **LA** = local anaesthetic; **ROP** = ropivacaine; → indicates followed by; * $p < 0.05$, ** $p < 0.001$ vs LEV.

Table IX. Efficacy of levobupivacaine (LEV) in patients (pts) undergoing vitreoretinal,[68] anterior chamber[65] or cataract[38,66,67] surgery. Onset and duration of motor block and duration of sensory block in pts in randomized, double-blind trials

Study	Regimen [no. of pts]	Mean[38,65,68] or median[66-68] time (min)			Akinesia[a]
		motor block onset[b]	motor block duration[c]	sensory block duration[d]	
Retrobulbar					
Aksu et al.[68]	LEV 5.0 mg/mL (5 mL) [45]	2.2	336	251	0
	BUP 5.0 mg/mL (5 mL) [45]	2.3	376	253	0
	LID 20 mg/mL (5 mL) [45]	2.0	220*†	136*†	1*†
Peribulbar					
Birt and Cummings[65]	LEV 7.5 mg/mL + HYA 75 U/mL (5–15 mL) [30]	2.8[e]			
	BUP 7.5 mg/mL + HYA 75 U/mL (5–15 mL) [30]	2.5[e]			
Di Donato et al.[66]	LEV 5.0 mg/mL + HYA 50 U/mL (6 mL) [100]	3‡‡	189‡‡	540‡‡	10‡
	ROP 7.5 mg/mL + HYA 50 U/mL (6 mL) [96]	5	140	380	9
Sub-Tenon					
McLure et al.[38]	LEV 7.5 mg/mL + HYA 15 U/mL (4 mL) [47]	5			1.6
	LID 20 mg/mL + HYA 15 U/mL (4 mL) [44]	3**			1.4
Raman et al.[67]	LEV 5.0 mg/mL + LID 20 mg/mL (4 mL) [34]	10			
	ART 40 mg/mL (4 mL) [31]	4§			

a Median akinesia score (range 0–12) 6 min after block[66] or mean score at the end of surgery,[38] or median akinesia score (range 0–5) 10 min after block.[68]

b Time to extraocular muscle akinesia.

c Time to offset of motor block.

d Time to offset of sensory block.

e Primary endpoint.

ART = articaine; **BUP** = bupivacaine; **HYA** = hyaluronidase; **LID** = lidocaine; **ROP** = ropivacaine; * $p < 0.05$, ** $p < 0.001$ vs LEV; † $p < 0.05$ vs BUP; ‡ $p < 0.01$, ‡‡ $p < 0.001$ vs ROP; § $p = 0.001$ vs LEV + LID.

In the peripheral nerve block trials, patients received a bolus dose of local anaesthetic,[37,60-62,64,69] except in one trial in which patients received a bolus dose followed by a continuous infusion.[63] In the ocular block trials, the local anaesthetic was injected in a single bolus,[38,65-68] and three trials included patients who required additional boluses.[38,65,68] See tables VIII and IX for patient numbers, type of surgery and details of the randomized treatment.

Upper or Lower Limb Surgery

Levobupivacaine was generally effective when administered as a peripheral nerve block in patients undergoing upper and lower limb surgery,[37,60-64] although in two trials[60,64] comparator agents had significantly better anaesthesia on some endpoints. Across all trials but one,[64] there were no significant treatment differences in the onset of sensory and motor block (block adequate for surgery), duration of analgesia, duration of motor block, or requirement for supplemental intravenous sedative or opioid analgesia during surgery (table VIII). Adequate analgesia to commence surgery was established within ≈30 minutes of injection in all levobupivacaine and comparator regimens, regardless of the type of block used, and persisted for >10 hours.

Supplemental intravenous sedatives or opioids were given in 4–73% and 20–50% of patients, respectively (table VIII). In four trials, patients required general anaesthesia or propofol infusion to complete the surgery,[60-63] although no patient required general anaesthesia to complete surgery in one trial of interscalene brachial plexus block[37] or after tibial/peroneal nerve block.[64] In the trial of tibial/peroneal nerve block, the time to onset of surgical block was significantly longer in levobupivacaine than ropivacaine recipients and a significantly lower proportion of ropivacaine than levobupivacaine recipients had an unsuccessful

ankle block (supplementary local anaesthetic required) within 30 minutes of injection (10% vs 25%; $p < 0.05$).[64] However, there were no significant differences in the intraoperative block efficacy in patients undergoing brachial plexus,[37,61] gluteal sciatic nerve[62] or popliteal sciatic nerve[63] blocks (table VIII). In the axillary brachial plexus trial, there were no significant between-group differences in quality of block 5, 15 and 30 minutes after injection, but at 45 minutes significantly ($p < 0.01$) more ropivacaine and bupivacaine recipients had complete sensory block (anaesthesia) in the innervation areas of the four nerves affected by the block.[60]

Combining psoas compartment tramadol with psoas compartment levobupivacaine did not have a significant effect on the onset and/or duration of surgical block and there was no additional analgesic benefit when levobupivacaine was combined with intravenous or psoas compartment tramadol.[69]

Eye Surgery

Levobupivacaine bulbar block provided a rapid onset of extraocular muscle block adequate for surgery in patients undergoing vitreoretinal,[68] anterior segment[65] or cataract[38,66,67] surgery. Time to adequate extraocular muscle block with levobupivacaine was not different from bupivacaine or lidocaine when administered by retrobulbar injection,[68] or from bupivacaine when administered by peribulbar injection,[65] whereas it was significantly shorter than with ropivacaine when administration was by peribulbar administration[66] (table IX). Peribulbar levobupivacaine had further advantages over ropivacaine in that the duration of sensory block was longer for levobupivacaine than ropivacaine[66] (table IX) and the average duration of surgery was significantly shorter (14 vs 16 minutes; $p < 0.001$).[66] After retrobulbar injection, levobupivacaine and bupivacaine led to a significantly longer duration of motor and sensory block than lidocaine[68] (table IX). Compared with both bupivacaine and lidocaine, intraoperative pain was significantly lower in the levobupivacaine group ($p < 0.05$), while surgeon and patient satisfaction were significantly higher ($p < 0.05$).[68] In patients undergoing anterior chamber surgery, there was no significant difference between levobupivacaine and bupivacaine recipients in pain reports or time to first postoperative analgesia.[65]

In trials of sub-Tenon block for cataract surgery, the onset of motor block was slower with levobupivacaine versus lidocaine[38] and for levobupivacaine plus lidocaine versus articaine[67] (table IX). The block was more effective in articaine recipients than levobupivacaine plus lidocaine recipients, as the median extraocular movement scores were significantly lower at all assessment points across the surgery ($p \leq 0.01$), and the surgeon-rated akinesia was higher ($p = 0.001$).[67] There were no significant differences between levobupivacaine plus lidocaine and articaine groups in patient- or surgeon-rated analgesia.[67] Although the time to motor block was significantly slower in levobupivacaine than lidocaine recipients, this was not considered a clinically important difference.[38] No significant differences were seen between levobupivacaine and lidocaine groups for injection to surgery time or in akinesia score at the end of surgery.[38]

4.1.4 Local Infiltration and Topical Administration

The efficacy of topical levobupivacaine eyedrops was compared with that of topical lidocaine[70-72] and ropivacaine[70] eyedrops in randomized, double-blind, single-centre trials in patients undergoing cataract removal (table X), and local infiltration with levobupivacaine was compared with bupivacaine in patients undergoing inguinal herniorrhaphy.[73]

Included patients were ASA physical status I–II,[73] I–III[70,72] or I–IV.[71] The mean age ranged from 63 to 75 years in cataract surgery patients[70-72] and the median ages were 59 (levobupivacaine) and 53 (bupivacaine) years in herniorrhaphy patients.[73]

See table X for patient numbers and details of the randomized treatments in cataract surgery trials. In the herniorrhaphy trial, patients were randomized to receive levobupivacaine 2.5 mg/mL ($n = 33$) or bupivacaine 2.5 mg/mL ($n = 33$) infiltrated in the region of the planned skin incision (20 mL intracutaneously, subcutaneously and to deeper layers), in the subfascia during surgery (20 mL) and prior to the closure of the oblique external fascia (10 mL), with a further 10 mL administered at any point during surgery if required.[73]

Table X. Efficacy of topical levobupivacaine (LEV) eyedrops in patients (pts) undergoing cataract removal. Results of randomized, double-blind trials. The analyses were in per-protocol[71] or intent-to-treat[70,72] populations. All data were estimated from graphs

Study	Regimen [no. of pts]	Pain[a]					
		application[71] or incision[70]	intraoperative	end of surgery	postop 30 min	postop 1 h	postop 2 h
Borazan et al.[70]	LEV 7.5 mg/mL (≈200 μL) [35]	1.0	1.3****	1.5**		1.4**	
	ROP 10 mg/mL (≈200 μL [35]	1.1	1.6**	1.6*		1.4**	
	LID 20 mg/mL (≈200 μL) [35]	1.3	2.1	2		1.7	
Di Donato et al.[71]	LEV 7.5 mg/mL (4 drops) [97]	2.1**	1.0**				0.5**
	LID 40 mg/mL (4 drops) [94]	2.8	1.7				2.8
Fernández et al.[72]	LEV 7.5 mg/mL (4 drops) [126]		1.2***	0.5***	0.2***		
	LID 20 mg/mL (4 drops) [120]		2.1	1.1	0.5		

a Mean pain score (verbal scale range 0–10[70,71] or modified Stevens scale [scale range 0–5]).[72]

LID = lidocaine; **Postop** = postoperative; **ROP** = ropivacaine; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$ vs LID.

Eye Surgery

In patients undergoing cataract removal, topical levobupivacaine provided more effective anaesthesia than lidocaine[70-72] and was not significantly different from ropivacaine on pain and patient and surgeon satisfaction endpoints.[70] In one trial, the time to onset of sensory block after topical application of local anaesthetic was significantly shorter in lidocaine 20 mg/mL than levobupivacaine 7.5 mg/mL recipients (1.6 vs 2.1 minutes; $p < 0.01$), but this difference was not clinically important; the duration of sensory block was longer in levobupivacaine than lidocaine recipients (59 vs 23 minutes; $p < 0.01$).[71]

Across all trials, patient pain scores were significantly higher in lidocaine than levobupivacaine recipients at most measured time points from application of drops through to 2 hours postoperatively (table X). Pain scores were also significantly lower in ropivacaine than lidocaine recipients intraoperatively through to 1 hour postoperatively, whereas there was no difference in scores between ropivacaine and levobupivacaine recipients at any time point.[70] Pain scores at 5 hours[72] or 24 hours[70] post-surgery were not significantly different between treatment groups.

In one trial, patients and surgeons were significantly ($p < 0.01$) more satisfied with levobupivacaine than lidocaine anaesthesia;[71] in a second trial, patient satisfaction did not differ between levobupivacaine and lidocaine groups, although the levobupivacaine group had significantly higher surgeon ratings than in the lidocaine group for patient cooperation ($p = 0.017$) and comfort in performing the surgical procedure ($p = 0.025$).[72] Similarly, patients and clinicians were significantly more satisfied with levobupivacaine and ropivacaine than with lidocaine anaesthesia (both $p < 0.01$ vs lidocaine).[70]

Inguinal Herniorrhaphy

Following inguinal herniorrhaphy, there were no significant differences between levobupivacaine and bupivacaine treatment groups on any measured endpoints (verbal rating of intraoperative pain, postoperative VAS pain scores, satisfaction with anaesthesia, and need for postoperative analgesics).[73] Moderate or severe intraoperative pain was reported by 36% and 21% of levobupivacaine and bupivacaine recipients and supplemental intraoperative local anaesthetic was required by three levobupivacaine and five bupivacaine recipients.[73]

4.2 Analgesia

This section summarizes data from trials that evaluated the analgesic effect of levobupivacaine when administered as an epidural or spinal-epidural block (section 4.2.1), peripheral nerve block (section 4.2.2), or by local infiltration or intra-articular injection (section 4.2.3).

4.2.1 Epidural and Spinal-Epidural Block

Randomized, double-blind[39,74-76] and observer-blind,[77] single-centre[74,75,77] and multicentre[39] trials compared epidural[39,74,76,77] or spinal-epidural[75] levobupivacaine analgesia with bupivacaine[39,74,75,77] or ropivacaine[74,76,77] in women

in labour[39,74,75,77] (tables XI and XII) or after lower limb surgery[76] (table XIII). In some trials, patients also received epidural fentanyl[74] or spinal-epidural sufentanil with[75] or without[76] adrenaline. Further randomized, observer-blind, single-centre[78] and multicentre[40] trials compared epidural levobupivacaine 1.0 mg/mL plus fentanyl 2 μg/mL infused continuously at 10 mL/hour with automated, intermittent 5 mL boluses for labour analgesia (following an intrathecal bolus of fentanyl 25 μg)[78] and compared epidural levobupivacaine plus morphine with morphine alone for total knee replacements.[40] In the latter trial, patients were randomized, after 24 hours of effective epidural anaesthesia with levobupivacaine, to a further 48 hours of treatment with epidural levobupivacaine 1.25 mg/mL (at the infusion rate that had been effective during the non-randomized treatment period) plus patient-controlled analgesia (PCA) with intravenous morphine, or to PCA intravenous morphine alone[40] (table XIII).

In the obstetric trials, the included women were healthy[39,77] or ASA physical status I[78] or I–II,[39,74] with uncomplicated, singleton pregnancies at full term,[39,74,75,77,78] and with a vertex presentation[74,75,77] with cervical dilation ≤5 centimetres.[75,77,78] In the lower limb surgery trials, included patients were ASA physical status I–II[76] or I–III[40] and weighing ≤100 kg.[76] The mean age ranged from 26 to 32 years for women in labour[39,74,75,77,78] and from 62–70 years in patients who had undergone lower limb surgery.[40,76]

Where specified, the primary endpoints were the duration of analgesia, which was the time from the first painless contraction to second successive painful contraction (equivalence criterion for levobupivacaine versus bupivacaine being that the upper/lower limits of the 90% CI for the difference in analgesia duration were <20 minutes),[39] the volume of local anaesthetic consumed,[76] or a difference in mean morphine consumption of ≥0.6 mg/h (effect size standard deviation ratio of ≥0.5).[40]

See tables XI–XIII for patient numbers and details of the randomized treatments.

Labour

Epidural or spinal-epidural levobupivacaine provided effective analgesia during labour.[39,74,75,77,78] Across the epidural levobupivacaine trials (table XI), there were no significant differences between levobupivacaine and comparator local anaesthetic groups according to analgesia or motor block

Table XI. Efficacy of epidural levobupivacaine (LEV) analgesia in pregnant women in labour at full term. Analgesia and motor block endpoints in patients (pts) in randomized, double-blind[39,74] or observer-blind[77] trials

Study	Regimen [no. of pts]	Time (mins)		% of pts	
		analgesia onset[a]	analgesia duration[b]	suppl LA	motor block[c]
Burke et al.[39]	LEV 2.5 mg/mL (10 mL) with 10 mL top-ups prn [68]	12	49[d]		34
	BUP 2.5 mg/mL (10 mL) with 10 mL top-ups prn [69]	12	51[d]		37
Camorcia and Capogna[77]	LEV 0.625 mg/mL + SUF 10 μg (20 mL) [34]	20	114*		91
	BUP 0.625 mg/mL + SUF 10 μg (20 mL) [35]	20	89		94
	ROP 1.0 mg/mL + SUF 10 μg (20 mL) [37]	21	119*		94
Sah et al.[74]	LEV 1.25 mg/mL + FEN 100 μg (8 mL) → LEV 1.25 mg/mL + FEN 2 μg/mL (at 12 mL/h) [54]	10		39	22
	BUP 1.25 mg/mL + FEN 100 μg (8 mL) → BUP 1.25 mg/mL + FEN 2 μg/mL (at 12 mL/h) [50]	12		36	34
	ROP 2.0 mg/mL + FEN 100 μg (8 mL) → ROP 1.0 mg/mL + FEN 2 μg/mL (at 12 mL/h) [50]	9		50	36

a Median[39] or mean[77] time to a painless contraction after first injection, or mean time to T10 sensory block plus pt comfort.[74]

b Median time from first painless contraction to second successive painful contraction[39] or mean time to request for pain relief.[77]

c Pts with a modified Bromage score of >0 after the first top-up of LA,[39] or <4 at 3 h,[74] or the pt was able to walk.[77]

d Primary endpoint; met equivalence criterion, with time difference between groups of −4 (90% CI −13, 6) and 90% CI limits <20 min.

BUP = bupivacaine; **FEN** = fentanyl; **LA** = local anaesthetic; **prn** = as required; **ROP** = ropivacaine; **SUF** = sufentanil; **suppl LA** = supplemental LA; → indicates followed by; * $p < 0.01$ vs BUP.

endpoints,[39,74,77] except that in one trial the duration of analgesia was longer in levobupivacaine and ropivacaine recipients than in bupivacaine recipients.[77] In one trial, the prespecified equivalence criterion for levobupivacaine versus bupivacaine was met for the duration of analgesia (primary endpoint)[39] [table XI]. There was no significant difference in the geometric mean area under the curve for pain versus time in levobupivacaine versus bupivacaine treatment groups (restricted to patients who did not have adequate analgesia after the first bolus and subsequent top-up).[39] There were also no significant differences between levobupivacaine, bupivacaine and ropivacaine treatment groups in mean VAS pain scores during labour.[74] Furthermore, there were no significant treatment differences in the percentage of patients requiring further local anaesthetic, the incidence of spontaneous vaginal delivery, or in other maternal or fetal/neonatal outcomes in three of the trials.[39,74,77]

Following spinal-epidural anaesthesia, there were no significant differences in the duration and quality of analgesia between spinal-epidural levobupivacaine and bupivacaine (both agents were combined with sufentanil and adrenaline), except that no levobupivacaine recipients had motor block, whereas 34% of bupivacaine plus sufentanil recipients had motor block (table XII).[75] There were no differences in the incidence of spontaneous vaginal delivery or other obstetric/neonatal outcomes.[75]

Automated, intermittent administration of epidural levobupivacaine may be better than continuous epidural infusion.[78] The automated administration treatment group (n = 30) experienced a lower incidence of breakthrough pain (10% vs 37%; $p < 0.05$) and higher satisfaction with analgesia (score of 97 vs 89; $p < 0.05$) [scored from 0 (very dissatisfied) to 100 (extremely satisfied)] than the continuous infusion group (n = 30). There were no significant between-treatment differences in the mean duration of analgesia, mean duration of labour, mean duration of painless labour or local anaesthetic consumption.[78]

Postoperative Analgesia after Lower Limb Surgery

Levobupivacaine provided effective postoperative analgesia in patients undergoing knee or hip replacement surgery.[40,76] Over a 48-hour observation period, patient-controlled epidural anaesthesia (PCEA) levobupivacaine led to a lower consumption of local anaesthetic agent plus sufentanil than PCEA ropivacaine (primary endpoint)[76] [table XIII], suggesting either a difference in potency between the two local anaesthetics or in duration of analgesia, favouring levobupivacaine. In the first 48 hours, the mean dose of local anaesthetic (223 vs 365 mg; $p = 0.007$) and the mean number of PCEA demands (28 vs 39; $p = 0.04$) was significantly lower with levobupivacaine than with ropivacaine, although the PCEA injection attempt ratio did not significantly differ between groups.[76] Across patients receiving PCEA levobupivacaine or ropivacaine, mean pain scores were <1.5 at rest and <2.5 on mobilization (VAS scale range 0–10), and there were no significant treatment differences.[76]

Table XII. Efficacy of spinal-epidural levobupivacaine (LEV) in pregnant women in labour at full term. Analgesia and motor block in patients (pts) who received LEV or bupivacaine (BUP) in a randomized, double-blind trial[75]

Regimen [no. of pts]	Analgesia onset[a] (min)	Analgesia duration; spinal (epidural)[b] [min]	Dose of epidural LA[c] (mg)	Motor block[d] (% of pts)
LEV 1.25 mg/mL + SUF 0.75 μg/mL + ADR 1 : 800 000 (2 mL IT with 10 mL epidural top-ups) [37]	5.1	94 (104)	27	0*
BUP 1.25 mg/mL + SUF 0.75 μg/mL + ADR 1 : 800 000 (2 mL IT with 10 mL epidural top-ups) [38]	4.6	95 (108)	28	34

a Mean time to first painless contraction.

b Mean time from complete analgesia to reappearance of pain.

c Mean dose.

d Modified Bromage score of 1.

ADR = adrenaline; **IT** = intrathecal; **LA** = local anaesthetic; **SUF** = sufentanil; * $p < 0.05$ vs BUP.

Table XIII. Efficacy of epidural (Epi) and spinal-Epi levobupivacaine (LEV) analgesia in patients (pts) after knee replacement[40] and knee or hip replacement.[76] Local anaesthetic (LA) consumed, morphine (MOR) consumed and motor block in pts in randomized, double-blind[76] and observer-blind[40] trials

Study	Regimen [no. of pts]	Median MOR consumed (mg/h)	LA plus SUF consumed		Motor block[a] (% of pts)
			24 h (mL)	48 h (mL)	
Casati et al.[40]	Epi LEV 1.25 mg/mL (≤16 mL/h for 24 h) → 48 h Epi LEV 1.25 mg/mL + PCA IV MOR[b] [96]	0.21*[c]			0[d]
	Epi LEV 1.25 mg/mL (≤16 mL/h for 24 h) → 48 h PCA IV MOR alone[b] [90]	0.43[c]			0[d]
Smet et al.[76]	PCEA LEV 1.25 mg/mL + SUF 1 μg/mL [40][e]		113	178†[c]	7.5
	PCEA ROP 1.65 mg/mL + SUF 1 μg/mL [38][e]		141	221[c]	2.6

a Bromage score of >0 during PCEA[76] or during day 2 of Epi LEV or PCA MOR.[40]

b MOR bolus of 1 mg with 6 min lockout period to a maximum of 24 mg per 4 h.

c Primary endpoint.

d Estimated from a graph.

e Epi analgesia (3 mL/h with additional 4 mL boluses as required [lockout 20 min]) was initiated after spinal anaesthesia with BUP 5.0 mg/mL plus SUF 5 μg (3 mL). The basal Epi infusion was continued for 24 h.

BUP = bupivacaine; **IV** = intravenous; **PCA** = patient-controlled analgesia; **PCEA** = patient-controlled epidural analgesia; **ROP** = ropivacaine; **SUF** = sufentanil; → indicates followed by; * $p = 0.005$ vs IV MOR alone; † $p = 0.02$ vs ROP.

Compared with recipients of PCA intravenous morphine alone, recipients of PCA intravenous morphine plus epidural levobupivacaine had a significantly lower hourly morphine consumption (primary endpoint) [table XIII].[40] Patients receiving epidural levobupivacaine in addition to PCA intravenous morphine also had significantly lower VAS pain scores during motion ($p < 0.05$) than patients who received PCA intravenous morphine alone at 6, 12, 18, 36, 42 and 48 hours.[40]

Few patients experienced motor block,[40,76] and there were no significant between-treatment differences in the incidence of motor block on PCEA[76] (table XIII), or during a 48-hour epidural analgesia treatment period.[40]

4.2.2 Peripheral Nerve Block

Randomized, double-blind, single-centre trials compared the postoperative analgesic effect of levobupivacaine with ropivacaine,[79] lidocaine[80] or saline,[80,81] administered as a femoral[79,81] or inferior alveolar nerve[80] block, in patients undergoing total knee replacement,[79] anterior cruciate ligament repair[81] or extraction of impacted molars.[80]

Where specified, patients were ASA physical status I or II[81] or II–III,[79] or assessed as healthy.[80] The mean age ranged from 24–28 years,[80,81] except in knee replacement patients, whose mean age was ≥70 years.[79]

Where specified, the primary endpoints were postoperative local anaesthetic consumption,[79] and proportion of patients who required analgesia in the first 2 hours, postoperatively.[80]

See table XIV for details of randomized treatments and patient numbers.

In patients undergoing lower limb surgery, femoral nerve block with levobupivacaine provided effective analgesia during the postoperative period, whether administered by patient-controlled femoral nerve analgesia,[79] or as a bolus with or without continuous levobupivacaine infusion.[81] Ropivacaine recipients consumed a 1.6-fold higher dose than did levobupivacaine recipients (primary endpoint) [table XIV], suggesting that ropivacaine was less potent than levobupivacaine.[79] However, there was no significant difference between treatments in the use of supplemental opioid analgesia (table XIV), nor in the number of patient-controlled analgesia attempts, additional boluses of local anaesthetic, total local anaesthetic volume, patient pain ratings or patient satisfaction.[79]

Compared with saline infusion, the levobupivacaine treatment groups (combined) had significantly lower cumulative oxycodone consumption

Table XIV. Postoperative analgesia with levobupivacaine (LEV) administered as a peripheral nerve block in patients (pts) in randomized, double-blind trials who were undergoing knee replacement,[79] anterior cruciate ligament (ACL) repair[81] or removal of impacted molars.[80] The analyses were in per-protocol[79,81] or intent-to-treat[80] populations

Study	Regimen [no. of pts]	Supplemental opioids[a]			LA[b]	
		% of pts	time to (min)[c]	dose (mg)	mL	mg
Femoral nerve block						
Heid et al.[79]	PCRA LEV 1.25 mg/mL (5 mL/h with 5 mL boluses and 30-min lockout) [30][d]	37		0	445	556*[h]
	PCRA ROP 2.0 mg/mL (5 mL/h with 5 mL boluses and 30-min lockout) [30][e]	57		11.2	465	930[h]
Williams et al.[81]	LEV 2.5 mg/mL bolus (30 mL) + saline infusion (270 mL at 5 mL/h) [n = 79][f]			79†		
	LEV 2.5 mg/mL bolus (30 mL) + LEV 2.5 mg/mL infusion (270 mL at 5 mL/h) [n = 76][f]			75†		
	Saline bolus (30 mL) + infusion (270 mL at 5 mL/h) [n = 78][f]			90		
Inferior alveolar nerve block						
Rood et al.[80]	LEV 7.5 mg/mL (2 mL in nerve, 1 mL buccal) [n = 30][g]	53[h]	258‡			
	LID 20 mg/mL + ADR 1 : 80 000 (2 mL in nerve, 1 mL buccal) [n = 31][g]	71[h]	86			
	Saline (2 mL in nerve, 1 mL buccal) [n = 32][g]	72[h]	93			

a Pts received opioids, postoperatively,[79] or supplemental analgesics in the first 2 h, postoperatively.[80]

b Mean local anaesthetic[79] or mean oxycodone[81] consumed during the d 1–3 postoperative period.

c Mean time to receiving supplemental opioids.

d Surgical anaesthesia was LEV 3.125 mg/mL by femoral (35 mL) plus sciatic (25 mL) nerve block plus general anaesthesia.

e Surgical anaesthesia was ROP 5.0 mg/mL by femoral (35 mL) plus sciatic (25 mL) nerve block plus general anaesthesia.

f Surgical anaesthesia was spinal bupivacaine 7.5 mg/mL (1.2–1.8 mL) plus propofol infusion.

g Pts received local anaesthetic after induction of general anaesthesia.

h Primary endpoint.

ADR = adrenaline; **LA** = local anaesthetic; **LID** = lidocaine; **PCRA** = patient controlled femoral nerve analgesia; **ROP** = ropivacaine; * $p < 0.0001$ vs ROP; † $p = 0.039$ (for LEV groups combined) vs saline; ‡ $p = 0.045$ vs LID.

on days 1–3 (table XIV).[81] During days 1–2 the levobupivacaine bolus plus infusion group consumed less oxycodone than the saline group (55 vs 70 mg; $p = 0.011$), but there were no significant between-treatment differences over the full days 1–4 observation period.[81] The levobupivacaine bolus and continuous infusion group also had a significantly lower proportion of patients with moderate-severe pain on movement than the levobupivacaine plus saline infusion and saline infusion groups on day 1 (18%, 33% and 46%, respectively; $p = 0.035$ vs levobupivacaine plus saline and $p < 0.001$ vs saline) and day 2 (20%, 35% and 42%, respectively; $p = 0.033$ vs levobupivacaine plus saline and $p = 0.003$ vs saline), postoperatively. The only factor consistently predicting lower pain scores across days 1–4 was membership in the levobupivacaine continuous infusion group (odds ratios 0.3–0.5; $p \leq 0.003$). Together, these findings suggest that peripheral nerve block with a levobupivacaine bolus followed by levobupivacaine infusion provides the most effective pain management strategy.[81]

In dental patients, inferior alveolar nerve levobupivacaine block provided more effective postoperative analgesia than saline or lidocaine plus adrenaline.[80] There was no significant between-group difference in the use of supplemental analgesia (primary endpoint), but levobupivacaine recipients had a ≈3-fold longer period before supplemental analgesia than saline or lidocaine plus adrenaline recipients (table XIV). Mean maximum VAS pain scores were 40, 53 and 48 in levobupivacaine, saline and lidocaine groups, respectively.[80]

4.2.3 Local Infiltration or Intra-Articular Injection

Randomized, double-blind[82-86] or observer-blind,[41] single-centre trials compared postoperative analgesia with levobupivacaine local infiltration[41,82-85] or intra-articular injection[86] with saline[82,83] or usual care,[41] bupivacaine[84] or lidocaine[85,86] in patients undergoing laparoscopic gynaecological surgery[82] inguinal herniorrhaphy,[83,84] nasal surgery[85] or knee arthroscopy[86] (table XV). A further randomized, observer-blind trial compared local infiltration subcutaneously of 10 mL of levobupivacaine 5.0 mg/mL (n = 30) with usual care (n = 30) in patients undergoing femoral artery percutaneous coronary intervention.[87]

Where specified, patients were ASA physical status I–II,[84-86] or I–III.[83] The mean age ranged from 32 to 65 years,[82-85,87] or was not reported.[41,86]

Where specified, the primary endpoints were the area under the curve for VAS scores (0–96 hours postoperatively) at rest in the supine position,[84] or any requirement for supplementary oral analgesia during the first 24 hours postoperatively.[86]

See table XV for patient numbers and details of the randomized treatments.

Levobupivacaine provided effective postoperative analgesia when given by local infiltration,[82-85,87] as did intra-articular injection of levobupivacaine in patients undergoing knee arthroscopy.[86] When compared with infiltration with saline, levobupivacaine recipients had lower requirements for supplemental analgesia (laparascopic gynaecological surgery), significantly longer time to supplemental analgesia (inguinal herniorrhaphy) and significantly lower VAS pain scores on movement from early in the postoperative to 12 (laparascopic gynaecological surgery)[82] and 24 (inguinal herniorrhaphy)[83] hours post-surgery (table XV; data not shown for all timepoints).[83] In inguinal herniorrhaphy patients, similar findings were evident according to VAS scores for pain while at rest.[83] The mean time to ambulation post-surgery was also significantly shorter in levobupivacaine than saline recipients undergoing laparoscopic gynaecological surgery (16 vs 22 hours post-surgery; $p = 0.041$).[82]

Peri-articular infiltration with levobupivacaine before wound closure after hip replacement may provide improved analgesia over no infiltration.[41] Although there were no significant differences in mean VAS pain scores in levobupivacaine infiltration or no infiltration groups at 6, 12 and 48 hours postoperatively, 24 hours after surgery levobupivacaine recipients had significantly lower scores than patients who received no infiltration (table XV). There were no between-group differences in morphine consumption or walking velocity.[41]

Following percutaneous coronary intervention, levobupivacaine recipients had lower postoperative pain scores during sheath removal (VAS 1.1 vs 2.2; $p = 0.02$), but not at time of sheath insertion (2.0 vs 1.8) or while waiting for sheath removal (0.8 vs 1.3).[87] Fewer levobupivacaine recipients received intravenous morphine while waiting for femoral sheath removal or during femoral sheath removal (7% vs 37% of usual care recipients).[87]

There were no significant differences between levobupivacaine and bupivacaine recipients in postoperative pain (primary endpoint) when infiltration with local anaesthetic was the sole anaesthetic intervention in patients undergoing inguinal herniorrhaphy.[84] Time-normalized AUC VAS pain scores were calculated for the period 0–96 hours and did not differ between levobupivacaine and bupivacaine groups (primary endpoint).[84] In levobupivacaine and bupivacaine groups, the AUC values were 8 and 6 (at rest) 17 and 15 (rising from supine to sitting) and 14 and 12 (walking). Bupivacaine recipients consumed a significantly lower dose of supplemental ibuprofen analgesia (table XV); however, the difference was only two 600 mg tablets of ibuprofen over 4 days.[84] There was no between-treatment difference in patient VAS satisfaction scores.[84]

Compared with lidocaine, patients undergoing septoplasty and rhinoplasty who received local infiltration with levobupivacaine were less likely than lidocaine plus adrenaline recipients to receive supplemental analgesia during the 24 hours after surgery (table XV) and had significantly lower VAS scores 30 minutes ($p < 0.0001$), 1 hour ($p = 0.002$), 2 hours ($p = 0.023$), 8 hours ($p < 0.0001$)

Table XV. Postoperative analgesia with local infiltration[41,82-85] or intra-articular injection[86] of levobupivacaine (LEV). Results of randomized, double-blind[82-86] and observer-blind[41] trials

Study	Surgery type	Regimen [no. of pts] (additional anaesthesia)	Supplemental analgesia		Postoperative pain during movement (at rest)[a]						
			% of pts[b]	onset (h)[c]	dose[d]	discharge	2–6 h	8 h	12 h	24 h	48 h
Comparisons with saline or usual care											
Alessandri et al.[82]	Laparoscopic	LEV 5.0 mg/mL (21 mL) [37] (GA)			9*		(5**)		(3**)	(3)	
	gynaecological	Saline (21 mL) [36] (GA)			63		(6)		(6)	(4)	
Ausems et al.[83]	Inguinal hernia	LEV 5.0 mg/mL (20 mL) [58] (GA or SA)	83	20*		15**				22**	20
		Saline (20 mL) [58] (GA or SA)	93	8		30				38	23
Murray et al.[41]e	Hip	LEV 2.0 mg/mL + ADR 1 : 200 000 (160 mL) [50] (SA)					11		6	5*	5
	arthroplasty	Usual care [50] (SA)					17		10	14	8
Comparisons with bupivacaine											
Kingsnorth et al.[84]	Inguinal hernia	LEV 2.5 mg/mL (50–60 mL) [30] (none)	97	10	63						
		BUP 2.5 mg/mL (50–60 mL) [30] (none)	87	10	44†						
Comparisons with lidocaine											
Demiraran et al.[85]	Nasal	LEV 2.5 mg/mL (5–10 mL) [30] (GA)	40‡				20‡	5‡‡	11‡	8	
		LID 20 mg/mL + ADR 1.25 : 100 000 (5–10 mL) [30] (GA)	60				32	16	21	6	
Jacobson et al.[86]	Knee	LEV 2.5 mg/mL (7 mL ID, 13 mL IA [40] (GA)	93[f]							3‡	
	arthroscopy	LEV 5.0 mg/mL (7 mL ID, 13 mL IA [40] (GA)	75‡§[f]							2‡	
		LID 10 mg/mL + ADR 5 μg/mL (7 mL ID, 13 mL IA [40] (GA)	95[f]							5	

a Mean[41,82,85] or median[83,86] VAS pain score on scale 0–10[82,86] or 0–100.[41,83,85]

b Analgesia received within 4 d[84] or 5 d;[83] or supplemental[85] or oral supplemental[86] analgesia within 24 h.

c Median time to the first analgesic dose.[83,84]

d Mean amount of keterolac consumed (mg) within 36 h, postoperatively,[82] or median dose ibuprofen (mg/h) consumed within 4 d.[84]

e Available as an abstract.

f Primary endpoint.

ADR = adrenaline; **BUP** = bupivacaine; **disch** = discharge; **GA** = general anaesthesia; **IA** = intra-articular; **ID** = intradermal; **LID** = lidocaine; **pts** = patients; **SA** = spinal anaesthesia; **VAS** = visual analogue scale; * $p < 0.05$, ** $p < 0.01$ vs saline or usual care; † $p < 0.05$ vs LEV; ‡ $p < 0.05$, ‡‡ $p < 0.0001$ vs LID; § $p < 0.05$ vs LEV 2.5 mg/mL.

and 12 hours (p = 0.011) after surgery, but not at 24 hours after surgery.[85] Intra-articular levobupivacaine 5.0 mg/mL recipients were significantly less likely than lidocaine or levobupivacaine 2.5 mg/mL recipients to receive supplemental analgesia during the 24 hours after knee arthroscopy (primary endpoint), and both levobupivacaine 5.0 mg/mL and levobupivacaine 2.5 mg/mL groups had lower pain scores than lidocaine recipients during this period[86] (table XV).

5. Tolerability

Levobupivacaine has been available for several years and its general tolerability profile is well established. This section reviews tolerability data reported in the clinical trials discussed in section 4, supplemented with data from the UK summary of product characteristics,[5] review articles[2,4,6] and individual case reports.[88-90] The focus is on the tolerability of levobupivacaine in clinical trials that fully reported these data. Most trials included monitoring for treatment-emergent adverse events, and in the case of parturient women, fetal and neonatal measures. Generally, the trials do not report specifically regarding infrequent, unwanted drug-related neurological adverse events, such as muscle twitching or seizures, except for trials of spinal anaesthesia for lower limb surgery,[58,59] which reported delays in voiding urine after surgery (section 5.2).

Based on clinical trial data and spontaneous reporting, the UK summary of product characteristics lists the most common adverse drug reactions as hypotension, nausea and anaemia (all at a frequency of ≥10%), and vomiting, dizziness, headache, pyrexia, procedural pain, back pain and fetal distress syndrome during labour epidural analgesia (all at a frequency of 1–9%).[5] As is generally case for adverse reactions reported in prescribing information, these reactions are not necessarily caused by levobupivacaine, as some may have been related to underlying conditions or surgical procedures.

Like other amide local anaesthetics, levobupivacaine is associated with cardiac toxicity, neurological injury after peripheral nerve block and unwanted CNS effects, although the risk for cardiac adverse events may be lower with levobupivacaine than with bupivacaine.[2,4] However, the claim for greater cardiac safety of levobupivacaine over bupivacaine is based to a large extent on preclinical studies in animals and human volunteers.[6]

Allergic-type reactions occur rarely and range in severity from urticaria to anaphylactoid-like symptomatology.[5] As with other local anaesthetics, accidental intrathecal injection can produce very high spinal anaesthesia associated with severe hypotension and loss of consciousness.[5]

There are three case reports of successful resuscitation after inadvertent intravenous injection.[88-90] The presentations were severe hypotension and bradycardia after a drug error;[88] loss of consciousness, convulsions, hypotension and changes in QRS morphology after presumed intravenous injection during lumbar plexus block;[89] and loss of consciousness and convulsions after spinal, sciatic nerve and continuous lumbar plexus blocks.[90] In all cases, resuscitation was successful with supportive measures, with or without pressor drugs and intravenous lipid emulsion.[88-90]

5.1 Epidural Block

Epidural levobupivacaine anaesthesia was generally well tolerated in patients undergoing Caesarean section,[34,44-47,50] lower abdominal,[48] lumbar spine[51] or lower limb surgery,[35,36] and when used for labour analgesia[39,77] and postoperative pain control.[40,76]

In patients undergoing levobupivacaine regional anaesthesia, hypotension and nausea were common adverse events. In women undergoing elective Caesarean section with epidural anaesthesia who received levobupivacaine or bupivacaine, hypotension was reported in 84% versus 100% (p = 0.053),[44] 73% versus 74%[34] and 39% versus 67% (p = 0.054) of patients.[45] In women undergoing urgent Caesarean section, there were no unexpected adverse events and there were no significant differences in the frequency of adverse events between levobupivacaine and comparator drugs (lidocaine plus bicarbonate plus adrenaline,[46] lidocaine plus adrenaline plus fentanyl

and ropivacaine[47]); intraoperative nausea and vomiting occurred more frequently when levobupivacaine was combined with fentanyl than when used alone (53% vs 18%; p = 0.004).[50]

In the largest trial of epidural levobupivacaine versus bupivacaine analgesia in women in labour (n = 137), 25% of patients overall (25 levobupivacaine and 17 bupivacaine recipients) experienced at least one treatment-emergent adverse event, with the most common being fetal distress and delayed delivery.[39] There were no significant between-treatment differences in neonatal outcomes.[39]

The reporting of serious or severe adverse events was inconsistent across the clinical trials. However, in patients undergoing abdominal,[48] lumbar spine[51] or lower limb[35,36] surgery, there were no treatment-related serious[35,48] or severe[36] adverse events. Furthermore, where specified, in women undergoing Caesarean section no treatment-related neonatal[44] or serious neonatal[34] adverse events were observed.

Following lower limb surgery, hypotension rates were 8% and 9% with levobupivacaine with or without morphine PCA,[40] and ≤20% with either levobupivacaine or ropivacaine.[76]

5.2 Spinal Block

Spinal levobupivacaine was generally well tolerated in patients undergoing Caesarean section,[52,53] lower abdominal surgery,[54] transurethral endoscopic surgery[55] and lower limb surgery,[56-59] and in women in labour.[75]

There were no significant treatment differences in hypotension, nausea and vomiting, or pruritus rates between levobupivacaine, bupivacaine and ropivacaine recipients in patients undergoing spinal anaesthesia for Caesarean section.[52,53]

In patients undergoing lower abdominal surgery, hypotension requiring ephedrine was more frequent in bupivacaine than levobupivacaine or ropivacaine recipients (43% vs 25% and 18%, respectively; p = 0.02).[54] Bradycardia was also more common in bupivacaine than ropivacaine recipients (p = 0.04), but not levobupivacaine recipients.[54]

In patients undergoing transurethral endoscopic surgery, intraoperative shivering was more common in the levobupivacaine than bupivacaine treatment group (26% vs 3%; p = 0.01), as was postoperative bradycardia (26% vs 6%; p = 0.02), but there were no significant between-group differences in other adverse events.[55] Intraoperatively, 6% and 11% of levobupivacaine and bupivacaine recipients were hypotensive (3% and 9%, respectively, received ephedrine to raise BP).[55]

Across trials of spinal levobupivacaine anaesthesia for lower limb surgery, hypotension rates were low.[56,57] In one trial, no patient required blood and haemodynamic variables were stable throughout surgery.[57] In another trial, 13% of levobupivacaine 5 mg/mL and 7% of ropivacaine 7.5 mg/mL recipients required intravascular volume expansion to treat hypotension.[59] In a third trial, two elderly patients who received bupivacaine (7%) and none who received levobupivacaine required treatment for severe hypotension and bradycardia.[56]

In a trial designed to detect urinary retention, there were no significant differences between levobupivacaine, ropivacaine and lidocaine in the incidence of postoperative micturition problems.[58] However, in a second trial, time to first voiding urine was significantly longer in levobupivacaine 7.5 mg recipients than levobupivacaine 5 mg or ropivacaine 7.5 mg recipients recipients (238 vs 190 and 189 minutes; p < 0.05), although the clinical significance of this delay is uncertain.[59]

When compared with spinal bupivacaine for labour analgesia, spinal levobupivacaine recipients had a significantly lower rate of squeezing impairment (58% vs 16%; p < 0.01), which was probably a manifestation of a lower rate of motor block (Bromage score 1 was 0% vs 34%; p < 0.05), while there were no differences in other maternal or neonatal tolerability outcomes.[75]

5.3 Nerve Plexus or Peripheral Nerve Block

Levobupivacaine given as a peripheral nerve block was also generally well tolerated.[37,65,68,69]

In a trial evaluating analgesia with levobupivacaine alone, levobupivacaine with intravenous tramadol or levobupivacaine with psoas compartment tramadol in patients undergoing total

hip or knee arthroplasty, 67%, 53% and 40% of patients, respectively, required intraoperative ephedrine for hypotension (decline in systolic BP ≥30%).[69] In addition to the peripheral nerve block, all patients received preoperative intravenous midazolam followed by spinal anaesthesia,[69] which may account for the high frequency of hypotension.

Few or no adverse events were reported in patients undergoing peribulbar, retrobulbar or sub-Tenon block during eye surgery. In one trial, 13% of levobupivacaine recipients and 17% of bupivacaine recipients patients had prolonged motor block resulting in residual akinesia and diplopia, and 13% and 10% had associated eye pain the day after surgery, which subsequently resolved in all patients.[65] In a separate trial, 1 of 34 patients (3%) who received levobupivacaine plus lidocaine had persistent diplopia, which resolved within 3 months after surgery.[67] Chemosis occurred in 18% and 21% of levobupivacaine and lidocaine recipients; in the corresponding groups, 36% and 26% had a small conjunctival haemorrhage.[38]

In patients who received an inferior alveolar nerve block for pain control following extraction of impacted molars, adverse events (nausea, abdominal discomfort, dizziness and feeling faint) occurred in 7%, 23% and 16% of patients in levobupivacaine, lidocaine and placebo groups, respectively.[80]

An open trial (available only as an abstract) assessed neurological status in patients after a popliteal sciatic nerve block with levobupivacaine 5.0 mg/mL plus adrenaline 1 : 200000 (0.5 mL/kg) [n = 512], with some patients requiring a further block with levobupivacaine 5.0 mg/mL (10 mL) plus lidocaine 20 mg/mL (10 mL) [n = 57].[91] Postoperative neurological symptoms occurred in 15% of patients who received only one popliteal sciatic nerve block and in 25% of patients who also required a supplemental block. Neurological symptoms were not persistent, with a median duration of 4 weeks and no patient had neurological symptoms for longer than 12 weeks.[91]

No severe[37] or serious[65] adverse events that were considered to be related to the study drug occurred in the two trials reporting these endpoints.

5.4 Local Infiltration or Topical Application

Topical levobupivacaine drops during cataract removal were well tolerated, as they were not associated with adverse effects,[71] drug-related severe adverse effects[72] or surgical complications.[70]

In one trial, levobupivacaine or bupivacaine local infiltration for inguinal herniorrhaphy was associated with bradycardia (heart rate <30 beats/minute) in two patients (one per treatment group), which could have resulted from manipulation of the spermatic cord.[73] One levobupivacaine recipient required further operation for a postoperative haematoma.[73]

Levobupivacaine infiltration for postoperative analgesia also appears to be well tolerated.[83,85] After herniorrhaphy, no episodes of infection, allergic reaction or wound healing disturbance related to wound infiltration with levobupivacaine were reported at surgery completion or at follow-up.[83]

6. Dosage and Administration

In the UK, levobupivacaine is available in 0.625, 1.25, 2.5, 5.0 and 7.5 mg/mL solutions.[5] Levobupivacaine 0.625 and 1.25 mg/mL is indicated for continuous epidural infusion for labour analgesia and for postoperative pain management.[5] Levobupivacaine 2.5, 5.0 and 7.5 mg/mL is indicated for surgical anaesthesia (epidural, intrathecal, peripheral nerve block, peribulbar nerve block or local infiltration), for postoperative or labour analgesia (single or multiple epidural boluses, or continuous epidural infusion) and for analgesia in children (ilioinguinal/iliohypogastric nerve block). In children, the safety and efficacy of levobupivacaine for indications other than ilioinguinal/iliohypogastric nerve block has not been established.[5]

The UK summary of product characteristics provides dose recommendations for commonly used levobupivacaine blocks (table XVI) and recommends that lower concentrations and doses are used for analgesia, whereas higher concentrations are recommended when profound or prolonged anaesthesia is required.[5] The maximum dose is based on the size and physical state of the patient and the type of anaesthesia to be administered, with

Table XVI. Dose guide for commonly used blocks in adults and children[5]

Indication and route of administration	Concentration (mg/mL)	Dose
Surgical anaesthesia		
Epidural Caesarean section (slow injection[a])	5.0	75–150 mg
Epidural other surgery (slow bolus[b])	5.0–7.5	50–150 mg
Intrathecal	5.0	15 mg[c]
Peripheral nerve	2.5–5.0	2.5–150 mg
Opthalmic peribulbar	7.5	37.5–112.5 mg
Local infiltration	2.5	2.5–150 mg
Labour analgesia		
Epidural bolus[d]	2.5	15–25 mg
Epidural infusion	0.625–1.25	5.0–12.5 mg/h
Postoperative analgesia		
Epidural infusion	0.625–2.5	12.5–18.75 mg/h
In children aged <12 y		
Ilioinguinal/iliohypogastric	2.5–5.0	0.625–2.5 mg/kg

a Injected over 15–20 min.

b Bolus administered over 5 min.

c Doses in the range of 5–15 mg were most commonly used in surgical anaesthesia clinical trials (section 4.1.2).

d Minimum recommended interval between intermittent injections of 15 min.

a recommended maximum single dose of 150 mg. Additional doses may be required when sustained motor and sensory block is needed, although the recommended maximum total dose over a 24-hour period is 400 mg. The dose for postoperative pain management should not exceed 18.75 mg/hour. In children, the recommended maximum dose for ilioinguinal/iliohypogastric nerve block is 1.25 mg/kg per side.[5]

The use of levobupivacaine requires that the administering or supervising clinician has necessary training and experience.[5] To prevent intravascular injection, careful aspiration is necessary before and during injection, including during administration of a bolus dose. Bolus doses require slow, incremental injection at a rate of 7.5–30 mg/minute, with concurrent observation of the patient's vital functions while maintaining verbal contact with the patient. The injection must be stopped immediately if toxic symptoms occur.[5]

General contraindications for regional anaesthesia must be taken into account when considering the use of levobupivacaine.[5] Specific contraindications include known hypersensitivity to amide anaesthetics or excipients, severe hypotension (hypovolaemic or cardiogenic shock), intravenous regional anaesthesia (Bier's block), and obstetrical paracervical block, because of observed fetal bradycardia associated with bupivacaine paracervical block. The levobupivacaine 7.5 mg/mL concentration is contraindicated in obstetric use, on the basis that cardiotoxic events have occurred with bupivacaine at this concentration in this clinical setting.[5]

Local prescribing information should be consulted for detailed information about storage and dilution, contraindications, special warnings, precautions, drug interactions and use in specific indications and special populations.

7. Place of Levobupivacaine in Regional Anaesthesia and Pain Management

Local anaesthetics are used for regional anaesthesia during surgery and for postoperative and labour pain management.[2,3] Epidural and spinal epidural blocks (known as neuraxial blocks) are particularly in use in obstetric anaesthesia and analgesia,[2] and increasingly these and peripheral nerve blocks are being used in other types of surgery.[92]

The agents commonly in use for regional anaesthesia include short-acting ester local anaesthetics (e.g. chloroprocaine, procaine), short- or medium-acting amides (e.g. lidocaine, articaine, mepivacaine), long-acting amides (e.g. levobupivacaine, bupivacaine, ropivacaine) and opioids (e.g. morphine, fentanyl).[2,3] The choice of local anaesthetic is determined by matching the patient's anaesthetic and/or analgesic requirements with the pharmacological properties of specific agents. Important characteristics to be considered include drug potency, speed of onset and duration of analgesia, degree of motor block, and overall toxicity profile, including cardiovascular toxicity with regular use and in the event of inadvertent intravenous injection.[3] The ester local anaesthetic drugs are used for procedures requiring a short duration of action, for local infiltration or topical administration, and occasionally for neuraxial or peripheral nerve blocks.[3]

Although there are differences between long-acting amide local anaesthetics in their duration of effects, relative potency, potential for toxicity and cost, there are no clear-cut advantages to one drug over another, and all are in use across a wide range of clinical indications.[2,3] Levobupivacaine was developed as an alternative to bupivacaine, as it was thought that as it is a levorotatory enantiomer, it would be less cardiotoxic than racemic bupivacaine.[6] Preclinical studies suggest that levobupivacaine is less cardiotoxic than bupivacaine, but clinical data confirming this are lacking (see below).

Based on relative potency studies in clinical populations, levobupivacaine appears to be less potent than bupivacaine and somewhat more potent than ropivacaine (section 2.2). Pharmacokinetic studies showed that systemic absorption of levobupivacaine was approximately dose-proportional following both epidural and brachial plexus block, leading to a widespread distribution in tissues. However, the rate of absorption was variable and depended on the route of administration and the vascularity of tissues at the site of administration (section 3.1).Therefore, it cannot be assumed that equivalent doses of long-acting amide local anaesthetics will produce equivalent effects, or that the effects will be similar between patients.

The majority of the levobupivacaine efficacy studies reviewed were small, single-centre trials with approximately 30–40 patients per treatment group, and the treatments used and trial methods were not always directly comparable across trials (section 4). Therefore, it is not possible to reach definite conclusions based on these trials, particularly with respect to the relative efficacy of levobupivacaine and its comparators. Nevertheless, levobupivacaine regional anaesthesia and analgesia was shown to be effective across a wide range of clinical populations and when administered by different routes. For instance, neuraxial administration of levobupivacaine provided effective anaesthesia or analgesia in patients undergoing elective Caesarean section, lower abdominal, urological, lumbar spine and lower limb surgery, and in women in labour (sections 4.1.1, 4.1.2 and 4.2.1). There were few significant differences between levobupivacaine, bupivacaine and ropivacaine treatment groups in onset or duration of sensory and motor block, pain relief and other important clinical endpoints (section 4.1.1, 4.1.2 and 4.2.1). However, in patients undergoing urgent Caesarean section, epidural lidocaine regimens were more effective, as the onset of sensory block in levobupivacaine recipients was significantly longer than in patients who received lidocaine in combination with bicarbonate and adrenaline or lidocaine with adrenaline and fentanyl (section 4.1.1).

Levobupivacaine administered as a peripheral nerve or ocular block provided effective anaesthesia and analgesia for patients undergoing upper limb, lower limb, eye or dental surgery (sections 4.1.3, 4.2.2 and 4.2.3). In upper and lower limb surgery, multiple trials showed no significant treatment differences between levobupivacaine, bupivacaine or ropivacaine, although supplementary anaesthesia or analgesia was required by a substantial minority across all treatment groups (section 4.1.3). Of note, in patients undergoing eye surgery, retrobulbar block with levobupivacaine led to a significantly faster and more prolonged sensory block than ropivacaine, and a significantly longer duration of sensory and motor block than lidocaine (section 4.1.3). By contrast, in sub-Tenon block, time to sensory block was significantly faster with lidocaine and articaine than levobupivacaine; the surgical block was also more effective with articaine than with levobupivacaine combined with lidocaine (section 4.1.3). In patients undergoing lower limb surgery who received a femoral nerve block, levobupivacaine was associated with significantly less local anaesthetic consumption following surgery than ropivacaine, while in dental patients, inferior alveolar nerve block with levobupivacaine provided more effective postoperative analgesia than lidocaine combined with adrenaline (section 4.2.2).

Topical application, local infiltration and intra-articular injection of levobupivacaine also provided effective anaesthesia and analgesia during or after inguinal herniorrhaphy, cataract, gynaecological and nasal surgery and after knee arthroscopy, albeit with a minority of herniorrhaphy

patients experiencing moderate or severe intraoperative pain (section 4.1.4). Both local infiltration and intra-articular injection of levobupivacaine provided more effective postoperative analgesia than saline or usual care following laparoscopic gynaecological surgery or inguinal herniorrhaphy, and pain relief was not significantly different from, or was significantly better than, comparator agents in patients undergoing inguinal herniorrhaphy, nasal surgery or knee arthroscopy (section 4.2.3).

Levobupivacaine was generally well tolerated in clinical trials (section 5). The most common adverse drug reactions in levobupivacaine recipients in clinical trials were hypotension, nausea, anaemia, vomiting, dizziness, headache, pyrexia, procedural pain, back pain and fetal distress syndrome (during labour epidural analgesia) [section 5].

Preclinical studies in animal models, and of low dose intravenous levobupivacaine in human volunteers, show that while levobupivacaine has cardiac effects, they are less pronounced than with bupivacaine at equivalent doses. The animal studies suggest that ropivacaine has the lowest cardiotoxicity (section 2.3). However, there were no consistent between-group differences in cardiac adverse events observed in the clinical trials. Generally, there was no significant difference in the incidence of hypotension between levobupivacaine and bupivacaine when administered by epidural (section 5.1) or spinal (section 5.2) injection, although in one trial, intraoperative hypotension was more common with spinal bupivacaine than with levobupivacaine.[54] Mixed results were seen in terms of bradycardia, with no significant difference between spinal levobupivacaine and bupivacaine recipients in one trial[54] and a significantly higher incidence of bradycardia with spinal levobupivacaine than with bupivacaine in another trial.[55]

In the trials reviewed in section 4, neurological toxicity was rarely reported. In a trial specifically designed to detect urinary retention and voiding effects, there were no significant differences in these problems between patients treated with levobupivacaine, ropivacaine or lidocaine (section 5.2).

Regional anaesthesia is in wide use in paediatric populations[93] and levobupivacaine is approved in the EU for ilioinguinal/iliohypogastric nerve block.[5] There are published data supporting its efficacy when administered as an ilioinguinal/iliohypogastric block[94,95] and by caudal[96,97] and spinal[98] routes in paediatric populations.

In conclusion, levobupivacaine is a long-acting amide local anaesthetic that is effective when administered as an epidural, spinal, peripheral nerve or ocular block, or by topical application or local infiltration. In comparative trials, its clinical effects were not generally significantly different from those of bupivacaine or ropivacaine, although there was some variability in efficacy findings in different clinical populations. Levobupivacaine was generally well tolerated. Levobupivacaine provides effective anaesthesia and analgesia for a wide range of clinical populations and is a useful alternative to bupivacaine.

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