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Efficacy of Levobupivacaine in Regional Anaesthesia - A Narrative Review

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ABSTRACT

Background: The pursuit of safer and more effective anesthetic agents continues to be a key focus in anesthesiology. Levobupivacaine, a purified derivative of bupivacaine, has emerged as a preferable alternative for regional anesthesia due to its enhanced safety profile. Clinical studies have shown that levobupivacaine provides similar efficacy to bupivacaine but with a more favorable pharmacokinetic profile. It has been well-tolerated in various regional anesthesia techniques, including bolus administration and continuous postoperative infusion, with few adverse drug reactions, typically linked to incorrect administration or pharmacological effects. Allergic reactions are rare. Comparative studies indicate that levobupivacaine and bupivacaine offer comparable surgical sensory blocks, adverse effects, and labour analgesia outcomes, with similar safety profiles for both maternal and fetal health.

Objectives: This review aims to examine the pharmacokinetic and pharmacological benefits of levobupivacaine, highlighting its safety and clinical applications based on current evidence.

Results: Levobupivacaine is generally more powerful than ropivacaine but less strong than bupivacaine, according to the majority of clinical investigations. A total of 60 studies were discovered. Some studies, such as those with unavailable full-text publications, were eliminated. Finally, 26 publications were chosen and studied since they were relevant to the current review aims. Sushma examined, in 60 patients receiving axillary block utilizing the nerve stimulation technique, the effects of 30 ml of 1.5% lidocaine with adrenaline compared to 30 ml of 0.333% levobupivacaine. Agarwal compared the effectiveness of bupivacaine and levobupivacaine in 56 patients receiving supraclavicular brachial plexus block. Levobupivacaine, according to the study, caused both motor and sensory blocks to start more quickly.

Conclusion: Levobupivacaine is a long-acting local anesthetic that closely resembles bupivacaine in its clinical effects, but it offers specific advantages such as reduced cardiotoxicity.

Keywords: *Levobupivacaine, Regional Anaesthesia, Local Anaesthetics*

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Introduction

Anesthesiology has traditionally placed a high priority on the search for novel, safer anesthetics. With the introduction of many newer and safer local anesthetics during the previous 20 years, regional anesthesia procedures have undergone tremendous change. Bupivacaine is one of these that is frequently used as a local anesthetic in regional anesthesia. Racemic mixtures of its two enantiomers, levobupivacaine (S (−) isomer and dextrobupivacaine (R (+) isomer, are sold commercially in a 50:50 ratio. The R (+) isomer of bupivacaine is mostly linked to severe adverse effects related to the central nervous system (CNS) and cardiovascular system, as described in the literature subsequently accidental intravascular administration or intravenous regional anesthesia. Levorotatory isomers, on the other hand, have shown a better pharmacological profile with fewer neurotoxic and cardiac side effects. Levobupivacaine's quicker rate of protein binding is responsible for its decreased toxicity. As a result, pure S (−) enantiomers of bupivacaine, like levobupivacaine and ropivacaine, have been utilized in medical settings. The usage of levobupivacaine is growing in a variety of healthcare settings and has just been available in the Indian market. With relation to its safety, risk, and therapeutic concerns, its growing usage emphasizes the necessity of thorough documentation and evidence-based literature (Bajwa and Kaur, 2013).

Regional anesthesia has been a standard practice for many years. These days, levobupivacaine is frequently used for operations like peripheral nerve blocks, caudal anesthesia, and spinal anesthesia. Physico-chemical properties.

What is The Purpose of The Review?

One of the most often utilized local anesthetics for central and peripheral nerve blocks at the moment is bupivacaine. It may, however, have major adverse effects on the heart, and levobupivacaine, a recently developed local anesthetic, is said to be safer in this regard. The experience with levobupivacaine is limited in peripheral blocks when compared to bupivacaine. Based on the increased rate of side effects associated with bupivacaine and the possibility of cardotoxic side effects, we believe levobupivacaine could be a better medication for brachial plexus blocks using the supraclavicular method. This review's goal is to demonstrate the same.

Pharmacodynamics

Levobupivacaine is a strongly protein-bound, lipid-soluble local anesthetic. Its dissociation constant (pKa) is higher than lidocaine's but similar to ropivacaine and bupivacaine. Its great potency, prolonged

duration of effect, and comparatively gradual onset are all attributed to these pharmacological characteristics (Kothari *et al*., 2020). Adverse effects can emerge from the blocking of impulse transmission in many tissues, just like with other local anesthetics (Sanford and Keating, 2010)

Relative Potency

Levobupivacaine is generally more powerful than ropivacaine but less strong than bupivacaine, according to the majority of clinical investigations (Sanford and Keating, 2010). Levobupivacaine's increased lipid solubility and special formulation help to explain some of the variations in potency between it and ropivacaine (Frawley *et al*., 2009). Compared to its racemate, levobupivacaine's normal formulation has 12.6% less active molecules (Kothari *et al*., 2020). A potency difference of more than 30% has been seen in recent investigations (Thalamati *et al*., 2021; Rangapriya *et al*., 2023), indicating that levobupivacaine may actually be more powerful than ropivacaine. There has been variation in the relative potency between the two; ratios ranging from 1 to 1.67 have been recorded (Frawley *et al*., 2009) Levobupivacaine is typically thought to be 1.5 times more powerful than ropivacaine when these variables and earlier research are taken into consideration.

Mechanism of Action

Levobupivacaine and bupivacaine have comparable pharmacodynamic characteristics and mechanisms of action. It acts on myelinated neurons by reversibly inhibiting sodium channels at the nodes of Ranvier, which causes a quicker onset than in unmyelinated nerves. Similarly, nerves with a smaller diameter are easier to block than those with a bigger one (Kothari *et al*., 2020)

Pharmacokinetics

Absorption

Epidural levobupivacaine has a biphasic absorption that is affected by age, drug concentration, tissue vascularity, and the method of administration. The analgesic effect can span three dermatomes in elderly people. Therefore, depending on their physical state, it is best to give older individuals lesser dosages of levobupivacaine (Sanford and Keating, 2010).

Distribution

Levobupivacaine is widely distributed throughout the body and demonstrates a strong affinity for plasma proteins (Sanford and Keating, 2010).

Metabolism and Excretion

Cytochrome P450 (CYP) enzymes in the liver metabolize levobupivacaine to produce desbutyl-levobupivacaine and 3-hydroxylevobupivacaine. The conjugates of 3-hydroxylevobupivacaine with glucuronic acid and sulfate ester are eliminated in the urine.

Indication/Clinical Uses

Levobupivacaine's good pharmacological profile has led to a notable increase in its use in recent years. Nowadays, it is frequently used in many different anesthetic treatments, such as local infiltration, peripheral nerve blocks, ocular blocks, brachial plexus blocks, subarachnoid blocks, and epidural anesthesia and analgesia. Levobupivacaine is also used for surgical pain control, labor analgesia, and acute and chronic pain management.

Methods

Over the course of 15 days, a thorough search was undertaken utilizing multiple search engines such as PubMed, Medline, the World Health Organization website, Google Scholar, and government websites. Policy papers, systematic reviews, meta-analyses, case-control studies, cohort studies, case-control surveys, and technical publication series were among the items used throughout the search. A total of 60 studies were discovered. Some studies, such as those with unavailable full-text publications, were eliminated. Finally, 26 publications were chosen and studied since they were relevant to the current review aims (Fig. 1).

Keywords used in the search include Levobupivacaine, subarchanoid block, epidural analgesia, and peripheral nerve block.

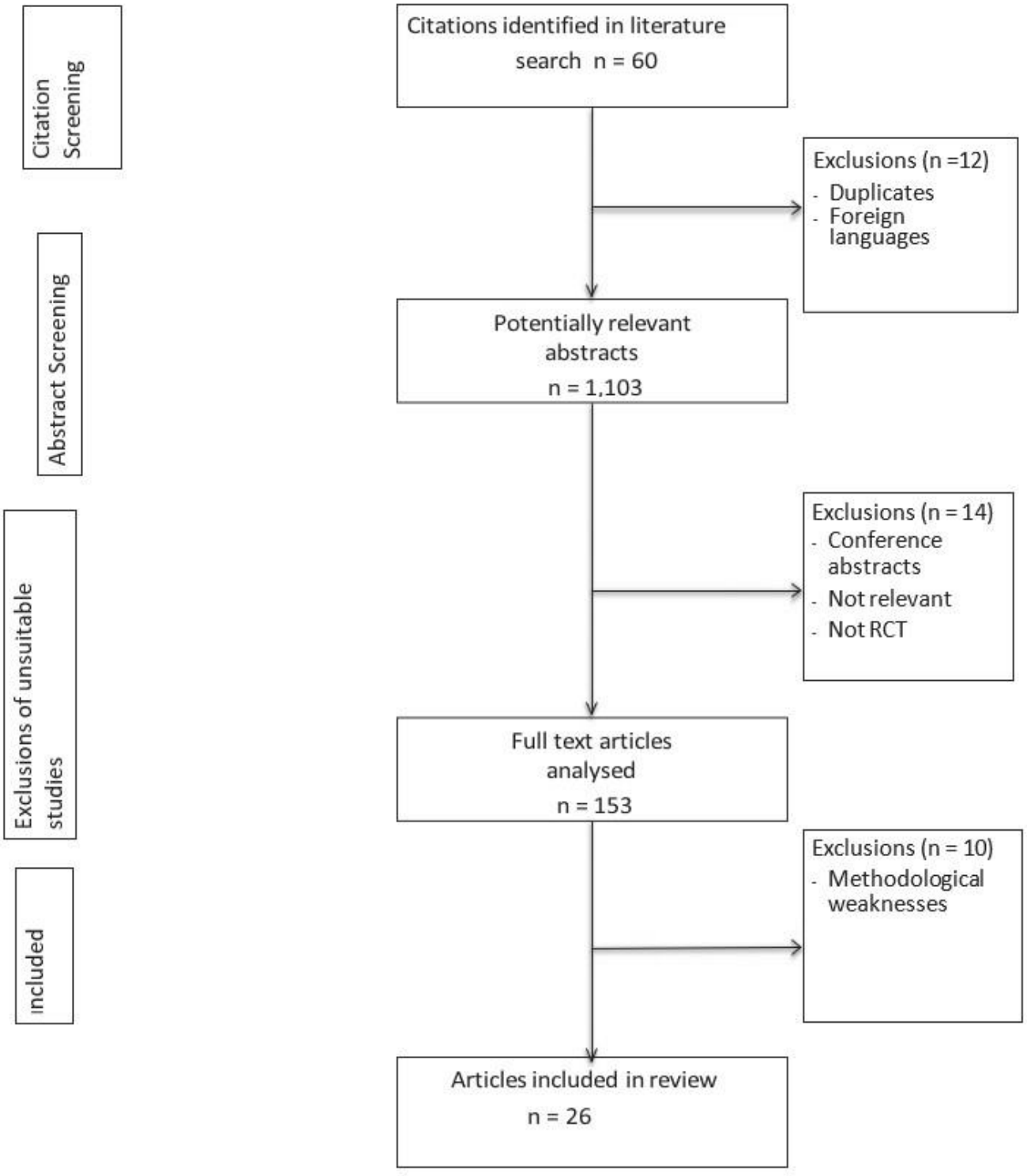
Citation Screening
Abstract Screening
Exclusions of unsuitable studies
included
Citations identified in literature search n = 60
Exclusions (n =12)
- Duplicates
- Foreign languages
Potentially relevant abstracts
n = 1,103
Exclusions (n = 14)
- Conference abstracts
- Not relevant
- Not RCT
Full text articles analysed
n = 153
Exclusions (n = 10)
- Methodological weaknesses
Articles included in review
n = 26

Figure 1

Review of Literature

Subarachnoid Block

Reason for the widespread use of spinal anesthesia is that it is a reasonably simple procedure that produces good surgical conditions by injecting a minimal quantity of medication at well-defined landmarks (Vanna *et al*., 2006).

Vanna O, *et al*. (2006) evaluated the effectiveness of isobaric levobupivacaine and hyperbaric bupivacaine in 70 patients having elective transurethral endoscopic surgery in a prospective, randomized trial. The duration of the sensory block, the time to two-segment regression, the time to T12 regression, the onset and offset of the motor block, the verbal numeric pain scores at the beginning of the operation, and the incidence of adverse events were among the parameters that they found to be comparable between the two groups. Regardless of whether isobaric or hyperbaric racemic bupivacaine was employed, intrathecal injection of levobupivacaine resulted in comparable hemodynamic alterations and adverse effects.

Mathur, *et al*. (2022) In a prospective, randomized research, the effectiveness of levobupivacaine as an adjuvant with or without fentanyl was assessed in 80 patients undergoing infraumbilical operations. According to the study, the quality of anesthesia and analgesia during and after surgery is improved when opioids are combined with intrathecal local anesthetics. In particular, it has been demonstrated that intrathecal fentanyl (25 μg) works well as an adjuvant to isobaric 0.5% levobupivacaine, providing patients having infraumbilical procedures with better block properties and fewer complications.

Sahin, *et al*. (2014) made a comparison between the anesthetic and clinical effects of isobaric levobupivacaine and isobaric bupivacaine in a randomized research with sixty patients having lumbar disc surgery under unilateral spinal anesthesia. Levobupivacaine group participants showed a quicker recovery period, which may be a disadvantage for treatments that take longer. On the other hand, this problem is manageable with cautious patient selection. Levobupivacaine's faster recovery period makes it possible to examine the nervous system after surgery sooner and to mobilize patients more quickly, both of which can aid in the healing process after surgery.

Glaser, *et al*. (2002) described the effectiveness of levobupivacaine and bupivacaine in patients who are having lower abdominal surgery. The results showed that 0.75% levobupivacaine produced sensory and motor blocks that were adequate for the procedure, similar to those obtained with the same volume

and concentration of bupivacaine. Furthermore, levobupivacaine often showed a longer-lasting sensory and motor blockage.

Guler, *et al*. (2012) described that both local anesthetics were shown to produce quick and efficient induction of surgical anesthesia in a prospective randomized research comparing the effectiveness of levobupivacaine and hyperbaric bupivacaine in 60 pregnant women undergoing cesarean sections. The study found that adding fentanyl as an adjuvant to levobupivacaine produced a reduction in motor block time as well as a decrease in adverse symptoms such nausea, bradycardia, and hypotension. This combination may therefore be a good substitute for cesarean sections.

Gulec D, *et al*. (2014) compared the effects of levobupivacaine and bupivacaine in a randomized research involving 100 elderly patients receiving spinal anesthetic for surgery. Levobupivacaine was shown to have an onset time for sensory block that was equivalent to that of bupivacaine, and it did not significantly alter hemodynamic measures such as systolic blood pressure. Its onset time for motor block was much prolonged, though. These outcomes propose that levobupivacaine could be an effective alternative to bupivacaine for spinal anesthesia in older patients of 65 years and above who are undergoing elective TUR-P or TUR-M procedures.

Epidural Anaesthesia

In various surgical procedures, levobupivacaine has proven to be an efficient epidural anesthetic and analgesic.

Kopacz, *et al*, (2000) examined the effectiveness of racemic bupivacaine and 0.75% epidural levobupivacaine in patients having lower abdominal surgery. They discovered that 0.75% levobupivacaine produced enough motor and sensory blocks for the operation, which were comparable to those acheived by the same amount and concentration of bupivacaine.

Moin, *et al*. (2013) compared the effectiveness of 15 ml of 0.5% bupivacaine with 15 ml of 0.5% levobupivacaine in an epidural anesthetic for 60 patients having elective lower abdominal surgery in a prospective, randomized research. Researchers found that when compared to 0.5% bupivacaine, 0.5% levobupivacaine produced a longer-lasting motor blockage and analgesia. 15 milliliters of 0.5% levobupivacaine given via the epidural route produced both a sustained sensory blockade and a deep and persistent motor blockade, according to the study's findings. Hence, for epidural blocking during lower abdominal procedures, 0.5% levobupivacaine is regarded as a secure and reliable local anesthetic.

Epidural Analgesia

Excellent postoperative analgesia can be achieved through a continuous epidural infusion of low-concentration local anesthetics, with or without the addition of adjuvants.

Uzuner, *et al*. (2011) compared the analgesic benefits of bupivacaine with fentanyl vs epidural levobupivacaine in 50 patients having major abdominal surgery in a prospective randomized research. The same concentration of bupivacaine and epidural levobupivacaine, when combined with fentanyl, was shown to produce consistent postoperative analgesia and was considered safe for the patients.

De Negri, *et al*. (2004) compared the effectiveness of levobupivacaine with 0.125% bupivacaine spinal infusions in 90 boys who had hypospadias surgery using a prospective randomized experiment. They found that the postoperative analgesia produced by levobupivacaine and bupivacaine was almost the same. On the other hand, patients who got levobupivacaine did not exhibit any symptoms of postoperative motor blockade, while 20% of patients who received bupivacaine experienced mild to moderate motor block.

Attri, *et al*. (2016) evaluated labor analgesia, including the onset and duration of sensory block, as well as mother and fetal outcomes, in 60 primiparous women by conducting a prospective randomized research comparing levobupivacaine and ropivacaine, both coupled with fentanyl. When compared to ropivacaine and fentanyl during labor, they discovered that levobupivacaine with fentanyl produced an earlier start and a longer duration of analgesia.

Kalsotra, *et al*. (2017) has performed a prospective randomized trial to compare the effects of epidural 0.5% bupivacaine and 0.5% levobupivacaine on anesthetic quality, incidence of side effects, and need for analgesia in elective hip and lower limb procedures, without the use of adjuvant medicine. Regarding motor and sensory blockade, start and regression timeframes, the time it takes for sensory block to reach T6, and visual analog scale scores, they could not find any statistically significant differences between the two medications. Levobupivacaine, on the other hand, demonstrated a marginal decrease in toxicity to the central nervous system and cardiovascular system (with an inconsequential p-value), suggesting that it is a viable substitute for bupivacaine. Thus, when applied epidurally, levobupivacaine can be utilized with comparable effectiveness and somewhat better safety than bupivacaine.

Thammaiah, *et al*. (2023) examined the effects of intermittent epidural boluses for combined spinal-epidural labor analgesia with 0.125% levobupivacaine and 0.2% ropivacaine, both with fentanyl as an

adjuvant. They discovered that when ropivacaine was used instead of levobupivacaine, analgesia set in more quickly. Levobupivacaine, on the other hand, produced analgesia that lasted considerably longer than ropivacaine.

Jadhav and Malde (2017) did a comparison research to see how well 0.25% levobupivacaine and 0.25% bupivacaine worked for caudal analgesia in 60 kids having herniotomies. They came to the conclusion that, in comparison to bupivacaine, levobupivacaine produced an equally efficient caudal block with acceptable perioperative analgesia. Levobupivacaine was also linked to a lower degree of residual motor blockage. Therefore, in pediatric herniotomy instances, 0.25% levobupivacaine at 0.75 ml/kg is seen to be a preferable choice over bupivacaine for caudal analgesia.

Peripheral Nerve Blocks

Levobupivacaine has become increasingly popular for peripheral nerve blocks, serving as an excellent alternative to bupivacaine and offering a longer duration of analgesia.

Brajkovic, *et al*. (2014) compared the anesthetic parameters, postoperative analgesia, and vasoactive characteristics of 0.5% levobupivacaine vs 0.5% bupivacaine in 60 patients having lower third molar surgery with mandibular nerve blocks in a prospective, randomized research. They found that, in comparison to 0.5% bupivacaine, 0.5% levobupivacaine produced better intraoperative anesthesia and more durable postoperative analgesia.

Pham Dang, *et al*. (2015) comparative randomized trial on 35 patients having ultrasound-guided sciatic block to evaluate the effectiveness of levobupivacaine in comparison with ropivacaine. The two anesthetics' onset periods were found to be the same; however, levobupivacaine produced a longer-lasting sensory block than ropivacaine.

Tavoletti, *et al*. (2020) described a case of a patient with Brugada syndrome who had a peripheral nerve block with levobupivacaine performed during lower limb surgery utilizing an external fixator. They observed that in the patient with Brugada syndrome, levobupivacaine produced a good analgesic while preserving hemodynamic and cardiac stability.

Sushma, *et al*. (2020) examined, in 60 patients receiving axillary block utilizing the nerve stimulation technique, the effects of 30 ml of 1.5% lidocaine with adrenaline compared to 30 ml of 0.333% levobupivacaine. It has been shown that levobupivacaine significantly extend both sensory and motor block duration compared to some other local anesthetics, although it typically has a slower onset of action.

Additionally, the analgesia in the levobupivacaine group lasted longer. There were no notable changes in hemodynamics or negative consequences in either group. A larger margin of clinical safety was made possible by levobupivacaine's longer duration of analgesia and less toxic potential.

Agarwal and Singh (2019) compared the effectiveness of bupivacaine and levobupivacaine in 56 patients receiving supraclavicular brachial plexus block. Levobupivacaine, according to the study, caused both motor and sensory blocks to start more quickly. According to these results, levobupivacaine could be a better option for supraclavicular brachial plexus block than bupivacaine. Figure 1 shows various citations, inclusions, exclusions and analyses articles.

What are The Limitations of The Review?

We had selected RCTs and Reviews from the inclusion criteria, we didn't exclusively take levobupivociane as a sole agent under metaanalysis. Also we didn't study levobupivocaine in extremes of ages and also in ASA (American society of anaesthesiologist) 3 patients.

Strength of The Study

We did an extensive search for the past 10 years for the relevant articles, around 160 articles were analysed and included only the valid ones. No bias was followed in the search engines.

Summary

Levobupivacaine is a long-acting local anesthetic that closely resembles bupivacaine in its clinical effects, but it offers specific advantages such as reduced cardiotoxicity. While it provides comparable motor blockade to bupivacaine, levobupivacaine has a safer pharmacological and clinical profile compared to its parent compound.

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