

# Enantiomeric Local Anesthetics: Can Ropivacaine and Levobupivacaine Improve Our Practice?

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**Abstract:** The novel, long-acting local anesthetics (LAs) ropivacaine and levobupivacaine were developed to offer a safer alternative to bupivacaine. The well-known toxic effects of bupivacaine on the central nervous system and the cardiovascular system seem to be less severe when comparable plasma levels of these pure levorotatory agents are reached. Although there is evidence of greater safety in the experimental setting, its actual impact on clinical practice remains unclear. Randomized, controlled trials using clinical endpoints have shown that the enantiomeric LAs are viable alternatives to bupivacaine, and may offer advantages in some settings where a greater differentiation between motor and sensory block may become evident. The available evidence seems to support the use of the novel LAs over bupivacaine whenever large doses are used or the risk of unintended intravascular injection is high, such as in continuous epidural analgesia or peripheral nerve blocks.

**Key Words:** Bupivacaine, levobupivacaine, ropivacaine, local anesthetics, peripheral nerve block, regional anesthesia techniques.

## INTRODUCTION

Ropivacaine and levobupivacaine are the two newest amino amide local anesthetics (LAs) available for clinical use. The development of these new drugs was prompted by the need for a wider safety margin, while preserving the desirable pharmacodynamic properties of bupivacaine, a potent, long-acting amino amide LA, which has been shown to have an unsatisfactory safety profile.

Ropivacaine and levobupivacaine are commonly referred to as pure (left) enantiomers, because of their physical properties. The term 'enantiomers' is used to identify the two possible versions of a chiral molecule, i.e., one that has a carbon atom bounded to four different atoms. The relative positions and spatial orientation of the carbon atom and its ligands may be viewed as those of the fingers of a hand, and the two different enantiomers, with respect to each chiral center, can be thought of as the right and left hand. Molecules with different spatial conformation at a chiral center (stereoisomers) may be distinguished because of the optical properties of said centers. A stereoisomer with a chiral center, which rotates the plan of incident polarized light in a clockwise fashion, is said to be a dextrorotatory, or R(+), stereoisomer. One which induces a counterclockwise rotation is a levorotatory, or S(-), stereoisomer. The two dextro- and levorotatory stereoisomers of a chiral center of the same molecule are thus called enantiomers.

Bupivacaine is available as an admixture of R(+)- and S(-)-bupivacaine, and is thus referred to as 'racemic.' Levobupivacaine is the formulation of the pure levorotatory enantiomer of bupivacaine. Ropivacaine, which has a different substitution at the nitrogen atom in the alkylic

group, is a derivative of bupivacaine also available as the pure S(-)-enantiomer. The spatial conformation of chiral centers may affect the interaction of a molecule with its receptors, determining a greater affinity to certain subtypes.

## EXPERIMENTAL EVALUATION OF SAFETY

Inadvertent vascular injection of LA or systemic absorption from the extravascular compartment may result in high plasma concentrations of the drug. Systemic LA toxicity is mainly observed in the central nervous system (CNS) and in myocardial tissue.

LA toxicity is especially a concern when large doses are used. This is the case with peripheral nerve blocks (PNB) and/or prolonged infusions for postoperative analgesia, for which large doses are commonly administered. The concentration of the administered solution may also influence LA pharmacokinetics, because a higher extra- to intravascular space gradient may facilitate absorption.

CNS adverse effects usually occur at lower plasma concentrations, and include cranial nerve dysfunction (dysarthria, auditory and visual defects, paresthesiae, abnormal taste sensation), inhibitory pathways dysfunction with twitching, tremors and tonic-clonic seizures. At higher LA concentrations, generalized CNS toxicity occurs with depression of all functions, leading to coma, sympathetic outflow depression and respiratory arrest.

Cardiac toxicity usually occurs at comparatively higher plasma levels. It often begins with negative inotropic effects, which may not be immediately apparent as CNS excitation leads to increased sympathetic tone. Cardiac arrest may result from profound myocardial depression with mechanical failure or fatal dysrhythmias. Ventricular fibrillation, preceded by severe hypotension, is the most common terminal arrhythmia in the experimental setting, and it appears as the main cause of death in most animal models of acute LA toxicity except when lidocaine is used [1].

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Pure left isomers appear to be safer than racemic bupivacaine when considering acute CNS toxicity. In animal studies, thresholds for seizure-like activity have been shown to be consistently higher when using levobupivacaine or ropivacaine as compared to bupivacaine [2]. Studies in volunteers have used early symptoms of CNS toxicity to detect plasma level thresholds in healthy subjects undergoing intravenous LA infusions. In humans, ropivacaine and levobupivacaine exhibit the same potency with respect to CNS symptoms [3], first occurring in the healthy volunteer after a 10 mg/min intravenous infusion of  $36.9 \pm 8.55$  mg of ropivacaine and  $39.2 \pm 17.54$  mg of bupivacaine ( $P = 0.595$ .) Ropivacaine indeed seems to have higher (15-50%) CNS toxicity thresholds when compared to bupivacaine [4-6]. In particular, early symptoms of CNS toxicity were initially observed at a ropivacaine plasma level of  $0.56 \pm 0.14$   $\mu\text{g/mL}$  in healthy subjects, as compared to bupivacaine levels of  $0.30 \pm 0.11$   $\mu\text{g/mL}$  ( $P < 0.001$ ) [5]. Such levels were those detected upon appearance of symptoms following a 10 mg/min intravenous infusion of a mean  $115 \pm 29$  mg ropivacaine and  $103 \pm 30$  mg racemic bupivacaine.

The myocardial depressant properties of long-acting LAs have been ranked by Heavner and colleagues in an isolated heart model, with ropivacaine being the least toxic, followed by levobupivacaine, racemic bupivacaine and pure R(+)-bupivacaine [7]. These results seem in accordance with those found by Groban *et al.*, who induced circulatory "collapse" (defined as hypotension with mean arterial pressure  $\leq 45$  mmHg, or mechanical arrest) in anesthetized dogs [8]. Resuscitation protocols were then applied. Although ultimately underpowered to detect differences between enantiomeric long-acting LAs in terms of mortality, this study reported lower efficacy of resuscitation efforts in animals receiving intravenous bupivacaine. Dogs receiving levobupivacaine had lower mortality, although ventricular fibrillation was not less frequent than with bupivacaine. Ropivacaine infusions caused the lowest mortality among long-acting anesthetics and lower incidence of ventricular fibrillation at higher doses ( $41.6 \pm 4.9$  mg/kg). It should be noted that these studies do not closely reflect typical clinical conditions, as they employed anesthetized animals in which the sympathetic component of CNS LA toxicity, and the subsequent hyperdynamic phase, are at least blunted. Studies in awake volunteers demonstrated similar threshold plasma levels for levobupivacaine- and ropivacaine-induced early myocardial depression using electrophysiological and echocardiographic endpoints [3]. The occurrence of comparable endpoints was earlier, or more pronounced, with intravenous bupivacaine than with intravenous levobupivacaine or ropivacaine in several other studies on healthy volunteers [4-6]. In particular, levobupivacaine induces significantly smaller reductions in stroke index and ejection fraction than bupivacaine at comparable plasma levels of 2.62 and 2.25  $\mu\text{g/mL}$ , respectively [6].

## CLINICAL APPLICATIONS

### Epidural Administration

Equipotent doses at similar volumes of ropivacaine and bupivacaine have been found to provide equivalent epidural

anesthesia/analgesia, with a similar profile of nerve block [9-15].

In general, levobupivacaine has been found to also provide similar effects when compared to racemic bupivacaine in either abdominal or lower limb surgery [16, 17]. Using up to 25 mL of 0.5% levobupivacaine versus 0.5% racemic bupivacaine, however, Faccenda and colleagues were able to demonstrate a longer, yet less pronounced motor block with levobupivacaine in patients undergoing elective caesarean section [18].

In the setting of lower limb surgery, patient receiving 15 mL of 0.5% ropivacaine for lumbar epidural anesthesia may have a higher incidence of inadequate intraoperative motor block compared to 0.5% levobupivacaine or bupivacaine [19]. When accounting for the supposed relative potency of levobupivacaine and ropivacaine derived from minimum LA concentration (MLAC) studies, 15 mL of 0.75% ropivacaine and 0.5% levobupivacaine were found to provide identical nerve block profiles for lumbar epidural anesthesia [20].

Ropivacaine has been extensively evaluated against bupivacaine for postoperative epidural analgesia. In thoracic surgery patients, Pouzeratte *et al.* reported a significant difference in effectiveness using 0.125% bupivacaine with 0.5  $\mu\text{g/mL}$  sufentanil vs. 0.125% ropivacaine with 0.5  $\mu\text{g/mL}$  sufentanil. In this study, bupivacaine and sufentanil appeared to be superior to ropivacaine and sufentanil, which in turn provided better analgesia than 0.2% ropivacaine alone. These results are in contrast with reports from several other studies [21-23], where adequate analgesia was found with both LAs in a mixture with opioids. Bertini and colleagues have evaluated 0.2% ropivacaine and bupivacaine for patient-controlled epidural analgesia (PCEA) after hip replacement surgery [24]. In this setting, the incidence of motor block was found to be significantly higher with bupivacaine. During epidural analgesia for labor, ropivacaine has been found in meta-analysis to be equivalent to bupivacaine in terms of quality of pain relief and side effects, mode of delivery and neonatal outcomes [25]. Significant heterogeneity between studies was found with regards to onset and duration of analgesia, and incidence of motor block. Although results from most studies seem to favor ropivacaine, additional research is needed to clarify the issue [25].

The question over the relationship of total LA dose and solution volume is still open in epidural analgesia with levobupivacaine, as well. Murdoch and colleagues reported higher incidence of motor block with increasing concentrations of this LA in orthopedic patients undergoing lumbar epidural analgesia after orthopedic surgery. In particular, 0.25% levobupivacaine provided the most morphine-sparing effect, but caused significantly more motor impairment than the 0.0625% solution [26]. It should be noted that this study used a fixed infusion rate of 6 mL/h, resulting in three different dosing profiles of 3.75, 7.50 and 15 mg/h. The latter dose was administered in patients undergoing thoracic epidural analgesia for abdominal surgery by Dermedde *et al.*, using solutions at different concentrations, ranging from 0.15% to 0.75% [27, 28]. The results were comparable for quality of analgesia and side effects, except for hypotension,

which had a lower incidence in the high-concentration (0.75% or 0.5%) groups. Similar doses at higher volume/lower concentration (10 mL/h of 0.15% levobupivacaine) led to a higher level of sensory block and higher incidence of hypotension with no better pain control [27]. These results seem to suggest that total administered mass is the main determinant of sensory and motor block characteristics of epidural anesthesia.

When comparing ropivacaine and levobupivacaine for epidural analgesia, there seems to be little difference in potency between the two LAs. Similar doses and concentrations were administered for pain relief in abdominal surgery patients [29, 30] and parturients [31]. The results seem to suggest similar potency, either with or without opioids in the LA solutions. In children undergoing postoperative analgesia after surgery for hypospadias, 0.125% solutions of bupivacaine, ropivacaine and levobupivacaine produced similar analgesia. Bupivacaine caused a higher incidence of motor block, whereas ropivacaine and levobupivacaine showed no significant differences [32].

### Intrathecal Administration

One of the main advantages of pure levorotatory LAs, safety, may be less appealing when considering spinal anesthesia, as the small doses used by the intrathecal route can rarely, if ever, cause systemic toxicity.

The relative potency of bupivacaine and its S(-)-stereoisomers has been extensively investigated in spinal anesthesia. Whereas levobupivacaine and bupivacaine exhibit equivalent potency, ropivacaine has been found to be roughly half as potent in healthy volunteers [33, 34]. Similar results were found in clinical practice by Gautier *et al.*, who reported a shorter-lasting spinal block with a higher incidence of 'poor' intraoperative anesthesia when comparing ropivacaine 10 mg with bupivacaine 8 mg for ambulatory surgery [35]. Ropivacaine 12 mg produced comparable analgesia, but also similar recovery profiles. High-dose (17.5 mg) 0.5% ropivacaine provided a similar block for hip arthroplasty when compared to 0.5% bupivacaine 17.5 mg, with faster sensory and motor function recovery profiles [36]. In accordance with its lower potency, spinal ropivacaine may represent a viable alternative for brief ambulatory surgical procedures or caesarean sections, as it may offer a faster recovery from the block [37-40] and a better hemodynamic profile [40]. The association of hyperbaric ropivacaine and fentanyl 20 µg may have a dose-sparing effect and lead to faster mobilization compared to higher-dose, normobaric ropivacaine alone [41].

When equipotent doses of levobupivacaine and ropivacaine were used for spinal anesthesia in knee arthroscopy patients (10 and 15 mg, respectively), Breebaart and colleagues reported no significant benefit in time to regression of the sensory block or time to discharge [42]. Casati *et al.* investigated the block profiles of 0.5% hyperbaric bupivacaine 8 mg, 0.5% hyperbaric levobupivacaine 8 mg and 0.5% hyperbaric ropivacaine 12 mg for unilateral spinal anesthesia for hernia repair [43, 43]. Also in this setting, equipotent doses of these LAs produced spinal block with comparable profiles. Intrathecal levobupivacaine appears to be clinically indistinguishable from racemic

bupivacaine [44], although a longer-lasting spinal block has been reported in parturients undergoing caesarean section with bupivacaine 8 mg compared to same-dose levobupivacaine and ropivacaine 12 mg [45].

### Peripheral Nerve Blocks

The relative potency of bupivacaine and ropivacaine in peripheral nerve blocks (PNBs) has been extensively evaluated. In general, 0.5% ropivacaine seems to be equipotent to 0.5% bupivacaine for PNBs [46, 47]. When higher doses are used (i.e., similar volumes of 0.75% ropivacaine), the onset time is significantly reduced and is equivalent to that of 2% mepivacaine [48]. The duration of analgesia seems to be equivalent to that of bupivacaine at both concentrations (around 10±2 hours) [49-54].

Ropivacaine may have an important clinical advantage over bupivacaine in PNBs for postoperative analgesia. Borgeat and colleagues investigated distal motor function of the upper limb in patients receiving either 0.2% ropivacaine or 0.15% bupivacaine for interscalene brachial plexus postoperative analgesia [52]. Although 0.2% ropivacaine preserved hand grip strength and caused significantly less paresthesiae, no difference in pain scores or LA consumption was noted.

There have been contrasting findings on the block profile of levobupivacaine as compared to ropivacaine. Liisanantti *et al.* reported slightly better motor and sensory blockade by ropivacaine than with same-dose levobupivacaine in axillary brachial plexus blocks [53]. However, Casati *et al.* found similar block profiles and quality of intra- and postoperative analgesia when using 30 mL of 0.5% ropivacaine or levobupivacaine, followed by continuous 0.125% levobupivacaine or 0.2% ropivacaine [54]. Total consumption of LA in the first 24 hours was less in the levobupivacaine group, possibly reflecting the longer duration of action of this LA. Further investigation with objective assessment of motor function may be necessary to clarify this issue.

Levobupivacaine has been evaluated in both the 0.25% and 0.5% concentrations for PNBs. Urbanek *et al.* and Cox *et al.* in three-in-one and supraclavicular brachial plexus blocks, respectively [55, 56]. The latter study reported slower onset and shorter duration of both anesthesia and analgesia. Also, a higher incidence of surgically inadequate blocks was noted with the lower concentration. In three-in-one blocks, similar onset times were found, but analgesia was shorter and failure rate higher with the lower levobupivacaine dose. Three other studies have reported that 0.5% levobupivacaine is clinically equipotent to same-dose ropivacaine or bupivacaine for sciatic nerve block. However, high-dose (i.e., same volume at a 0.75% concentration) levobupivacaine seems to have longer duration of analgesia and shorter onset time than same-dose ropivacaine [57-59]. A difference between 0.75% bupivacaine and 0.5% levobupivacaine was not noted in peribulbar anesthesia for eye surgery [60].

Levobupivacaine has been evaluated for continuous sciatic nerve block for postoperative analgesia. At a 0.2% concentration, it has been found to provide equivalent analgesia compared to 0.2% ropivacaine, but also a higher

degree of motor block. Also, there was no significant reduction in total LA consumption. The 0.125% concentration appears to offer a similar profile of pain relief without adversely affecting the recovery of motor function [61].

## CONCLUSION

Although a lot of attention has been focused on defining the relative potencies of bupivacaine, levobupivacaine and ropivacaine, the most interesting data from a clinical point of view are those about the safety and efficacy of these drugs.

The two new LAs are effective in the clinical setting. Adequate anesthesia for surgery, with a profound sensory and motor block, can be obtained with both levobupivacaine and ropivacaine at concentrations between 0.5% and 0.75%. Although the available data supports an increased potency, and thus duration of anesthesia, with high-dose levobupivacaine or racemic bupivacaine as compared to ropivacaine, these differences do not appear to be clinically relevant. This is especially true as continuous epidural or peripheral infusions of LA in the postoperative period are considered the best practice for locoregional analgesia in the postoperative period.

It appears that at low doses (or concentrations), ropivacaine may offer a better differentiation between sensory and motor block. This finding is not supported by all studies, especially those where low-concentration LAs are used for labor analgesia. Indeed, although more focused randomized trials are needed to define this issue, there is evidence that equipotent levobupivacaine (i.e., supposing a 1.5 potency ratio of levobupivacaine to ropivacaine) offers a comparable block profile.

Safety is the second point where pure left isomers are thought to surpass their racemic counterpart. Studies on animals confirm their generally better safety, with ropivacaine emerging as the safest long-acting LA. Higher plasma levels may be reached without evidence of toxicity as compared to racemic bupivacaine, and the myocardial depressant effects of the new LAs seem to occur at a noticeably higher plasma concentration than the CNS ones. Clearly, systemic toxicity is a minor concern in spinal anesthesia. In fact, in this setting, the use of ropivacaine or levobupivacaine could only be expected to raise costs and decrease safety, as hyperbaric formulations are not commercially available, and thus need to be manually prepared. Indeed, a better safety profile has clinical relevance in the setting of large-volume infusions of LA, such as prolonged epidural analgesia or lower limb multiple nerve blocks.

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