Systematic Review and Meta-Analysis

Levobupivacaine versus ropivacaine for brachial plexus block: A systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background and Aims: Brachial plexus block (BPB) is advantageous for elective orthopaedic or reconstructive upper limb surgery. However, the optimal local anaesthetic in BPB remains debatable. Therefore, we aim to investigate the efficacy and safety of levobupivacaine versus ropivacaine in BPB for upper limb surgery. **Methods:** A systematic review and meta-analysis synthesising randomised controlled trials (RCTs), retrieved by systematically searching PubMed, EMBASE, WOS, SCOPUS, Google Scholar, and CENTRAL since inception till June 2024. Continuous and dichotomous outcome variables were pooled using mean difference (MD) and risk ratio (RR), with a 95% confidence interval (CI), using Stata v. 17. We assessed heterogeneity using the Chi-square test and I^2 statistic. **Results:** Sixteen RCTs and 939 patients were included. Levobupivacaine was significantly associated with a longer sensory block duration [MD: 1.66 (95% CI: 1.43, 1.89), $P < 0.001$] and motor block duration [MD: 1.18 (95% CI: 0.11, 2.26), $P = 0.03$]. However, there was no difference between both groups in time to sensory block [MD: −0.30 (95% CI: −1.31, 0.71), $P = 0.56$], time to motor block [MD: −0.29 (95% CI: −1.26, 0.67), $P = 0.55$], pain score [MD: −0.48 (95% CI: −2.13, 1.16), $P = 0.56$], rescue analgesia rate [RR: 0.94 (95% CI: 0.74, 1.20), $P = 0.64$], and complications [RR: 0.47 (95% CI: 0.20, 1.13), $P = 0.09$]. **Conclusions:** Levobupivacaine is significantly associated with a longer duration of sensory and motor block in patients undergoing BPB for upper limb surgery compared to ropivacaine, with a similar safety profile. However, there was no difference regarding the time to onset of the sensory or motor block.

Keywords: Analgesia, brachial plexus block, levobupivacaine, meta-analysis, ropivacaine, surgery, systematic review, upper limb

INTRODUCTION

The role of peripheral nerve plexus blocks in modern anaesthesia is vital, ensuring surgery can be performed safely without significant adverse effects.[1] Peripheral nerve blocks offer significant intraoperative pain relief, leading to reliable postoperative pain control.[2] This technique, specifically brachial plexus block (BPB), is advantageous for elective orthopaedic

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or reconstructive upper limb surgery and emergency surgeries.[3] However, the optimal local anaesthetic in BPB is yet to be decided.

Several local anaesthetics (e.g. lignocaine, bupivacaine, ropivacaine, and levobupivacaine) are being investigated for BPB.[4,5] Traditionally, bupivacaine is preferred for BPB due to its long-lasting effects and optimal sensory to motor neural block ratio.[6] However, when bupivacaine was used clinically, it was reported that some patients experienced toxic effects on their heart and central nervous system, which were specifically associated with the dextro enantiomer of bupivacaine.[5,6] In response, researchers started developing alternative local anaesthetics with all the beneficial characteristics of bupivacaine while avoiding any toxic drawbacks.[4,5]

Consequently, levobupivacaine and ropivacaine, long-lasting local anaesthetics, were developed to provide prolonged pain relief without bupivacaine side effects.[7] Several randomised controlled trials (RCTs) have investigated levobupivacaine versus ropivacaine in BPB with conflicting findings.[1,2,5,8–20] Therefore, this systematic review and meta-analysis aim to comprehensively synthesise the current evidence on the comparative efficacy and safety of levobupivacaine versus ropivacaine in BPB for patients undergoing upper limb surgery. We explored the comparative effectiveness and safety of levobupivacaine versus ropivacaine across preoperative (time to sensory and motor block), intraoperative (surgery duration and conversion rate to general anaesthesia), and postoperative outcomes (sensory and motor block durations) in BPB for patients undergoing upper limb surgery by synthesising evidence from RCTs.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[21] and the Cochrane Handbook for Systematic Reviews and Meta-Analyses[22] were employed to carry out this systematic review and meta-analysis. The corresponding review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42024588740).

Data sources and search strategy

A systematic electronic search was conducted on 9 June 2024 using the following databases: PubMed (MEDLINE), Web of Science (WOS), Scopus, CENTRAL, Embase, and Google Scholar. The search strategy included the following search string "(ropivacain* OR "ropivacaine hydrochloride" OR "ropivacaine monohydrochloride" OR naropeine OR naropin OR "LEA 103" OR "LEA-103" OR "AL 381" OR "1 Propyl 2',6' pipecoloxylidide" OR "(S)-Ropivacaine" OR "84057-95-4" OR "rocaine") AND (levobupivacaine OR chirocaine OR "(S)-bupivacaine" OR "(-)-bupivacaine" OR "L(-)-bupivacaine" OR "Levobupivacaine HCl" OR "Levobupivacaine hydrochloride") AND ("brachial plexus block*" OR '"brachial plexus anesthesia" OR "brachial plexus analges*" OR "upper limb surger*" OR "shoulder surger*" OR "hand surger*" OR "elbow surger*" OR "arm surger*" OR "forearm surger*" OR "brachial plexus" OR "brachial block" OR "brachial plexus nerve block*")". No filters or limits were used during the search process, except for Scopus, in which we limited the search to titles, abstracts, and keywords. Further details on each database's search terms and results are shown in Supplementary Table 1. Furthermore, a manual search of the included trial list of references was conducted to detect any missed eligible records.

Eligibility criteria

We included RCTs that followed the following PICO criteria: population (P), adult patients undergoing BPB regardless of the approach (supraclavicular, infraclavicular, interscalene, or axillary) for upper limb surgery; intervention (I) levobupivacaine irrespective of the concentration; control (C), ropivacaine regardless of the concentration (O): preoperative outcomes (time to sensory and motor block), intraoperative outcomes (patients converted to general anaesthesia and surgery duration), and postoperative outcomes (duration of sensory block, duration of motor block, visual analogue scale (VAS) pain score at 24 hours, rescue analgesia, and complications (the incidence of local and systemic adverse events)). However, we excluded observational studies, conference abstracts, posters, reviews, animal studies, and in-vitro studies. We also excluded RCTs that investigated other patient populations, such as lower limb surgery.

Study selection

Two independent investigators conducted the screening process using the Covidence online tool (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.). After eliminating duplicates, we evaluated each obtained record independently in two

steps: title/abstract screening and full-text screening. Any differences were settled through discussion to reach a consensus.

Data extraction

A pilot extraction was conducted after obtaining the full texts of the relevant publications to design an Excel (Microsoft, USA) extraction form, which was divided into three sections: summary characteristics of the included trials (first author name, year of publication, country, study design, number of centres, sample size, intervention details, and primary outcome); baseline characteristics of the included participants [number of patients in each group, age, gender, American Society of Anesthesiologists (ASA) category, and baseline vitals]; and the outcome data [preoperative outcomes (time to sensory and motor block), intraoperative outcomes (patients converted to general anaesthesia and surgery duration), and postoperative outcomes (duration of sensory block, duration of motor block, VAS pain score at 24 hours, rescue analgesia, and complications]. Two reviewers independently extracted the data, and any differences were settled by discussion and agreement with a senior author. Dichotomous outcomes were extracted in event and total format, while continuous outcomes were extracted in mean and standard deviation. If the data was reported in median and interquartile range or range, we followed the formulas provided by Wan *et al*.[23] to convert it to mean and standard deviation.

Risk of bias and certainty of evidence

The risk of bias in included studies was assessed using the revised Cochrane Collaboration tool for RCTs (ROB 2).[24] Two reviewers evaluated each study independently for selection, performance, reporting, attrition, and overall biases, with disagreements resolved through consensus. To investigate the certainty of evidence, Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) recommendations[25,26] were followed, considering inconsistency, imprecision, indirectness, publication bias, and risk of bias. The evaluation was carried out for each outcome, and the decisions were justified and documented. Any discrepancies were settled through discussion.

Statistical analysis

Stata MP Version 17, Stata Corp (Texas, USA), was used to conduct the statistical analysis. To pool the results of dichotomous outcomes, we used the risk ratio (RR), whereas for continuous outcomes, we used Cohen's d, both with a 95% confidence interval (CI). The fixed-effects model was used unless there was significant heterogeneity, where we implemented the random-effects model instead. Statistical heterogeneity among the included studies was assessed using the Chi-square and I-squared tests (I^2). A *P* value of the Chi-square test less than 0.1 was considered significant for possible heterogeneity, while I^2 values $\geq$50% indicated significant heterogeneity. On significant heterogeneity, a sensitivity analysis using the leave-one-out model was performed by excluding each study at a time and observing the potential impact on the overall effect estimate to ensure that the effect estimate was not driven heavily by a certain study. We also used the Galbraith plot to detect any heterogeneity across studies. Finally, publication bias was evaluated visually using funnel plots or statistically using Egger's test.[27]

RESULTS

Search results and study selection

After the search, 1270 studies were identified and evaluated for screening based on their titles and abstracts. Thirty-five full-text articles were screened after removing 572 irrelevant records and 708 studies that did not meet the inclusion criteria after title and abstract screening. Nineteen were found to be unrelated and excluded, leaving 16 RCTs[1,2,5,8–20] to be included in qualitative and quantitative assessments [Figure 1].

Characteristics of included studies

Sixteen RCTs and 939 patients were included in our analysis.[1,2,5,8–20] BPB approach varied among the included trials as follows: interscalene approach in three trials,[11,18,20] supraclavicular approach in seven trials,[1,5,8,10,13,14,19] infraclavicular approach in three trials,[9,12,17] and axillary approach in three trials.[2,15,16] Notably, eight trials were conducted in India.[1,5,8,10,13,14,19,20] Further summary characteristics of the included trials and baseline characteristics of the included patients are outlined in Tables 1 and Supplementary Table 2, respectively.

Risk of bias and certainty of evidence

Six trials had an overall low risk of bias.[2,11,12,14,16,18] Seven trials had some concerns of bias overall, either due to the lack of information on randomisation or a published protocol.[1,5,8,9,13,15,19] Finally, three trials had an overall high risk of bias[10,17,20] [Figure 2]. A GRADE evidence profile outlines the detailed certainty of evidence assessment [Supplementary Table 3].

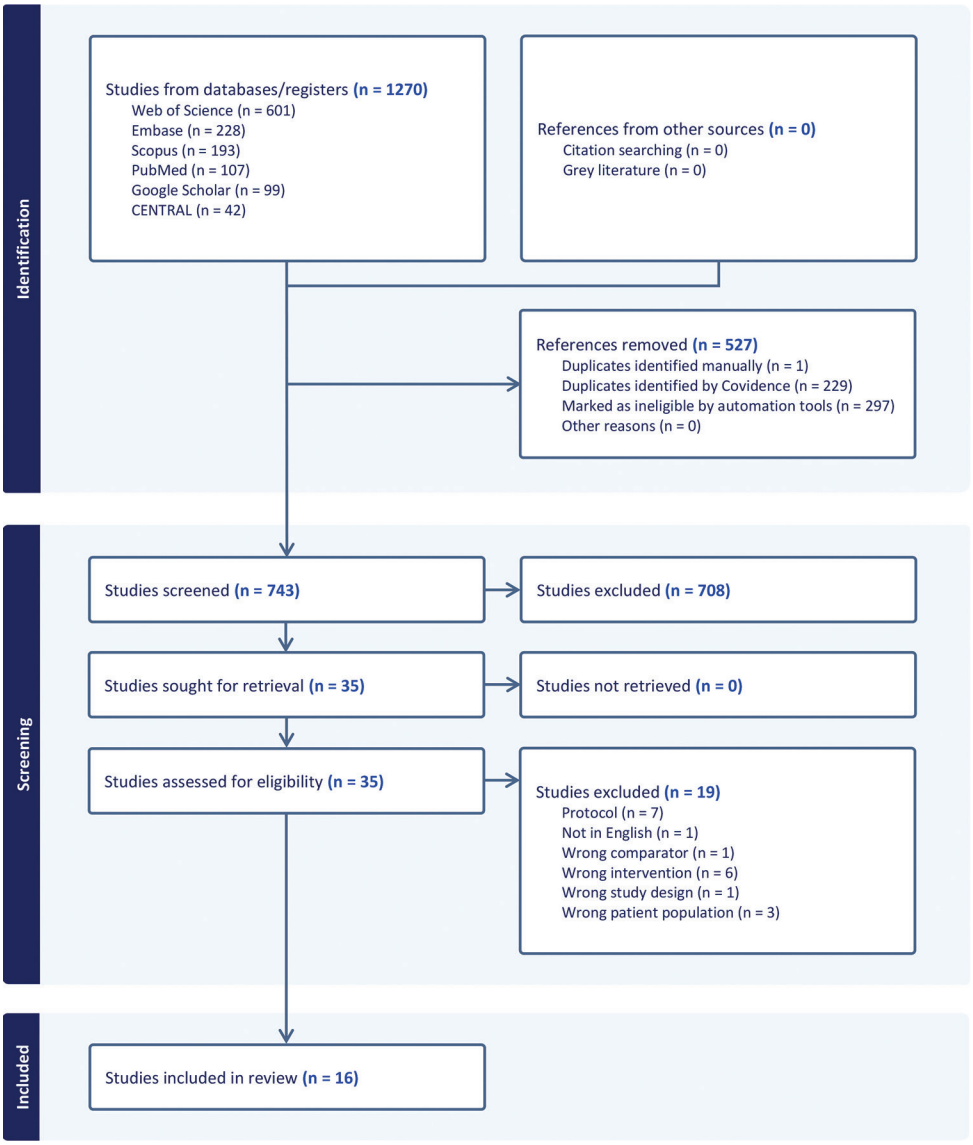

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the screening process

Preoperative outcomes

There was no difference between both groups in time to sensory block [MD: −0.30 (95% CI: −1.31, 0.71), $P = 0.56$] [Figure 3a] and time to motor block [MD: −0.29 (95% CI: −1.26, 0.67), $P = 0.55$] [Figure 3b]. Pooled studies were heterogeneous in time to sensory block ($I^2 = 92.68\%$, $P < 0.0001$) and time to motor block ($I^2 = 85.22\%$, $P < 0.0001$).

Leave-one-out sensitivity analysis showed consistent results after excluding each study at a time to sensory block [Supplementary Figure 1] and time to motor block [Supplementary Figure 2]. Galbraith plot showed that some studies were outliers and most likely responsible for the observed heterogeneity: time to sensory block [Supplementary Figure 3] and time to motor block [Supplementary Figure 4]. In addition, the test for the subgroup analysis based on the BPB approach was not significant with respect to time to sensory block ($P = 0.250$) [Supplementary Figure 5]; however, it was significant in time to motor block ($P < 0.0001$) [Supplementary Figure 6]. Finally, there was a significant publication bias either assessed visually or statistically by Egger's test in time to sensory block ($P = 0.0055$) [Supplementary Figure 7] and time to motor block ($P = 0.0206$) [Supplementary Figure 8].

Intraoperative outcomes

There was no difference between both groups in patients converted to general anaesthesia [RR: 1.30 (95% CI: 0.38, 4.45), $P = 0.68$] [Figure 4a] and surgery duration [MD: −1.63 (95% CI: −7.19, 3.94), $P = 0.57$] [Figure 4b]. Pooled studies were homogenous in time to patients converted to

Table 1: Summary characteristics of the included RCTs

Study ID	Study Design	Country	*n*	BPB Approach	Surgery	Concentration (%)		Adjuvant Drugs	Postoperative Rescue Analgesia
						Levobupivacaine	Ropivacaine		
Borghi *et al*. 2006[18]	RCT	Italy	72	Interscalene	Open shoulder	0.25	0.25 or 0.4	Midazolam (0.03 mg/kg) and sufentanil (0.15 μg/kg)	Ketoprofen (100 mg) Maximum of three times a day. If ineffective, tramadol (100 mg)
Casati *et al*. 2003[11]	RCT	Italy	47	Interscalene	Open shoulder	0.5	0.5	Midazolam (0.05 mg/kg) and 20 mg of 2% lidocaine	Tramadol (100 mg)
Chauhan *et al*. 2020[10]	RCT	India	60	Supraclavicular	Elbow, forearm, and hand	0.5	0.5	Glycopyrrolate (0.2 mg), ranitidine (50 mg), and ondansetron (4 mg)	NA
Cline *et al*. 2004[2]	RCT	USA	54	Axillary	Upper limb	0.5	0.5	Epinephrine (1:200,000 unit), midazolam (0–5 mg), & fentanyl (0–150 μg)	NA
Dua *et al*. 2016[20]	RCT	India	60	Interscalene	Upper limb	0.5	0.5	NA	NA
González-Suárez *et al*. 2009[15]	RCT	Spain	86	Axillary	Upper limb	0.33	0.5	Bupivacaine 0.5%	Ketorolac (30 mg), which was repeated every 8 hours for the first 24 hours, and metamizol (2 g) was administered if the visual analogue scale scores 30 min after ketorolac administration was greater than 3.
Jyothirmayee *et al*. 2022[8]	RCT	India	60	Supraclavicular	Upper limb	0.5	0.5	NA	NA
Karthik *et al*. 2022[13]	RCT	India	60	Supraclavicular	Upper limb	0.5	0.5	NA	NA
Kim *et al*. 2021[12]	RCT	South Korea	46	Infraclavicular	Elbow, forearm, and hand	0.25	0.375	Dexmedetomidine (1 μg/kg) was loaded over 10–15 min, followed by a continuous infusion of 0.5–1.0 μg/kg/h.	NA
Liisanantti *et al*. 2004[16]	RCT	Finland	60	Axillary	hand, wrist or forearm	0.5	0.5	Diazepam (0.1–0.15 mg/kg orally or 0.05–0.07 mg/kg	Non-steroidal anti-inflammatory drug or paracetamol
Mageswaran *et al*. 2010[17]	RCT	Malaysia	52	Infraclavicular	hand, wrist or forearm	0.5	0.5	NA	NA
Khursheed Mir *et al*. 2021[14]	RCT	India	56	Supraclavicular	Forearm	0.5	0.5	NA	NA
More *et al*. 2023[5]	RCT	India	80	Supraclavicular	Upper limb	0.5	0.5	Lignocaine (1%), glycopyrrolate (0.004 mg/kg), ondansetron (0.1 mg/kg), and midazolam (0.03–0.05 mg/kg)	NA
Piangatelli *et al*. 2006[9]	RCT	Italy	30	Infraclavicular	Forearm and hand	0.5	0.75	Atropine (0.01 mg/k) & midazolam (0.1–0.2 mg/kg)	NA
Shahid *et al*. 2021[1]	RCT	India	56	Supraclavicular	Forearm	0.5	0.5	Lignocaine (1.5 mL)	NA
Thalamati *et al*. 2021[19]	RCT	India	60	Supraclavicular	Upper limb	0.5	0.75	NA	NA

RCT=randomised controlled trial, BPB=brachial plexus block, NA=not available

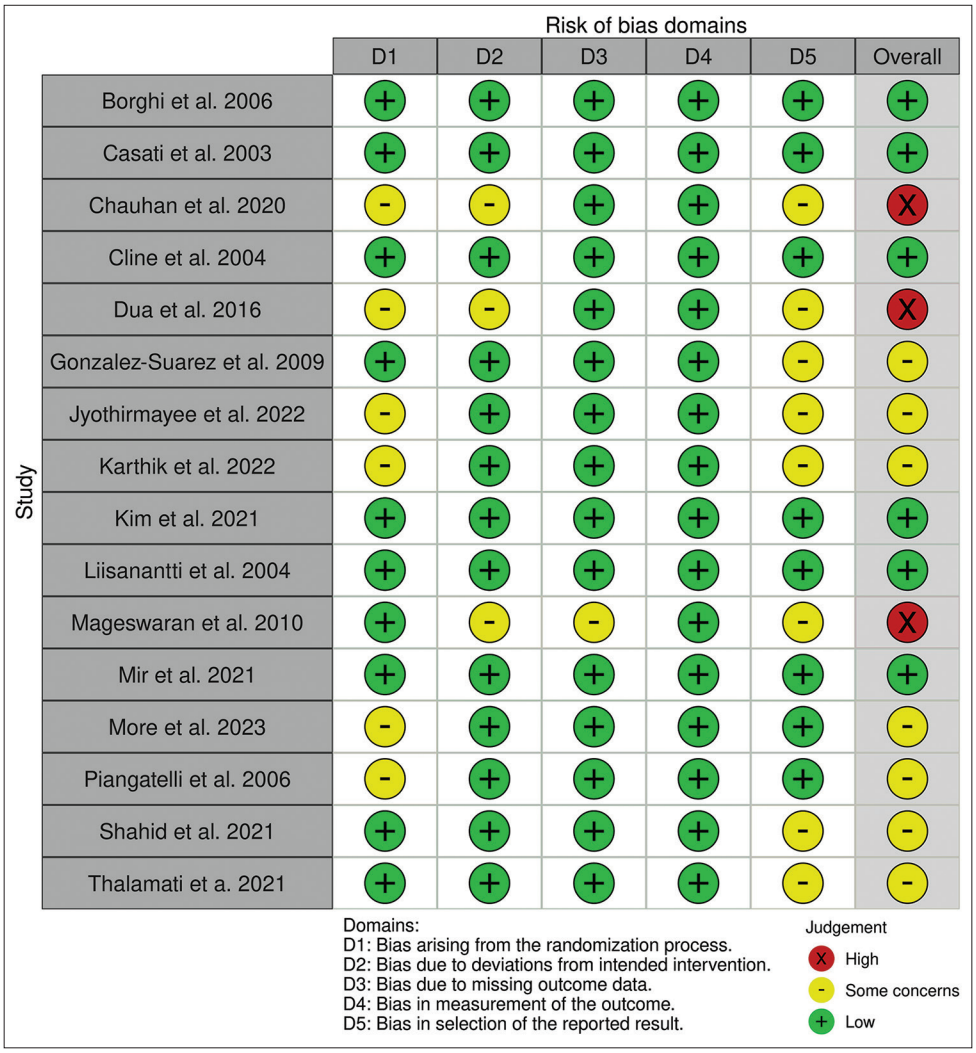

Figure 2: Quality assessment of risk of bias in the included trials. The upper panel presents a schematic representation of risks (low = green, unclear = yellow, and high = red) for specific types of biases of each study in the review. The lower panel presents risks (low = green, unclear = yellow, and high = red) for the subtypes of biases of the combination of studies included in this review

general anaesthesia (I^2 = 0%, P = 0.95) and surgery duration (I^2 = 0%, P = 0.62).

Postoperative outcomes

Levobupivacaine was significantly associated with a longer sensory block duration [MD: 1.66 (95% CI: 1.43, 1.89), P < 0.001] [Figure 5a] and motor block duration [MD: 1.18 (95% CI: 0.11, 2.26), P = 0.03] [Figure 5b]. However, both the groups were not different with respect to VAS [MD: −0.48 (95% CI: −2.13, 1.16), P = 0.56] [Figure 6a], rescue analgesia [RR: 0.94 (95% CI: 0.74, 1.20), P = 0.64] [Figure 6b], and complications [RR: 0.47 (95% CI: 0.20, 1.13), P = 0.09] [Figure 6c].

Pooled studies were homogenous in sensory block duration (I^2 = 6.65%, P = 0.38), rescue analgesia (I^2 = 0%, P = 0.98), and complications (I^2 = 92.88%, P < 0.0001). However, pooled studies were heterogeneous in motor block duration (I^2 = 0%, P = 0.98) and VAS score (I^2 = 76.97%, P = 0.01). Leave-one-out sensitivity analysis showed consistent results after excluding each study at a time in motor block duration, except after excluding Cline *et al*.[2], there was no difference between both groups (P = 0.103) [Supplementary Figure 9] and VAS pain score [Supplementary Figure 10]. Galbraith plot showed that some studies were outliers and most likely responsible for the observed heterogeneity: motor block duration [Supplementary Figure 11] and VAS score [Supplementary Figure 12].

In addition, the test for the subgroup analysis based on the BPB approach was not significant with respect to motor block duration (P = 0.60) [Supplementary Figure 13], rescue analgesia (P = 0.77) Supplementary Figure 14], and

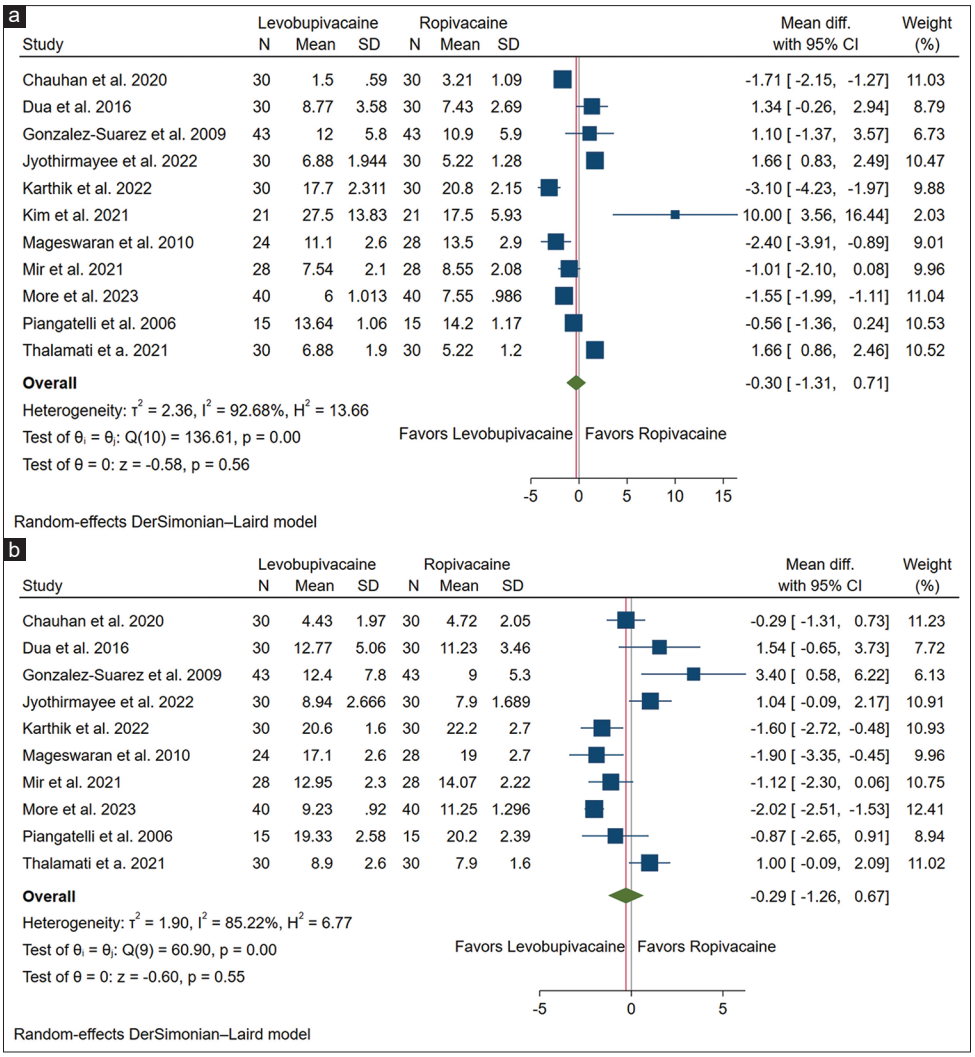

Figure 3: Forest plot of the (a) time to sensory block, and (b) time to motor block. CI = confidence interval, SD = standard deviation, n = number of patients, mean diff = mean difference

complications (P = 0.99) [Supplementary Figure 15]; however, it was significant with respect to sensory block duration (P = 0.04) [Supplementary Figure 16]. Finally, there was no publication bias either assessed visually or statistically by Egger's test in sensory block duration (P = 0.5536) [Supplementary Figure 17], motor block duration (P = 0.956) [Supplementary Figure 18], and complications (P = 0.636) [Supplementary Figure 19].

DISCUSSION

After synthesising 16 RCTs with 939 patients, there was no difference between levobupivacaine and ropivacaine with respect to time to sensory block, time to motor block, the rate of patients converted to general anaesthesia, surgery duration, VAS pain score after 24 hours, rescue analgesia rate, and the incidence of complications. However, levobupivacaine was significantly associated with a longer duration of sensory and motor block.

Levobupivacaine and ropivacaine are categorised as amino-amide local anaesthetics and are optically pure S-enantiomers of bupivacaine.[12] They have comparable pharmacologic characteristics, specifically, the same ionised constant (pKa = 8.1) associated with onset time.[28] However, levobupivacaine has a liposolubility of 30, while ropivacaine has a liposolubility of 2.8.[29] Findings from previous *in vitro* studies suggested that a higher lipid solubility expedites the onset time in isolated nerve fibres.[12] However, these findings may not always be reliable in a real-world clinical setting, and numerous reports have emphasised the importance of considering it in conjunction with other variables.[28] This can explain our finding that despite

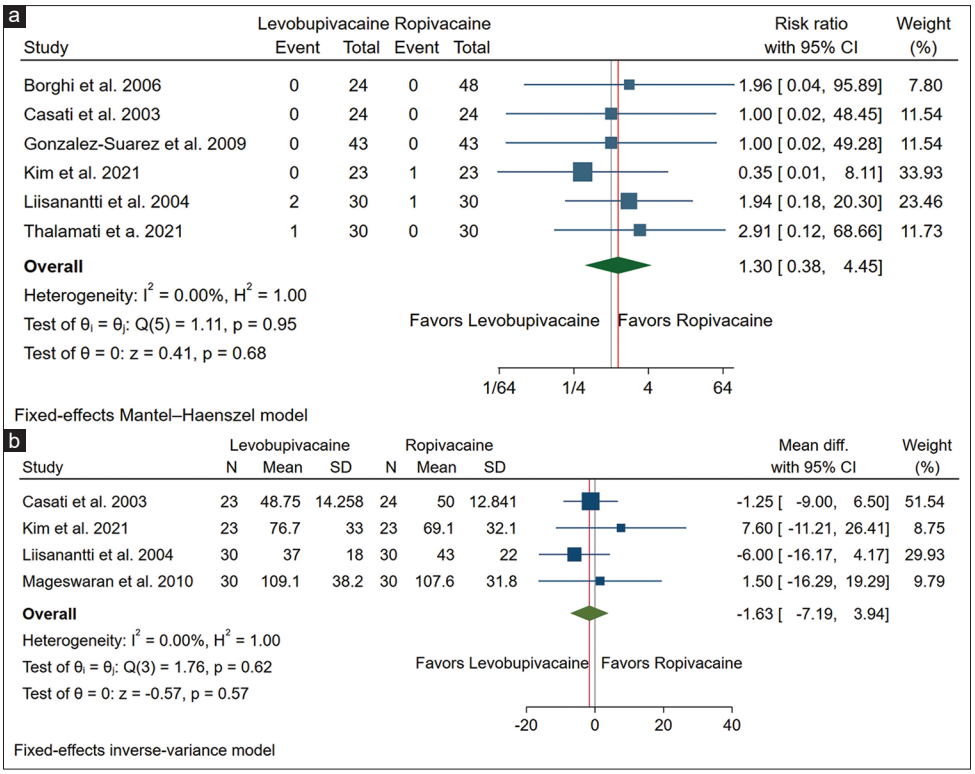

Figure 4: Forest plot of the (a) patients converted to general anaesthesia, and (b) surgery duration. CI = confidence interval, SD = standard deviation. N = number of patients

the higher liposolubility of levobupivacaine, there is no difference between the two drugs regarding sensory and motor onset time.

Additionally, it is crucial to consider the variations in molarity caused by differences in molecular weight and the presentation, either as a hydrochloride salt or a base. It has been reported that 225 mg of ropivacaine is equivalent in potency to 150 mg of levobupivacaine.[30] Borghi *et al*.[18] noted that a 0.25% concentration of levobupivacaine produced anaesthesia of similar quality to a 0.4% concentration of ropivacaine. However, it provided better anaesthesia than a 0.25% concentration in a similar clinical setting. In addition, equimolar doses of the two drugs exhibited comparable onset and duration of nerve block on isolated nerves.[31] Taking this into account, ropivacaine may have equal potency to levobupivacaine, but other factors need to be considered due to the complexity of clinical practice.[32] The absorption rate of both drugs varied greatly depending on the density of blood vessels in different regions and how they were administered despite their widespread distribution in tissues. We cannot conclude that equal doses of local anaesthetics will have the same effects.[32]

Despite this indifference in time to the sensory and motor block, levobupivacaine was associated with a longer sensory and motor block duration. Basic investigations indicate that levobupivacaine and racemic bupivacaine are approximately 50% more effective than ropivacaine in inhibiting tetrodotoxin-resistant sodium ion channels, further supported by animal studies.[32,33] A potential explanation for the higher potency of levobupivacaine is that ropivacaine concentrations were administered as a hydrochloride salt. In contrast, levobupivacaine concentrations were administered as a base, leading to a 13% underestimation in concentration.[34] It is also vital to note that More *et al*.[5] had 70% of the analysis weight in the pooled analysis of sensory block duration. Thus, it can substantially affect the pooled effect size, and the results must be interpreted cautiously. Still, there was no significant heterogeneity among the included studies, and levobupivacaine showed the same effect in the subgroup analysis according to the approach, even in different subgroups, such as axillary block. Moreover, the block duration was reported to be influenced by the protein-bound level, causing highly protein-bound drugs to have a more prolonged effect.[35] Nevertheless, there was a

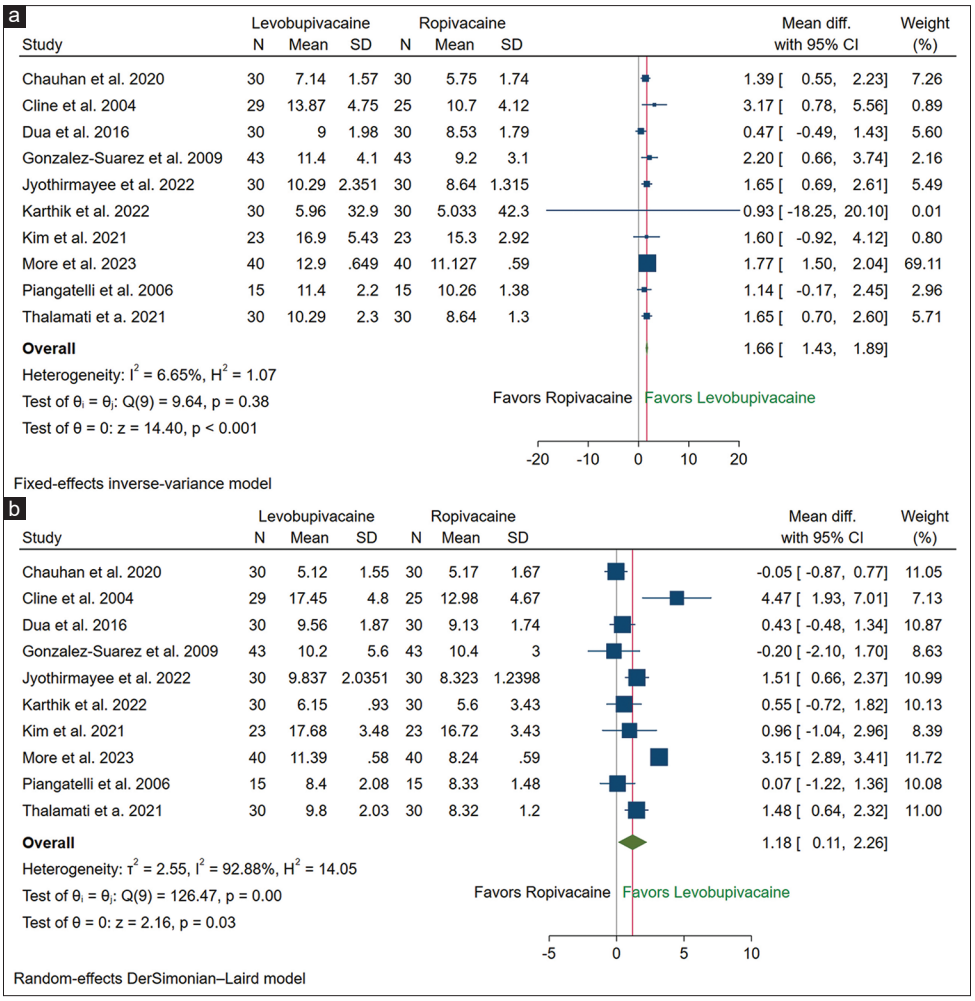

Figure 5: Forest plot of the (a) sensory block duration, and (b) motor block duration. CI = confidence interval, mean diff = mean difference, SD = standard deviation. N = number of patients

slight but insignificant difference in protein binding percentage (94% for ropivacaine compared to 95% for levobupivacaine).[32,36] Finally, the duration of analgesia is associated with variations in clinical factors, such as the technique used for blocking and the extent of surgical procedures.[2]

Regarding the safety profile, there was no difference in complications, and all the reported adverse effects were essentially nausea or vomiting, except for a hematoma at the insertion site with ropivacaine.[14] However, adverse events cannot always be attributed to local anaesthetics, as surgical procedures or underlying conditions may cause them.[32] In addition, when comparing the central nervous system and cardiovascular effects of two drugs under equal conditions, there were no significant differences in the mean percentage changes of relevant parameters, such as stroke index, cardiac index, PR interval, and convulsive threshold dose.[32,37] Overall, both local anaesthetics were well tolerated by patients in clinical practice.[32]

Strengths and limitations

To the extent of our knowledge, this is the first systematic review and meta-analysis to investigate the efficacy and safety of levobupivacaine versus ropivacaine in BPB; thus, it is considered the best available evidence in this regard. Still, our review has a few limitations. Firstly, we included small single-centre trials with a relatively small sample size, undergoing different upper limb procedures, affecting the generalisability of our findings. Secondly, the drug concentration, volume, and administration approach were variable among the included studies, and we could only conduct a subgroup analysis based on the administration approach. However, the analgesic effect of different approaches (axillary, supraclavicular, infraclavicular, or interscalene) was equivalent.[38]

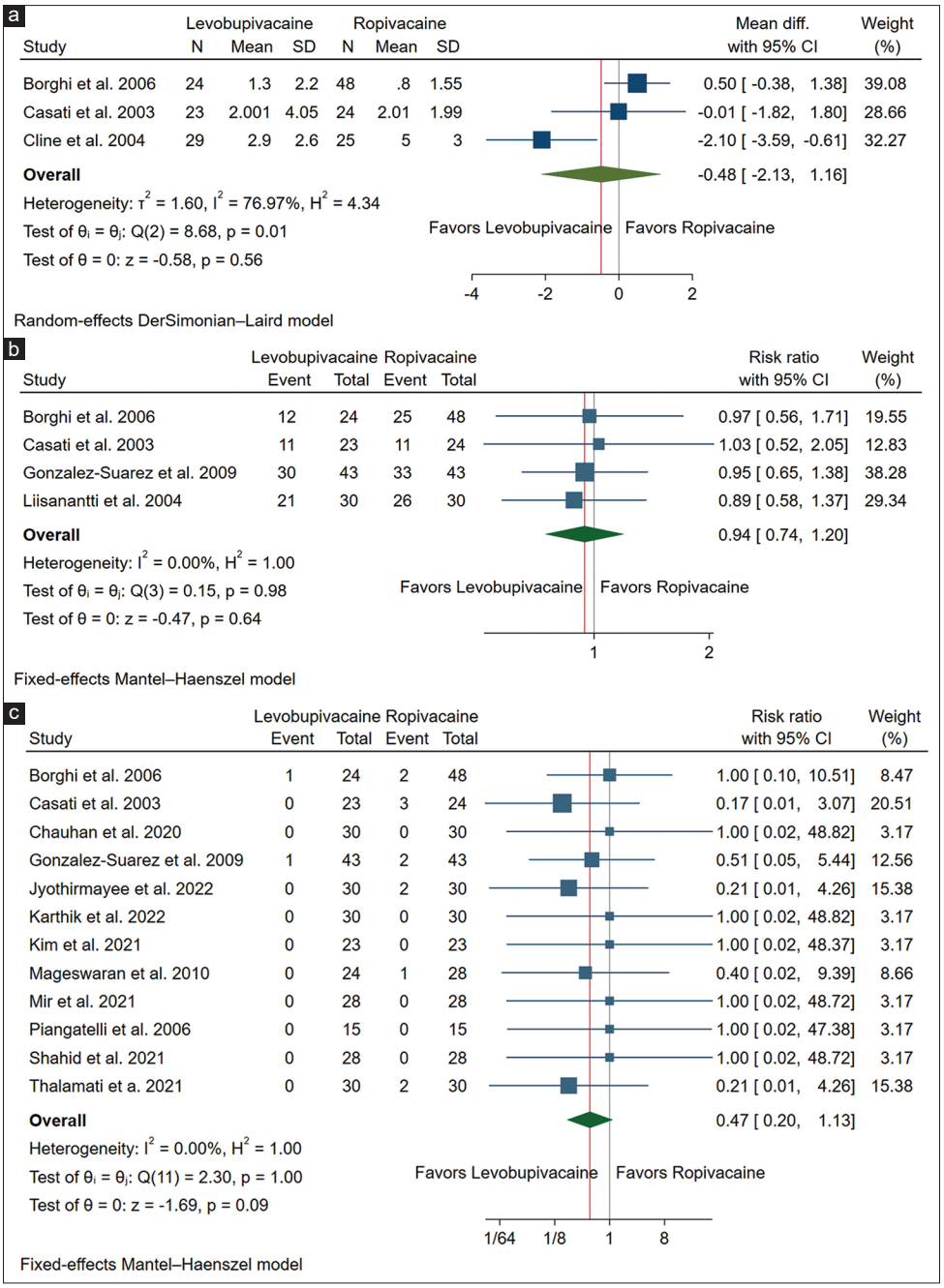

Figure 6: Forest plot of the (a) visual analogue scale (VAS) pain score, (b) rescue analgesia, and (c) complications. CI = confidence interval, mean diff = mean difference, SD = standard deviation. N = number of patients

Thirdly, all included trials included patients with ASA physical status I or II; thus, our data cannot be generalised on ASA III. Furthermore, some trials involved using adjuvants with the drugs of interest to prolong and intensify the analgesic effect, which can affect our findings, and we could not conduct a subgroup analysis based on that due to the variability in adjuvant drugs among the included trials. Finally, we noticed significant heterogeneity in some outcomes, which significantly impacted the certainty of evidence; however, we highlight several reasons for this heterogeneity that align with the complexity of clinical practice.

Implications for clinical practice

Ropivacaine has the advantage of promoting faster motor function recovery after surgery compared to levobupivacaine. However, levobupivacaine offers advantages in terms of a more extended sensory block, although it does have the drawback of a delayed

motor block. Therefore, if the priority is to minimise postoperative pain, levobupivacaine should be taken into account; however, it may not be the most suitable option if prompt restoration of motor function is desired.[14] In addition, when a surgical peripheral nerve block is administered in the clinical setting, a rapid onset of action is vital for various reasons. Local anaesthetics that act quickly can enhance the efficiency of operating room management, alleviate surgeons' concerns about time, and improve patient satisfaction by reducing anxiety.[12] In this regard, both drugs seem to have equivalent time of onset. Nevertheless, for situations requiring an immediate and complete sensory and motor block, combining other local anaesthetics with quicker onset may be helpful to or include adjuvants.[12,39] However, given that the toxicity of local anaesthetics can build up over time, it is crucial to carefully decide the total volume of mixed anaesthetics, considering the patient's characteristics.[40]

CONCLUSION

Levobupivacaine is significantly associated with a longer duration of sensory and motor block in patients undergoing BPB for upper limb surgery compared to ropivacaine, with a similar safety profile. Hence, if the priority is to decrease postoperative pain, levobupivacaine should be considered; however, ropivacaine should be the best option if a quick return of motor function is the priority. However, there was no difference regarding the time to sensory or motor block, patients converted to general anaesthesia, surgery duration, VAS pain score after 24 hours, and rescue analgesia rate. In addition, the current evidence remains uncertain and dependable on small single-centre RCTs, warranting further investigation.

Study data availability

The data for this systematic review and meta-analysis may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared.

Supplementary material

Visit journal website for supplementary tables and figures associated with this article.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Search Strategy			
Database	**Search Terms**	**Search Field**	**Search Results**
Pubmed	(ropivacain* OR “ropivacaine hydrochloride” OR “ropivacaine monohydrochloride” OR naropeine OR naropin OR “LEA 103” OR “LEA-103” OR “AL 381” OR “1 Propyl 2’,6’ pipecoloxylidide” OR “(S)-Ropivacaine” OR “84057-95-4” OR “rocaine”) AND (levobupivacaine OR chirocaine OR “(S)-bupivacaine” OR “(-)-bupivacaine” OR “L(-)-bupivacaine” OR “Levobupivacaine HCl” OR “Levobupivacaine hydrochloride”) AND (”brachial plexus block*” OR ‘”brachial plexus anesthesia” OR ”brachial plexus analges*” OR “upper limb surger*” OR “shoulder surger*” OR “hand surger*” OR “elbow surger*” OR “arm surger*” OR “forearm surger*” OR “brachial plexus” OR “brachial block” OR ”brachial plexus nerve block*”)	All Fields	107
Cochrane	(ropivacain* OR “ropivacaine hydrochloride” OR “ropivacaine monohydrochloride” OR naropeine OR naropin OR “LEA 103” OR “LEA-103” OR “AL 381” OR “1 Propyl 2’,6’ pipecoloxylidide” OR “(S)-Ropivacaine” OR “84057-95-4” OR “rocaine”) AND (levobupivacaine OR chirocaine OR “(S)-bupivacaine” OR “(-)-bupivacaine” OR “L(-)-bupivacaine” OR “Levobupivacaine HCl” OR “Levobupivacaine hydrochloride”) AND (”brachial plexus block*” OR ‘”brachial plexus anesthesia” OR ”brachial plexus analges*” OR “upper limb surger*” OR “shoulder surger*” OR “hand surger*” OR “elbow surger*” OR “arm surger*” OR “forearm surger*” OR “brachial plexus” OR “brachial block” OR ”brachial plexus nerve block*”)	All Text	42
WOS	(ropivacain* OR “ropivacaine hydrochloride” OR “ropivacaine monohydrochloride” OR naropeine OR naropin OR “LEA 103” OR “LEA-103” OR “AL 381” OR “1 Propyl 2’,6’ pipecoloxylidide” OR “(S)-Ropivacaine” OR “84057-95-4” OR “rocaine”) AND (levobupivacaine OR chirocaine OR “(S)-bupivacaine” OR “(-)-bupivacaine” OR “L(-)-bupivacaine” OR “Levobupivacaine HCl” OR “Levobupivacaine hydrochloride”) AND (”brachial plexus block*” OR ‘”brachial plexus anesthesia” OR ”brachial plexus analges*” OR “upper limb surger*” OR “shoulder surger*” OR “hand surger*” OR “elbow surger*” OR “arm surger*” OR “forearm surger*” OR “brachial plexus” OR “brachial block” OR ”brachial plexus nerve block*”)	All Fields	601
SCOPUS	(ropivacain* OR “ropivacaine hydrochloride” OR “ropivacaine monohydrochloride” OR naropeine OR naropin OR “LEA 103” OR “LEA-103” OR “AL 381” OR “1 Propyl 2’,6’ pipecoloxylidide” OR “(S)-Ropivacaine” OR “84057-95-4” OR “rocaine”) AND (levobupivacaine OR chirocaine OR “(S)-bupivacaine” OR “(-)-bupivacaine” OR “L(-)-bupivacaine” OR “Levobupivacaine HCl” OR “Levobupivacaine hydrochloride”) AND (”brachial plexus block*” OR ‘”brachial plexus anesthesia” OR ”brachial plexus analges*” OR “upper limb surger*” OR “shoulder surger*” OR “hand surger*” OR “elbow surger*” OR “arm surger*” OR “forearm surger*” OR “brachial plexus” OR “brachial block” OR ”brachial plexus nerve block*”)	Title, Abstract, Keywords	193
Google Scholar	(ropivacain* OR “ropivacaine hydrochloride” OR “ropivacaine monohydrochloride” OR naropeine OR naropin OR “LEA 103” OR “LEA-103” OR “AL 381” OR “1 Propyl 2’,6’ pipecoloxylidide” OR “(S)-Ropivacaine” OR “84057-95-4” OR “rocaine”) AND (levobupivacaine OR chirocaine OR “(S)-bupivacaine” OR “(-)-bupivacaine” OR “L(-)-bupivacaine” OR “Levobupivacaine HCl” OR “Levobupivacaine hydrochloride”) AND (”brachial plexus block*” OR ‘”brachial plexus anesthesia” OR ”brachial plexus analges*” OR “upper limb surger*” OR “shoulder surger*” OR “hand surger*” OR “elbow surger*” OR “arm surger*” OR “forearm surger*” OR “brachial plexus” OR “brachial block” OR ”brachial plexus nerve block*”)	All Fields	99
EMBASE	(ropivacaine OR naropeine OR naropin) AND (levobupivacaine OR chirocaine) AND (brachial plexus block OR brachial plexus anesthesia OR brachial plexus analgesia OR upper limb surgery OR shoulder surgery OR hand surgery OR elbow surgery OR arm surgery OR forearm surgery OR brachial plexus nerve block)	All Fields	228

Supplementary Table 2: Baseline characteristics of the participants

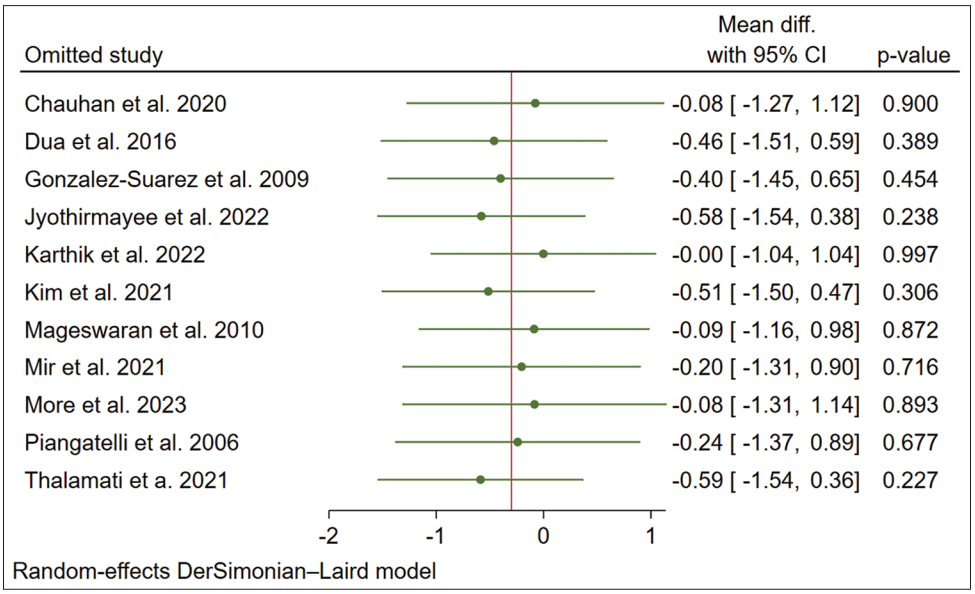
Study ID	Number of Participants in Each Group		Age (Years), Mean (SD)		Gender (Male/Female)	
	Levobupivacaine	Ropivacaine	Levobupivacaine	Ropivacaine	Levobupivacaine	Ropivacaine
Borghi *et al*. 2006 (R 0.25%)[18]	24	24	53±16	53±12	17/7	13/11
Borghi *et al*. 2006 (R 0.4%)[18]		24		51±17		14/10
Casati *et al*. 2003[11]	23	24	49.5±13.48	51.5±14.382	14/9	11/13
Chauhan *et al*. 2020[10]	30	30	36.13±12.44	41.4±12.88	21/9	21/9
Cline *et al*. 2004[2]	29	25	29.7±10.9	27.0±7.5	24/5	19/6
Dua *et al*. 2016[20]	30	30	NA	NA	NA	NA
Gonzalez-Suarez *et al*. 2009[15]	43	43	43±12	40±15	NA	NA
Jyothirmayee *et al*. 2022[8]	30	30	35.47±12.792	36.43±14.862	20/10	23/7
Karthik *et al*. 2022[13]	30	30	39.46±9.11	40.63±9.27	21/9	23/7
Kim *et al*. 2021[12]	23	23	53.5±16.2	56.6±14.9	16/7	11/12
Liisanantti *et al*. 2004[16]	30	30	48±12	47±11	11/19	19/11
Mageswaran *et al*. 2010[17]	24	28	32.9±13.3	33.9±12.4	19/5	23/5
Mir *et al*. 2021[14]	28	28	30.93±11.04	31.14±11.76	22/6	19/9
More *et al*. 2023[5]	40	40	38.98±14.375	38.93±12.350	NA	NA
Piangatelli *et al*. 2006[9]	15	15	53±13	51±14	9/6	8/7
Shahid *et al*. 2021[1]	28	28	30.93±11.04	31.14±11.76	22/6	19/9
Thalamati *et al*. 2021[19]	30	30	35.47±12.80	36.43±14.86	20/10	23/7

Study ID	ASA status, *n* (%)					
	ASA 1		ASA 2		ASA 3	
	Levobupivacaine	Ropivacaine	Levobupivacaine	Ropivacaine	Levobupivacaine	Ropivacaine
Borghi *et al*. 2006 (R 0.25%)[18]	13 (54.16)	10 (41.7)	8 (33.3)	4 (16.7)	3 (12.5)	0
Borghi *et al*. 2006 (R 0.4%)[18]		12 (50)		11 (45.8)		1 (0.4)
Casati *et al*. 2003[11]	NA	NA	NA	NA	NA	NA
Chauhan *et al*. 2020[10]	27 (90)	25 (83.33)	3 (10)	5 (16.67)	NA	NA
Cline *et al*. 2004[2]	NA	NA	NA	NA	NA	NA
Dua *et al*. 2016[20]	NA	NA	NA	NA	NA	NA
Gonzalez-Suarez *et al*. 2009[15]	NA	NA	NA	NA	NA	NA
Jyothirmayee *et al*. 2022[8]	16 (53.3)	16 (53.3) 24 (80)	6 (20)	14 (46.6)	NA	NA
Karthik *et al*. 2022[13]	21 (70)	22 (73)	9 (30)	8 (27)	NA	NA
Kim *et al*. 2021[12]	NA	NA	NA	NA	NA	NA
Liisanantti *et al*. 2004[16]	NA	NA	NA	NA	NA	NA
Mageswaran *et al*. 2010[17]	NA	NA	NA	NA	NA	NA
Mir *et al*. 2021[14]	18 (67.8)	17 (60.7)	10 (32.2)	11 (39.3)	NA	NA
More *et al*. 2023[5]	26 (65)	29 (72.5)	14 (35)	11 (27.5)	NA	NA
Piangatelli *et al*. 2006[9]	12 (80)	13 (86.67)	3 (20)	2 (13.3)	NA	NA
Shahid *et al*. 2021[1]	18 (64.3)	17 (60.7)	10 (35.7)	11 (39.3)	NA	NA
Thalamati *et al*. 2021[19]	24 (80)	16 (53.3)	6 (20)	14 (46.6)	NA	NA

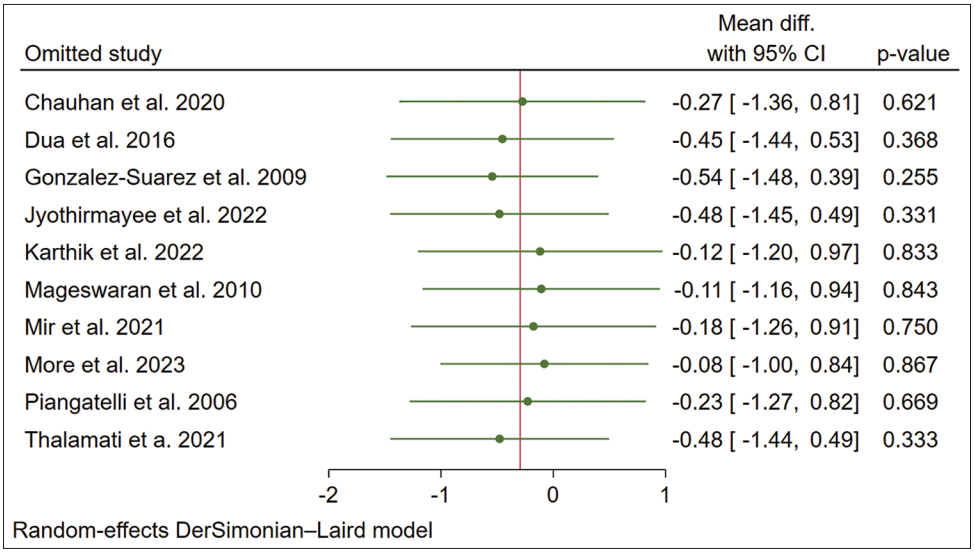
NA=not available; SD=standard deviation; ASA=American Society of Anesthesiologists

Supplementary Table 3: GRADE Evidence Profile											
Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With [Ropivacaine]	Study event rates (%) With [Levobupivacaine]	Relative effect (95% CI)	Anticipated absolute effects Risk with [Ropivacaine]	Anticipated absolute effects Risk difference with [Levobupivacaine]
Time to Sensory Block											
646 (11 RCTs)	very serious[a]	very serious[b]	not serious	serious[c]	publication bias strongly suspected[d]	⊕◯◯◯ Very low	325	321	-	325	MD 0.3-minute lower (1.31 lower to 0.71 higher)
Time to Motor Block											
604 (10 RCTs)	very serious[a]	very serious[b]	not serious	not serious	publication bias strongly suspected[d]	⊕◯◯◯ Very low	304	300	-	304	MD 0.29-minute lower (1.26 lower to 0.67 higher)
Patients Converted to General Anaesthesia											
372 (6 RCTs)	not serious	not serious	not serious	very seriouse	none	⊕⊕◯◯ Low	2/198 (1.0%)	3/174 (1.7%)	RR 1.30 (0.38 to 4.45)	2/198 (1.0%)	3 more per 1,000 (from 6 fewer to 35 more)
Surgery Duration											
213 (4 RCTs)	not serious	not serious	not serious	very serious[f]	none	⊕⊕◯◯ Low	107	106	-	107	MD 1.63 hour lower (7.19 lower to 3.94 higher)
Sensory Block Duration											
596 (10 RCTs)	serious[g]	not serious	not serious	not serious	none	⊕⊕⊕◯ Moderate	296	300	-	296	MD 1.66 hour higher (1.43 higher to 1.86 higher)
Motor Block Duration											
596 (10 RCTs)	very serious[g]	very serious[b]	not serious	serious[c]	none	⊕◯◯◯ Very low	296	300	-	296	MD 1.18 hour higher (0.11 higher to 2.26 higher)
VAS Pain Score											
173 (3 RCTs)	not serious	very serious[b]	not serious	very serious[f]	none	⊕◯◯◯ Very low	97	76	-	97	MD 0.48 lower (2.13 lower to 1.16 higher)
Rescue Analgesia											
265 (4 RCTs)	not serious	not serious	not serious	serious[h]	none	⊕⊕⊕◯ Moderate	95/145 (65.5%)	74/120 (61.7%)	RR 0.94 (0.74 to 1.20)	95/145 (65.5%)	39 fewer per 1,000 (from 170 fewer to 131 more)
Complications											
685 (12 RCTs)	very serious[g]	not serious	not serious	very seriouse	none	⊕◯◯◯ Very low	12/357 (3.4%)	2/328 (0.6%)	RR 0.47 (0.20 to 1.13)	12/357 (3.4%)	18 fewer per 1,000 (from 27 fewer to 4 more)

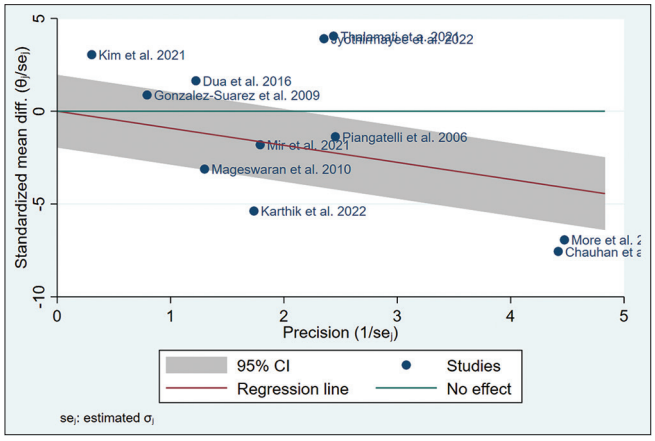
CI=confidence interval; MD=mean difference; RR=risk ratio. a. Chauhan *et al*., Dua *et al*., and Mageswaran *et al*. had an overall high risk of bias, with 28% of the analysis weight. b. I^2 >75%. c. A wide confidence interval that does not exclude the appreciable harm/benefit. d. A significant Egger's test. e. A wide confidence interval that does not exclude the appreciable harm/benefit, with a low number of events (<300 events). f. A wide confidence interval that does not exclude the appreciable harm/benefit, with a low number of participants (<300 participants). g. Chauhan *et al*., and Dua *et al*. had an overall high risk of bias & Gonzalez-Suarez *et al*., Jyothirmayee *et al*., Karthik *et al*., More *et al*., and Piangatelli *et al*. had some concerns of bias. h. Low number of events



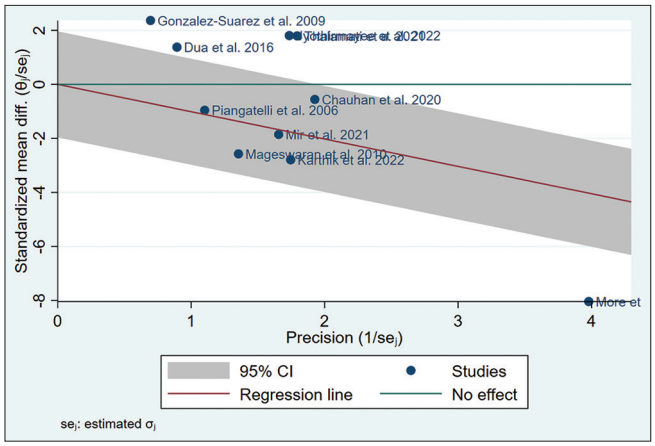
Supplementary Figure 1: Sensitivity analysis of time to sensory block. CI = confidence interval



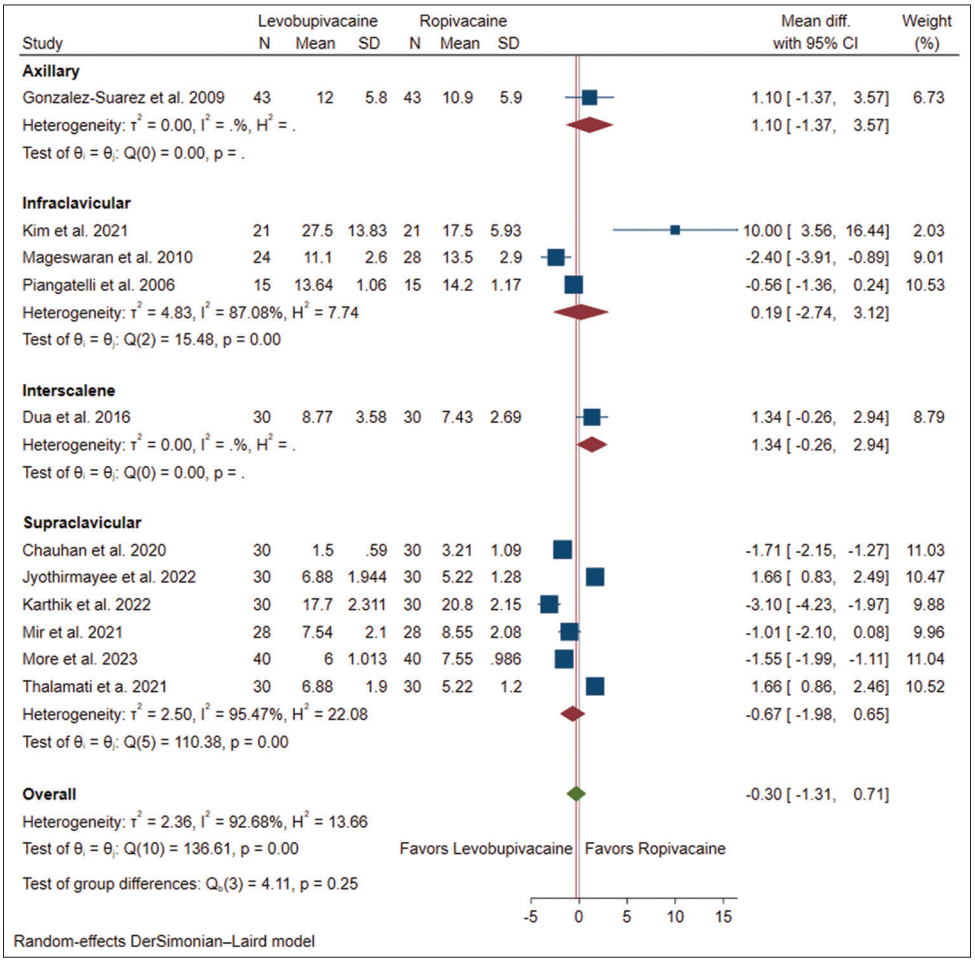
Supplementary Figure 2: Sensitivity analysis of time to motor block. CI = confidence interval



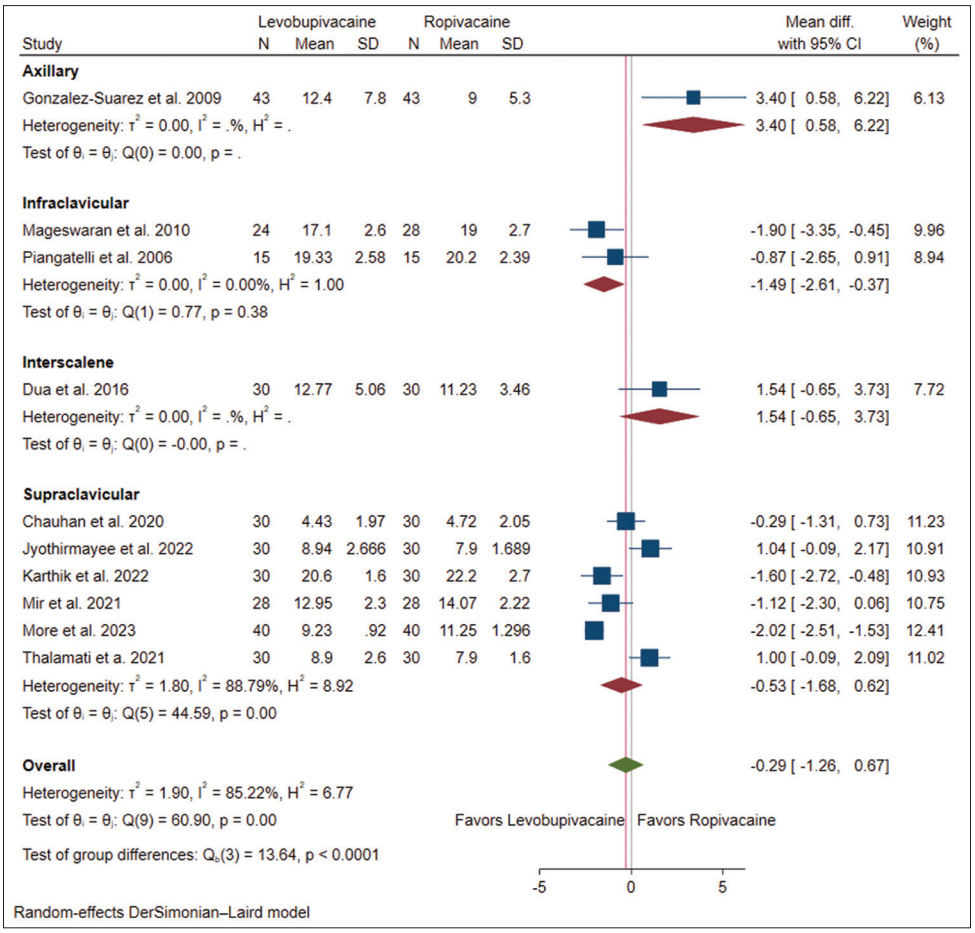
Supplementary Figure 3: Galbraith plot of time to sensory block. CI = confidence interval, mean diff = mean difference



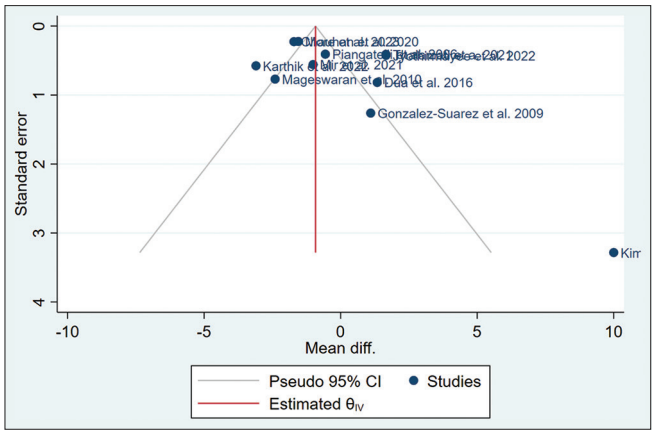
Supplementary Figure 4: Galbraith plot of time to motor block. CI = confidence interval, mean diff = mean difference



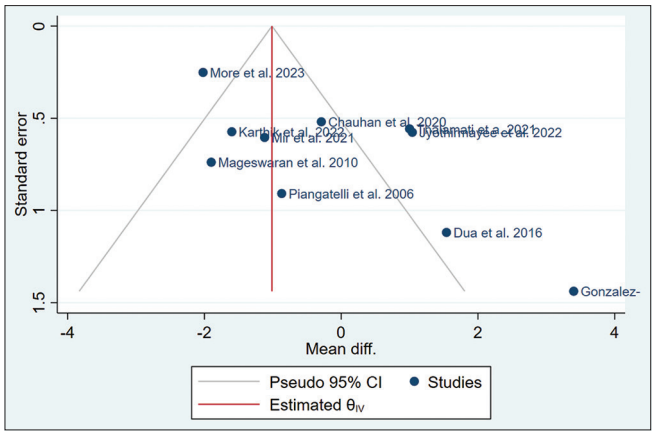
Supplementary Figure 5: Subgroup analysis based on the brachial plexus block approach of time to sensory block. CI = confidence interval, SD = standard deviation, mean diff = mean difference



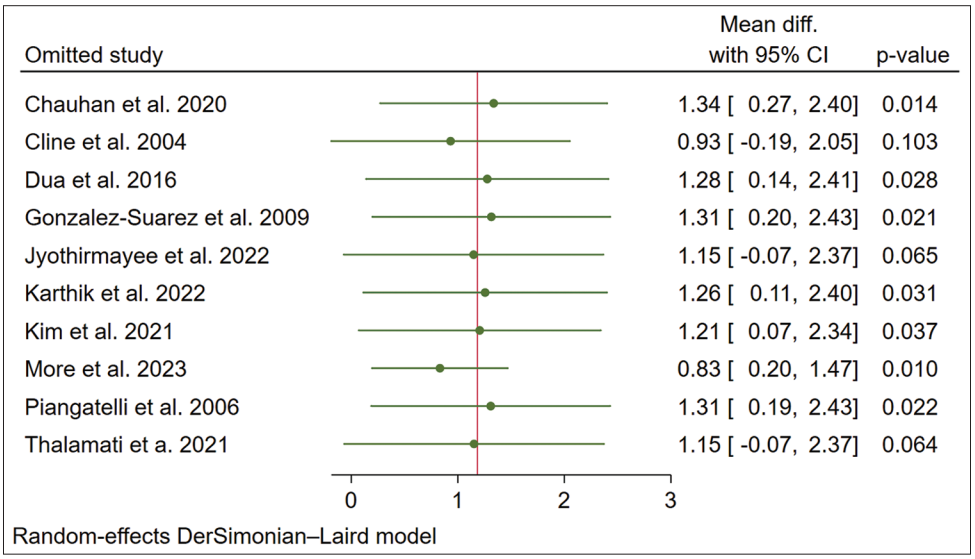
Supplementary Figure 6: Subgroup analysis based on the brachial plexus block approach of time to motor block. CI = confidence interval, SD = standard deviation, mean diff = mean difference



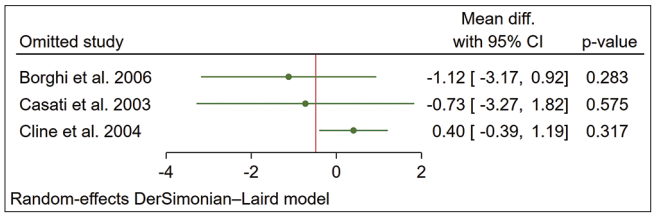
Supplementary Figure 7: Funnel plot of time to sensory block. CI = confidence interval



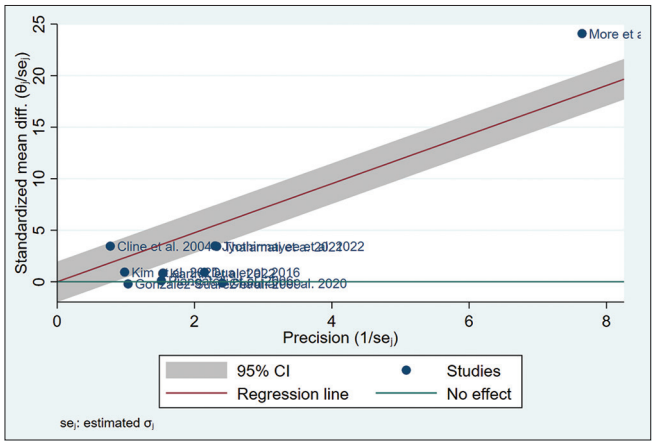
Supplementary Figure 8: Funnel plot of time to motor block. CI = confidence interval



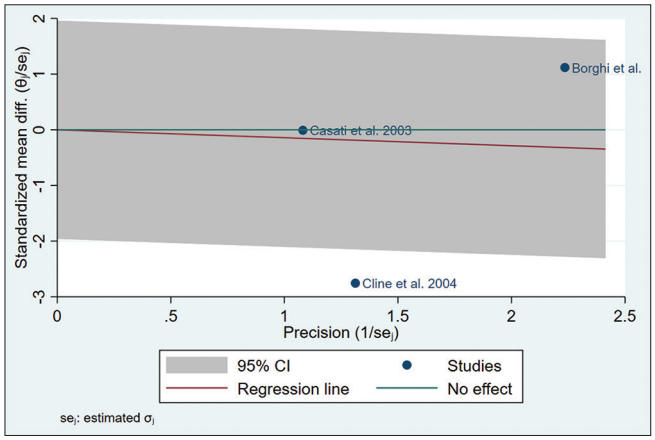
Supplementary Figure 9: Sensitivity analysis of motor block duration. CI = confidence interval, mean diff = mean difference



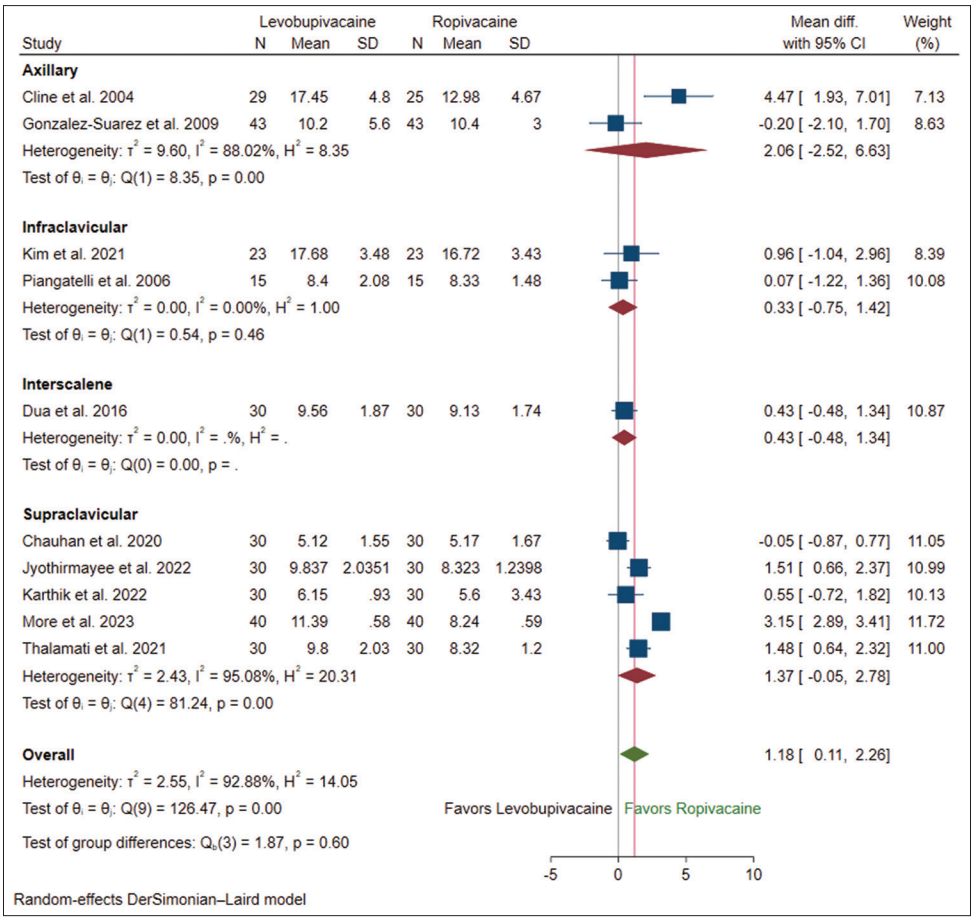
Supplementary Figure 10: Sensitivity analysis of VAS pain score. CI = confidence interval, mean diff = mean difference



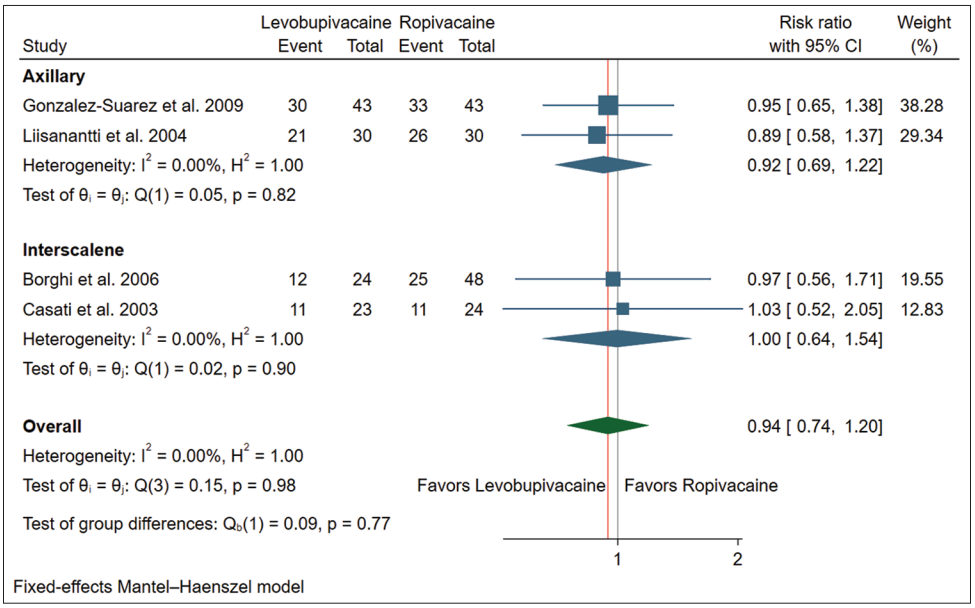
Supplementary Figure 11: Galbraith plot of motor block duration. CI = confidence interval, mean diff = mean difference



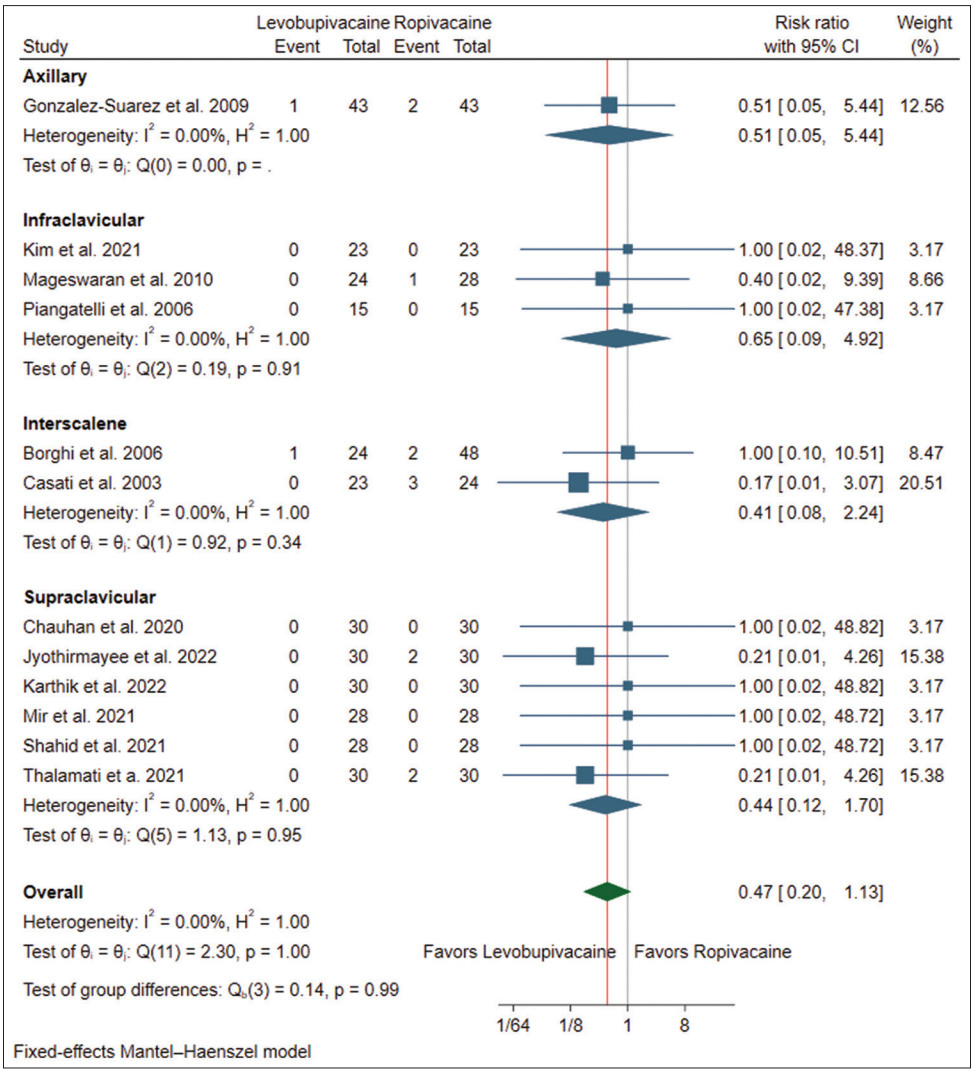
Supplementary Figure 12: Galbraith plot of VAS pain score. CI = confidence interval, mean diff = mean difference



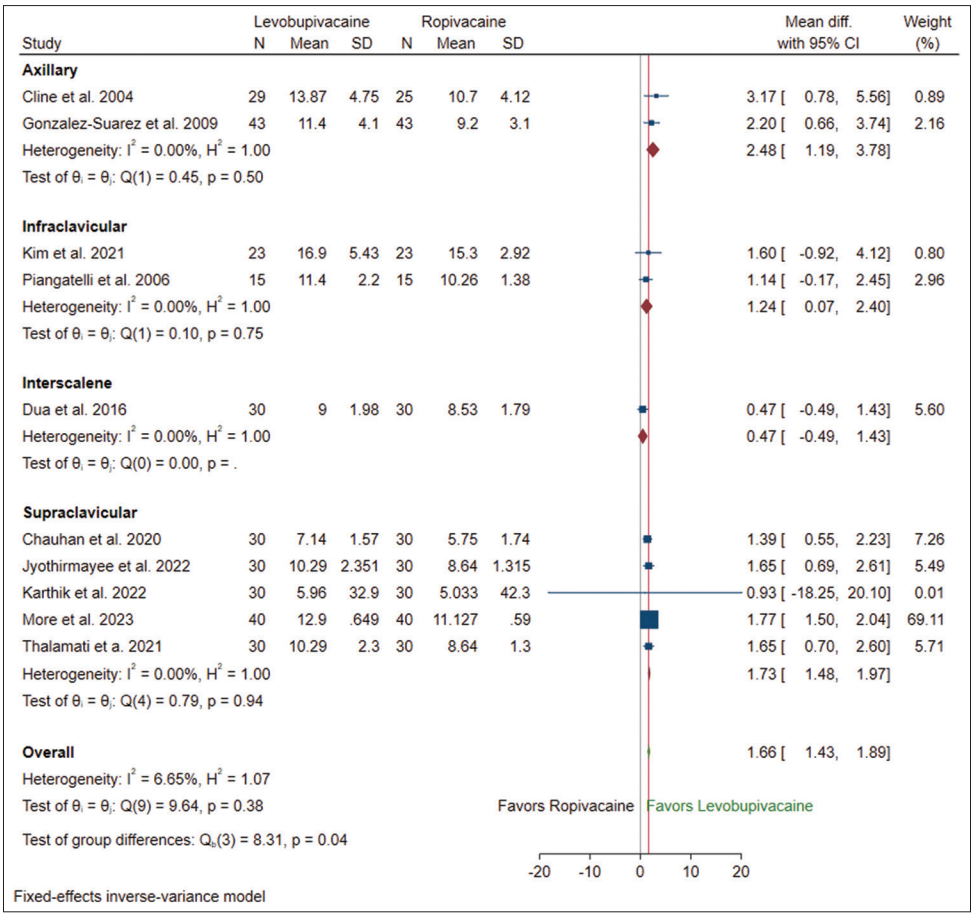
Supplementary Figure 13: Subgroup analysis based on the brachial plexus block approach of motor block duration. CI = confidence interval, SD = standard deviation, mean diff = mean difference



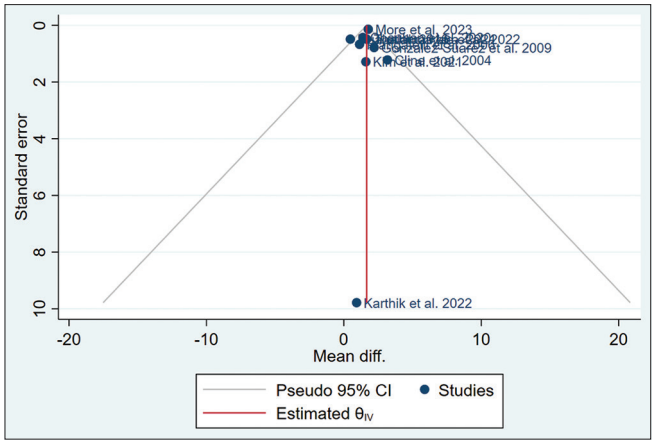
Supplementary Figure 14: Subgroup analysis based on the brachial plexus block approach of rescue analgesia. CI = confidence interval



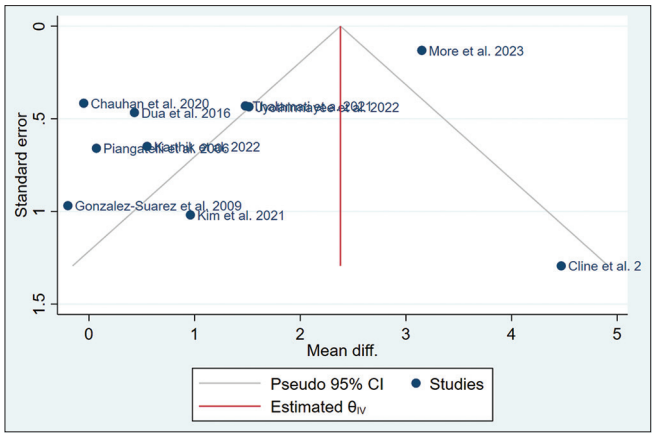
Supplementary Figure 15: Subgroup analysis based on the brachial plexus block approach of complications. CI = confidence interval



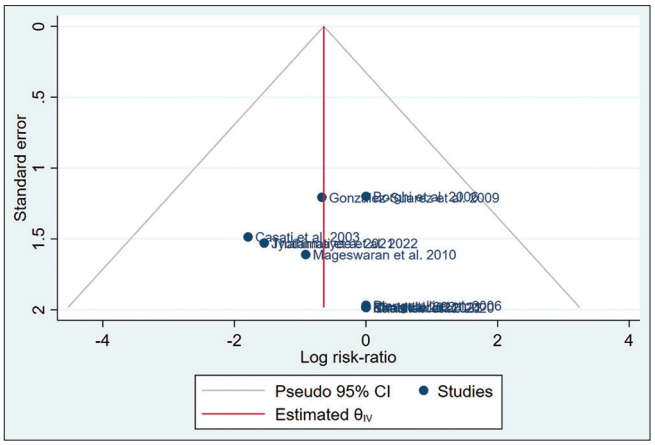
Supplementary Figure 16: Subgroup analysis based on the brachial plexus block approach of sensory block duration. CI = confidence interval, SD = standard deviation, mean diff = mean difference



Supplementary Figure 17: Funnel plot of sensory block duration. CI = confidence interval



Supplementary Figure 18: Funnel plot of motor block duration. CI = confidence interval, mean diff = mean difference



Supplementary Figure 19: Funnel plot of complications. CI = confidence interval