Efficacy of long-acting local anesthetics versus their mixture with shorter-acting local anesthetics for peripheral nerve blocks guided by ultrasound: a systematic review with meta-analysis of randomized controlled trials

Natanael Pietroski dos Santos [1], Vanessa de Paula Silva [2], Guilherme Stéfano da Silva Oliveira [2], Victor Cardoso Musacchio [2], Vanessa Henriques Carvalho [3]

[1]FMABC University Center, Santo André, SP, Brazil
[2]Hospital das Clínicas de São Bernardo do Campo, São Bernardo do Campo, SP, Brazil
[3]State University of Campinas, Campinas, SP, Brazil

Correspondence to
Dr Natanael Pietroski dos Santos; pietroski@gmail.com

Received 2 October 2024
Accepted 17 December 2024
Published Online First
8 January 2025

ABSTRACT

Background/importance Local anesthetic (LA) mixtures are used in peripheral nerve blocks (PNB) to improve onset, though study results remain conflicting.

Objective This systematic review and meta-analysis compared the efficacy outcomes of long-acting LA to their mixture with shorter-acting LA in ultrasound-guided PNB. The primary outcome was sensory block onset.

Evidence review We searched WoS, Scopus, MEDLINE, EMBASE, BVS/LILACS, and Cochrane databases from 1998 to 2024 for randomized controlled trials (RCTs). We conducted a random-effects meta-analysis, evaluated the risk of bias (RoB) with RoB 2.0, performed sensitivity analyses, assessed non-reporting bias with DOI plots and Luis Furuya-Kanamori index, and evaluated strength of evidence with Grading of Recommendations Assessment, Development and Evaluations.

Findings We included 10 RCTs (516 participants). Mixture of LA may have no effect on sensory block onset (mean difference (MD) −1.62 min, 95% CI: −4.04 to 0.81; I^2=81.50%, 95% CI: 62.82% to 90.80%; prediction interval (PI)=−7.78 to 4.55; very low certainty) and motor block onset (MD −5.60 min; 95% CI: −14.54 to 3.33, I^2=98.89%, 95% CI: 98.50% to 99.18%; PI=−31.90 to 20.69; very low certainty), while it may reduce the duration of sensory block (MD −2.16 hours, 95% CI: −4.16 to −0.17; I^2=90.77%, 95% CI: 84.22% to 94.60%; PI=−7.24 to 2.92; very low certainty).

Conclusions LA mixtures may not affect sensory and motor block onset in ultrasound-guided PNB but could shorten the duration of sensory blockade.

INTRODUCTION

In several situations, the ideal local anesthetic (LA) should have a pharmacodynamic profile that combines a short block onset time with a long sensory block duration. Because such LA does not exist, combinations of long-acting and shorter-acting LAs have been proposed to improve clinical efficacy in regional anesthesia, though studies present conflicting results. Data from trials guided by nerve stimulation suggest that LA mixtures could both reduce[1–3] or have no effect[4–6] on sensory block onset, and similar uncertainty extends to their impact on analgesia duration.[1 2 4–6]

In recent decades, the adoption of ultrasound guidance for peripheral nerve blocks (PNB) has significantly changed practice.[7 8] Consequently, data from pre-ultrasound studies may not adequately inform current practice or expectations regarding block onset. To the best of our knowledge, this is the first meta-analysis to evaluate the effects of LA combinations in PNB.

This systematic review with meta-analysis of randomized controlled trias (RCTs) aims to bridge the gap in the evidence of "to mix or not to mix LAs" according to the onset of the sensory block—our primary objective—and secondary outcomes related to ultrasound-guided (US-guided) regional anesthesia. We hypothesize that the sensory onset of blockade is not affected by the LA mixture.

METHODS

We followed the Cochrane Handbook for Systematic Reviews of Interventions[9] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[10] and RAPM[11 12] guidelines. The protocol was registered (CRD42024504086; first submitted on January 30, 2024) before data extraction; however, it has not been published in a peer-reviewed journal. The registry was updated once, but we followed the original protocol. Post hoc, we included the evaluation of non-reporting bias using DOI plots and the Luis Furuya-Kanamori (LFK) index.[13] We also estimated post hoc a minimally clinically important difference (MCID) of 5 min for sensory block onset, on the precedent of this value being also considered a margin of non-inferiority for block onset.[14]

Search strategy

We conducted searches across Web of Science, Scopus, MEDLINE (via PubMed), EMBASE (via Elsevier), BVS/LILACS (via Biblioteca Virtual em Saúde), and the Cochrane Database (via Cochrane Library)—includes protocols registered at ClinicalTrials.gov, from 1998 to March 5, 2024. The start year considered the time when adequate

To cite: Pietroski dos Santos N, Silva VdP, Oliveira GSdS, *et al*. *Reg Anesth Pain Med* 2026;**51**:132–141.

sonographic information for the performance of peripheral nerve blocks had been described.[15] Studies were limited to those published in English, Spanish, Portuguese, and French. The search was conducted by NPdS. After selecting eligible studies, we screened their reference lists to identify additional RCTs. We also planned to search systematic reviews as sources for RCTs, and this was carried out as part of our search strategy. A list of terms searched is available in online supplemental material 1 S1. The search strategy structure adopted a PICO-style approach, including terms related to PNB, fascial blocks, long-acting LA (bupivacaine, levobupivacaine, or ropivacaine), shorter-acting LA (mepivacaine or lidocaine), and onset/latency.

Eligibility criteria

We included studies that met all the following criteria: (1) Population: participants of all ages submitted to US-guided regional anesthesia; (2) Intervention: one intervention arm with a mixture or sequential administration of long-acting and shorter-acting LAs; (3) Comparison: one comparison arm with long-acting LAs; (4) Outcome: data on sensory block onset; and, (5) Type of study: RCTs with randomization at the individual level. We did not include studies with (1) neuraxial anesthesia, (2) ophthalmologic blocks, (3) digital blocks, and (4) the use of adjuvants, except epinephrine. Epinephrine was accepted as an adjuvant because it is a commercially available combination to most LA.

Selection process

For the study selection process, we used the free and unrestricted version of the PICO Portal (PICO Portal, New York, New York, USA. Available at www.picoportal.org). Its automated system excludes duplicates and marks ineligible files. Two reviewers, selected from a team of four (NPdS, VdPS, GSdSO, VCM) independently screened each title and abstract of identified articles. All four reviewers were equally qualified to screen titles and abstracts, and the specific reviewers varied by study. Full texts of studies that satisfied the eligibility criteria were retrieved. Two reviewers, selected from a team of four (NPdS, VdPS, GSdSO, VCM) independently reviewed all full texts. All four reviewers were equally qualified for the task, and the specific reviewers varied by study. Reviewers were blinded to each other's decisions in the first decision. For each paper, once two reviewers had completed screening, the PICO Portal created a list of documents with screening disagreements. Disagreements between individual judgments for these previously mentioned and the following steps were resolved through discussion and consensus or the involvement of a third reviewer (VHC).

Data collection, extraction and management

Two reviewers, selected from a team of four (NPdS, VdPS, GSdSO, VCM), independently extracted the data into Google Sheets. All four reviewers were equally qualified to perform data extraction, and the specific reviewers varied by study. For each paper, once two reviewers had completed data extraction, their entries were cross-checked to ensure consistency and accuracy. A list of variables collected is available in our protocol. Data from the figures were extracted using WebPlotDigitalizer V.4.7. Four authors of the included papers were contacted once for unreported data and additional details; none answered. When reports on multiple concentrations were provided in a study, we included those that reflected a 1:1 ratio in the mixture and twice the LA mass in the arm with long-acting LA. A 2:1 mixture was the only option for one study.[16] Parametric data were included in the meta-analysis as provided in the original studies, but those described by median and IQRs were transformed[17 18] if the data were not considered sufficiently skewed to comprise the overall estimates.[19] Significantly skewed data were not transformed nor included in the meta-analysis.

Outcomes

The primary outcome of this review was to estimate the onset time of sensory block. Secondary outcomes included the onset of motor block, duration of motor and sensory blockade, postoperative morphine equivalent consumption at 24 hours, block failure, and occurrence of adverse events.

Data synthesis and statistical analysis

We analyzed the data in RStudio V.2023.12.1+402 using R package (meta) V.6.5–0. The Doi plots were generated using the doiplot function from the (metasens) package V.1.5–2.

Calculation of effect sizes

We calculated effect sizes as the mean difference (MD) for continuous outcomes and as relative risk (RR) for dichotomous outcomes. For pain, the Visual Analog Scale (VAS) and the Numeric Rating Scale (NRS) can be considered interchangeable for acute pain,[20] nonetheless, no numerical conversion was necessary since all studies reported pain on a scale of 0–10. Whenever available, we prioritized reports of overall 24-hour pain. When only data from multiple intervals were provided, we calculated the average of the intervals' means and SD, assuming equal sample sizes across time points.

Pooling of effect sizes

We conducted a random-effects meta-analysis using the restricted maximum-likelihood approach to calculate the between-study heterogeneity (τ^2).[21] The effect sizes for continuous outcomes were pooled using the inverse variance method, while for dichotomous outcomes we used the Mantel-Haenszel method, with a continuity correction of 0.5 applied in studies presenting zero cell frequencies. For all outcomes, to address uncertainty in effect size estimates, we applied the Knapp-Hartung adjustment, which provides more reliable CIs.[22] We used 95% CIs to indicate the precision of the pooled effect estimate, which represents the range within which we are 95% confident the true pooled effect lies across all studies. In other words, "we are 95% confident that the pooled effect is between a and b".[23] We also calculated prediction intervals (PI) to aid in the clinical interpretation of the heterogeneity by estimating what true treatment effects can be expected in future studies. The PI are considered more valid regarding estimating statistical heterogeneity since they are based on an absolute scale (τ) versus I^2, which is a proportional metric.[24] We did not perform adjustments for the multiple statistical tests considering each outcome.[25]

Clinical heterogeneity of included studies was assessed by comparing study design characteristics, participant characteristics and definitions of outcomes. Statistical inconsistency was measured using Cochran's Q test (χ^2 test) and the I^2 statistic. An I^2 greater than 50% was considered to indicate significant inconsistency. We planned subgroup analyses and meta-regression, as appropriate, if high heterogeneity was suspected and more than 10 studies were included in one outcome. The planned subgroups analyses were: (1) age: ≤ 12 years old versus >12 years old; (2) variation of definitions on sensory block latency as determined by the studies; (3) type of long-acting LA; (4) type of short-acting LA; (5) location of block: perineural at upper limbs, perineural at lower limbs, and fascial blocks; (6) the use

of a mixed solution or sequential administration of LA; (7) meta-regression for drug dosages. Because all meta-analyses included fewer than 10 studies, no subgroup analyses were performed. Sensitivity analyses for influence analysis were based on the leave-one-out method, while for outliers analysis, we used the R package find.outliers.[26] We also assessed the results when trials at high risk of bias were excluded. We performed a narrative synthesis for data not pooled in the meta-analyses.

We planned to analyze the impact of non-reporting bias with funnel plots, which are an adequate tool for 10 or more studies. Alternatively, and post hoc, we used Doi plots, which are a robust tool when at least five studies with data other than zero are analyzed.[13] Doi plots also allow for a quantitative measurement of non-reporting bias, the LFK index.[13] The LFK index is suggestive of non-reporting bias and plot asymmetry when values exceed±1.00.[13]

Quality assessment

The methodological quality of the individual studies was evaluated independently by two reviewers, selected from a team of four (NPdS, VdPS, GSdSO, VCM), using the Cochrane "Risk of bias" assessment tool 2.0.[27] All four reviewers were equally qualified to perform the risk assessment. For each paper, once two reviewers had completed the risk evaluation, their entries were cross-checked. The overall quality of evidence was assessed using the software GRADEpro GDT: GRADEpro Guideline Development Tool (McMaster University and Evidence Prime) based on the principles of Grading of Recommendations Assessment, Development and Evaluations. Four reviewers (NPdS, VdPS, GSdSO, VCM) evaluated each outcome.

RESULTS

From the 3,942 records identified, 1,398 duplicates and 10 files of supplemental material were excluded, 2,534 titles and abstracts were screened, and 25 were sought for full-text retrieval. After non-retrieval and exclusions (online supplemental material 1 S2), 10 RCTs were included in the meta-analysis (figure 1).[28] No studies were excluded due to language restrictions. Characteristics of the included studies are available in table 1. All participants were adults (n=516), and most studies evaluated brachial plexus blocks (seven RCTs). The included studies compared bupivacaine (seven RCTs), ropivacaine (two RCTs), and levobupivacaine (one RCT) in the arm with long-acting LA. Interventions were performed with lidocaine (eight RCTs) and mepivacaine (two RCTs). Funding was not informed by three of the included studies, while six were performed without external funding, and one study was sponsored (table 1). All studies were analyzed

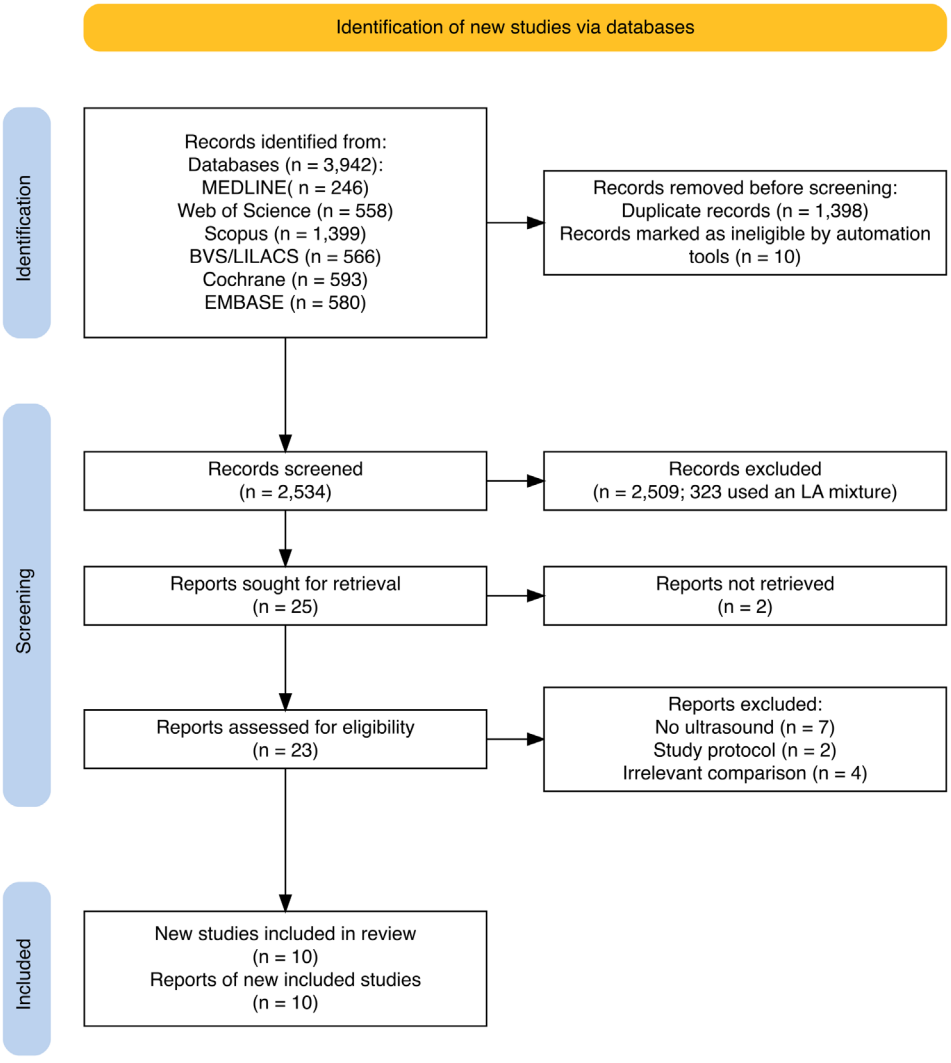

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of study inclusion. LA, local anesthetic.

Table 1 Characteristics of studies

Study	Country	Sample size, N (I/C)	Age (yr), mean±SD or median (IQR)	Sex (F/M)	Type of block | approach	Intervention	Control	Funding_sources
Gadsden, 2011[32]	USA	43 (21/22)	I: 55.8±15.3 C: 54.3±10.2	I: 15/8 C: 15/8	BPB: interscalene (US) | in-plane technique, LA near the superior trunk	0.5% B (15 mL) + 1.5% M (15 mL)	0.5% B (30 mL)	No external funding
Laur, 2012[33]	USA	58 (27/31)	I: 36 (28 – 48) C: 43 (32 –59)	I: 23/8 C: 19/8	BPB: infraclavicular (US+NS)| in-plane technique, LA near the posterior cord, medial cord, and lateral cord	0.5% B (20 mL) + 1.5% M w/ epi. (20 mL)	0.5% B (40 mL)	Not available
Valery, 2013[30]	Belarus	40 (20/20)	I: 42 (28 – 55) C: 41 (37 – 39)	I: 4/16 C: 8/12	Sciatic nerve (US+NS)| posterior approach, LA in the fascial sheath of the sciatic nerve	0.75% R (5 mL) + 1% L (5 mL)	0.75% R (10 mL)	No external funding
Pongraweewan, 2016[16]	Thailand	90 (44/46)	I: 65±13 C: 58±15	I: 22/22 C: 28/18	BPB: infraclavicular (US+NS)| in-plane technique, LA near the lateral cord and posterior cord	0.5% B (20 mL) plus 2% L (10 mL)	0.5% B (30 mL)	Not available
Župčić, 2017[36]	Croatia	90 (40/40)	I: 60 (55 – 67) C: 54.5 (60 – 60)	I: 40/0 C: 40/0	Paravertebral (US+NS)| in-plane technique, LA in the paravertebral space	0.5% LB (14 mL) + 2% L (7 mL)	0.5% LB (21 mL)	No external funding
Taha, 2018[34]	UAE	48 (24/24)	I: 29±9.2 C: 26.3±6.3	I: 3/21 C: 4/20	Femoral nerve (US) | in-plane technique, LA around the femoral nerve	0.2% R (7.5 mL) + 1% L w/ epi. (7.5 mL)	0.2% R (15 mL)	Not available
Bobik, 2020[35]	Poland	30 (19/20)	I: 51.8±18.8 C: 46±18.1	I: 6/13 C: 8/12	BPB: axillary (US+NS)| LA near radial, ulnar, median and musculocutaneus nerves	0.5% B w/ epi. (15 mL) + 2% L (15 mL)	0.375% B w/ epi. (30 mL)	No external funding
Almasi, 2020[31]	Hungary	31 (17/14)	I: 55.8±4.2 C: 51.8±5.3	I: 8/9 C: 11/3	BPB: supraclavicular+axillary (US) | in-plane technique, single injection cluster approach	0.5% B (15 mL) + 1% L (15 mL)	0.5% B (20 mL) + NS* (10 mL)	Supported by Pecsi Tudomanyegyetem, Altalanos Orvostudomanyi Kar, Hungary
Mohammed Abdelhady, 2022[29]	Egypt	44 (22/22)	I: 48.95±10.08 C: 44.78±8.33	I: 18/4 C: 19/3	BPB: axillary (US) | in-plane technique, identification of each nerve	0.5% B (15 mL) + 2% L (15 mL)	0.5% B (30 mL)	No external funding
Sripriya, 2024[37]	India	42 (21/21)	I: 44±13 C: 37±13	I: 7/14 C: 7/14	BPB: supraclavicular (US) | either in-plane or out-of-plane technique, random multiple site subfascial injections	0.5% B (10 mL) + 2% L (10 mL)	0.5% B (20 mL)	No external funding

B, bupivacaine; BPB, brachial plexus block; C, control; epi, epinephrine; I, intervention; L, lidocaine; LA, local anesthetic; LB, levobupivacaine; M, mepivacaine; NS*, normal saline; NS, nerve stimulation; R, ropivacaine; US, ultrasound; yr, year.

per-protocol. A summary of findings is presented in table 2, while the detailed evidence profile can be found in table 3.

Overall, the risk of bias was low and high risks were mainly due to deviations from intended interventions, missing outcome data, and the risk of measuring outcomes in a single-blinded study[29] (figure 2). Six studies lacked a public protocol register.[30–35]

Time to sensory block onset

The mixture of LAs was compared with long-acting LAs in 10 studies, and we included 7 (n=336) in the meta-analysis (figure 3a). The estimated MD was −1.62 min towards the mixture of LA (95% CI: −4.04 to 0.81, very low certainty). The very low level of certainty is supported by 95% CIs and PIs that included zero, a large amount of inconsistency as well as wide 95% CIs for I^2, and a large amount of asymmetry suggestive of non-reporting bias based on the Doi plot and LFK index (online supplemental figure S1a). The result was sustained after excluding studies at high risk of bias (online supplemental figure S2b). Sensitivity analysis did not find outliers or influential studies. Thus, the pooled data for sensory onset did not suggest a statistically significant reduction in the onset of sensory block when a mixture of LA was administered, moreover, it did not reach the MCID of 5 min.

The studies with skewed distribution were not included in the meta-analysis. Valery and Aliaksei[30] reported onset reduction with LA mixture (n=20): 12 min (IQR: 10–13) versus single LA (n=20): 30 min (IQR: 28–30); p<0.05, while Laur *et al*[33] reported no difference with mixture (n=27): 6 min (IQR: 3–6) versus single LA (n=31): 6 min (IQR: 3–12); p=0.570.[35] One study presented conflicting results for the outcome.[36]

Duration of sensory block

Eight out of nine studies that reported the duration of sensory block were included in the meta-analysis (figure 3b). Overall, sensory pain duration was determined as the return of sensation or first pain. The MD on duration of sensory block of these 416 participants was −2.16 hours towards the mixture of LAs (95% CI: −4.16 to −0.17, very low certainty). The very low level of certainty is supported by 95% PIs that included zero, a large amount of inconsistency as well as wide 95% CI for I^2. Sensitivity analysis did not show outliers, and the exclusion of studies at high risk of bias did not change significance (online

Table 2 Summary of findings—mixture of LA compared to long-acting LA in ultrasound-guided peripheral nerve blocks

Outcomes	LA mixture Mean (SD) events/n (%)	Long-acting LA Mean (SD) events/n (%)	Mean difference or Risk ratio (95% CI)	Number of participants (studies)	Quality or certainty of the evidence (GRADE)
Sensory block onset, minutes	10.52 (3.95)	12.14 (4.74)	−1.62 (−4.04 to 0.81)	336 (7 studies)	⊕◯◯◯ VERY LOW
Duration of sensory block, hours	8.23 (3.81)	10.39 (4.23)	−2.16 (−4.16 to 0.17)	416 (8 studies)	⊕◯◯◯ VERY LOW
Motor block onset, minutes	13.08 (10.76)	18.68 (11.16)	−5.60 (−14.54 to 3.33)	334 (7 studies)	⊕◯◯◯ VERY LOW
Duration of motor block, hours	9.29 (5.33)	12.57 (5.90)	−3.28 (−7.48 to 0.92)	264 (5 studies)	⊕◯◯◯ VERY LOW
Pain in 24 hours, NRS	1.82 (0.97)	1.71 (0.85)	0.11 (−0.76 to 0.99)	243 (4 studies)	⊕⊕◯◯ LOW
Oral morphine equivalent consumption in 24 hours, mg	0/40 (0.0)[36]	0/40 (0.0)[36]	–	80 (1 study)	⊕◯◯◯ VERY LOW
Sensory block failure	20/214 (9.3)	6/211 (2.8)	0.44 (0.03 to 6.69)	425 (9 studies)	⊕◯◯◯ VERY LOW
PONV	2/40[36] 3/22[29]	1/40[36] 2/22[29]	–	124 (2 studies)	⊕⊕⊕◯ MODERATE
Bradycardia	1/82 (1.2)	3/82 (3.7)	1.62 (0.00 to 400714348.65)	164 (3 studies)	⊕◯◯◯ VERY LOW
Hypotension	0/20 (0.0)[30] 9/40 (22.5)[36]	0/20 (0.0)[30] 2/40 (5.0)[36]	–	120 (2 studies)	⊕◯◯◯ VERY LOW
Dizziness	4/40 (10%)[36]	4/40 (10)[36]	–	80 (1 study)	⊕◯◯◯ VERY LOW
Postoperative neurological symptoms	0/21 (0.0)[37]	0/21 (0.0)[37]	–	42 (1 study)	⊕⊕◯◯ LOW

Population: patients submitted to ultrasound-guided peripheral nerve blocks intervention: LA mixture comparator: long-acting LA. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
GRADE, (Grading of Recommendations Assessment, Development and Evaluation) Working Group grades of evidence; LA, local anesthetic; mg, milligrams; NRS, Numeric Rating Scale; PONV, postoperative nausea and vomiting.

supplemental figure S2b). Excluding any of four[29 31 32 36] influential studies could make the results statistically insignificant, suggesting that these studies significantly impact the robustness and generalizability of the results. The DOI plot did not suggest non-reporting bias (online supplemental figure S1b). One study with a low risk of bias[37] presented a skewed distribution and was not included in the meta-analysis. The authors observed a reduction of 3.9 hours of the sensory block when the LA mixture was administered.

Time to motor block onset

Seven out of eight studies (334 participants) that reported the time to motor block onset were included in the meta-analysis (figure 3c). The MD was −5.60 min towards the mixture of LAs (95% CI: −14.54 to 3.33, very low certainty). The very low level of certainty is supported by 95% CIs and PIs that included zero, a large amount of inconsistency as well as wide 95% CI for I^2, and a large amount of asymmetry suggestive of non-reporting bias based on the Doi plot and LFK index (online supplemental figure S1c). Sensitivity analysis demonstrated that the studies from Valery and Aliaksei[30] and Almasi *et al*[31] are possible outliers, but their exclusion did not affect the findings (MD −2.85, 95% CI: −10.62 to 4.92; Q(5)=106.30, p<0.0001, τ^2=49.87, I^2=95.3%, 95% CI: 92.1% to 97.2%). There were no significantly influential studies that could change the outcome, nor did the exclusion of studies at high risk of bias (online supplemental figure S2c).

Duration of motor block

Five studies with 264 participants reported the duration of motor block, and all were included in the meta-analysis (figure 3d). The MD was −3.28 hours towards the mixture of LAs (95% CI: −7.48 to 0.92, very low certainty). The very low level of certainty is supported by 95% CIs and PIs that included zero, a large amount of inconsistency as well as wide 95% CI for I^2, and a large amount of asymmetry suggestive of non-reporting bias based on the Doi plot and LFK index (online supplemental figure S1d). Sensitivity analysis did not show outliers. Also, influential analysis after the exclusion of four studies[29 32 33 35] did not alter significance, and the exclusion of studies at high risk of bias[16 29 35] resulted in an insufficient number of trials for meta-analysis as defined by our protocol.

Mean pain score in 24 hours

Four studies, including 243 participants, reported pain scores up to 24 hours (figure 3e). The MD considering the NRS was 0.11 towards single LA (95% CI: −0.76 to 0.99, low certainty). The low level of certainty is supported by 95% CIs and PIs that included zero, a large amount of inconsistency as well as wide 95% CI for I^2, and a large amount of asymmetry suggestive of non-reporting bias based on the Doi plot and LFK index (online supplemental figure S1e). There were no outliers or influential studies, and the exclusion of studies at high risk of bias (online supplemental figure S2d) did not change the result.

Morphine equivalent consumption

Župčić *et al*[36] measured 12 hours and 24 hours postoperative opioid consumption, but neither group required its administration.

Block failure

9 out of 10 studies, with a total of 425 participants, reported a quantifiable measure of sensory block failure (figure 3f). The RR of block failure was 0.44 towards the LA mixture (95% CI: 0.03 to 6.69; very low certainty). The very low level of certainty is supported by 95% CIs and PIs that included zero, a large amount of inconsistency as well as wide 95% CIs for I^2. Sensitivity analysis did not identify outliers or any influential study. Exclusion of studies at high risk of bias maintained similar results

Table 3 Evidence profile: mixture of LA compared to long-acting LA in ultrasound-guided peripheral nerve blocks

Outcomes	Limitations	Inconsistency/ heterogeneity	Indirectness	Imprecision	Publication bias	MD or RR (95% CI)	Number of participants (studies)	Quality or certainty of the evidence (GRADE)
Sensory block onset, minutes	Measurement in time intervals ranging from 1 to 10 min	I^2=81%, p value<0.001	Not serious	95% CI and PI that included zero	Strongly suspected*	−1.62 (−4.04 to 0.81)	336 (7 studies)	⊕◯◯◯ VERY LOW
Duration of sensory block, hours	Mostly based on patient - initiated report	I^2=91%, p value<0.001	Potential indirectness†	Serious†‡	Not detected	−2.16 (−4.16 to 0.17)	416 (8 studies)	⊕◯◯◯ VERY LOW
Motor block onset, minutes	Measurement in time intervals ranging from 1 to 10 min	I^2=99%, p value<0.001	Not serious	95% CI and PI that included zero	Strongly suspected*	− 5.60 (−14.54 to 3.33)	334 (7 studies)	⊕◯◯◯ VERY LOW
Duration of motor block, hours	Mostly based on patient - initiated report	I^2=86%, p value<0.001	Not serious	95% CI and PI that included zero	Strongly suspected§	−3.28 (−7.48 to 0.92)	264 (5 studies)	⊕◯◯◯ VERY LOW
Pain in 24 hours, NRS	Not all included studies reported overall 24 hours pain	I^2=97%, p value<0.001	Not serious	95% CI and PI that included zero	Strongly suspected¶	0.11 (−0.76 to 0.99)	243 (4 studies)	⊕⊕◯◯ LOW
Oral morphine equivalent consumption in 24 hours, mg	Single study	Affected by potential previous diclofenac sodium administration	Not serious	Not detected	Outcome under-reported	–	80 (1 study)	⊕◯◯◯ VERY LOW
Sensory block failure	Definitions varied or were not reported	I^2=59%, p value<0.001	Not serious	95% CI and PI that included zero	Insufficient number of trials with event	0.44 (0.03 to 6.69)	425 (9 studies)	⊕◯◯◯ VERY LOW
PONV	No serious limitation	Comparable number of events in both groups	Not serious	Not detected	Outcome under-reported	–	124 (2 studies)	⊕⊕⊕◯ MODERATE
Bradycardia	No serious limitation	I^2 = 48%, p=0.17	Not serious	95% CI and PI that included zero	Outcome under-reported	1.62 (0.00 to 400714348.65)	164 (3 studies)	⊕◯◯◯ VERY LOW
Hypotension	Almasi *et al*[31] did not provide quantifiable data	All cases occurred in Župčić *et al*[36]	Potential indirectness**	Very serious**	Outcome under-reported	–	120 (2 studies)	⊕◯◯◯ VERY LOW
Dizziness	No evaluation of intensity	Not detected	Not serious	Not serious	Outcome under-reported	1	80 (1 study)	⊕◯◯◯ VERY LOW
Postoperative neurological symptoms	No serious limitation	Not detected	Not serious	Not serious	Outcome under-reported	1	42 (1 study)	⊕⊕◯◯ LOW

*Suggests more publication of studies favoring LA mixture.
†Use of pain or first sensation to define duration.
‡Influential studies could impact the robustness of results.
§Suggests more publication of studies reporting reduced duration with LA mixture.
¶Suggests more publication of studies reporting reduced pain with long-acting LA.
**Paravertebral block performed by Župčić *et al*[36] could influence the applicability of results specifically for this outcome.
LA, local anesthetic; MD, mean difference; PI, prediction interval; PONV, postoperative nausea and vomiting; RR, risk ratio.

(online supplemental figure S2e). One study[16] did not provide the precise number of block failures, but reported no significant difference between groups.

Adverse events

Postoperative nausea and vomiting

Two studies with a total of 124 participants reported postoperative nausea and vomiting (PONV). In Župčić *et al*[36] there were two episodes in the LA mixture group (n=40) and one for single LA (n=40), while Mohammed Abdelhady *et al*[29] reported three episodes in the LA mixture group (n=22) and two in the single LA (n=22). Therefore, the mixture of LA results in little to no difference in PONV.

Bradycardia

Three out of four studies with 164 participants reported quantitative results of bradycardia. The RR was 1.62, favoring single LA (95% CI: 0.00 to 400714348.65, very low certainty) (online supplemental figure S3). The very low level of certainty is supported by 95% CIs and PIs that included zero. Sensitivity analysis did not identify outliers or any influential study. The exclusion of one study[29] at high risk of bias resulted in an insufficient number of trials for meta-analysis as defined by our protocol. These analyses suggest that the evidence is very uncertain about the effect of a mixture of LA on the occurrence of bradycardia. One study[31] did not report the precise number of participants with bradycardia but mentioned no significant difference between groups.

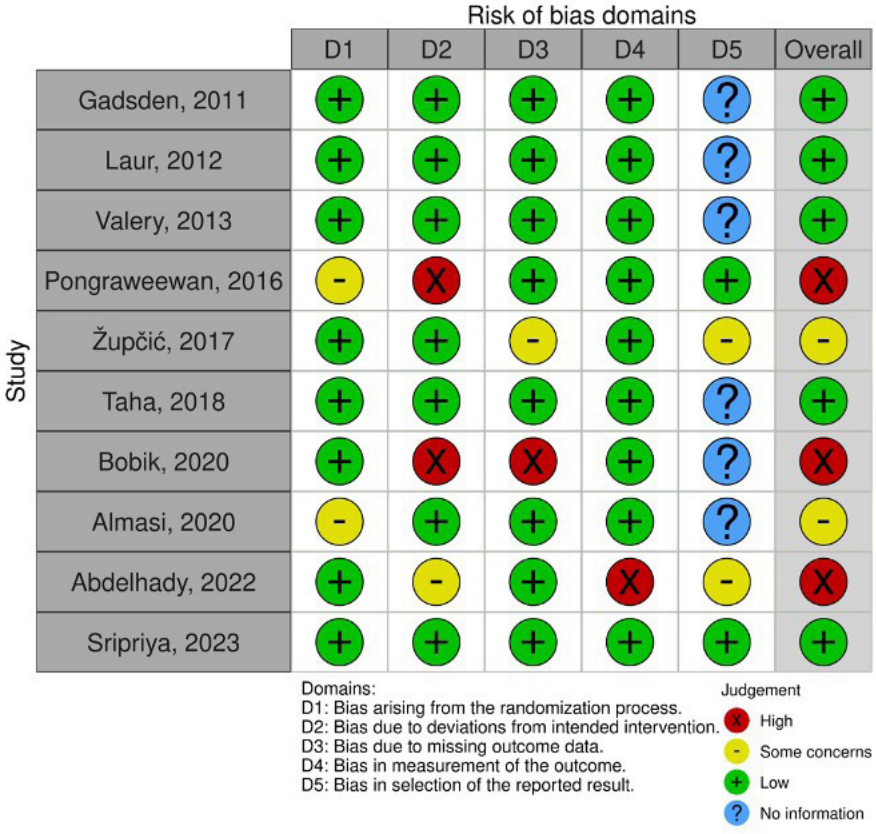

Figure 2 Risk of bias for individual studies and domains.

Hypotension

Three studies recorded data on hypotension, but Almasi *et al*[31] did not provide quantitative data, while reported no difference between groups. Valery and Aliaksei[30] did not observe cases of hypotension, and therefore we did not pool data to avoid results with lack of generalizability and robustness. Župčić *et al*,[36] in a study on paravertebral blocks, reported more cases of hypotension in the group with LA mixture (9/40) when compared with single LA (2/40).

Dizziness

While evaluating dizziness, Župčić *et al*[36] (n=80) reported four episodes in each group.

Neurological symptoms

Sripriya *et al* (2024)[37] (n=42) evaluated neurological symptoms at 24 hours, and they were not reported in either group.

DISCUSSION

Overall findings

In this systematic review and meta-analysis of 10 studies and 516 participants, we compared efficacy and safety outcomes between long-acting LAs and their mixture with shorter-acting LAs for US-guided regional anesthesia. The main findings from the pooled analyses were: (1) a mixture of LA may have no effect on sensory and motor block onset; (2) a mixture of LA may reduce the duration of sensory block; (3) the evidence is very uncertain about the effect of a mixture of LA on the duration of motor block, mean pain in 24 hours, sensory block failure and bradycardia.

Implications for research

Faster onset is claimed as an advantage for LA mixture,[38] but our analysis suggests that LA mixture in US-guided regional anesthesia may have no effect on sensory and motor block onset, although the evidence is very uncertain. Part of this uncertainty could be attributed to divergent methods of data collection, such as testing participants in time intervals ranging from every 1[16 35] to every 10[37] min. Thus, studies that performed evaluations at longer intervals could be overestimating the results in our findings. By comparison, none of the studies that tested onsets at intervals ≤3 min found significant differences.[16 31 35] For this reason, we suggest that future clinical trials should evaluate onsets every 3 min. Nevertheless, our pooled estimates might be negatively biased due to missing studies, as indicated by the non-reporting bias analysis. Despite these challenges, we should investigate the underlying mechanisms driving the expected onset changes with LA mixtures.

Classically, there are two main reasons for changes in the onset of blocks with LA mixture:[39] LA dilution and pH changes. First, dilution could impact the ability of LA to penetrate the nerve membrane, a process dependent on the LA gradient, which decreases the proportion of each LA when a mixture is used. Thus, with a lower LA gradient, a reduction of onset time is not expected. Moreover, the timing of the mixture may not be relevant, as even sequential administration, aiming to temporarily dispose of a non-diluted solution, did not reduce block onset.[6 40 41] Second, pH changes influence the amount of the non-ionized LA in a solution, but not proportionally to the quantity of short-acting LA in the solution. Although simple mean calculation would suggest that the same amount of ropivacaine (pH 4.22) when added to lidocaine (pH 6.58) would result in a

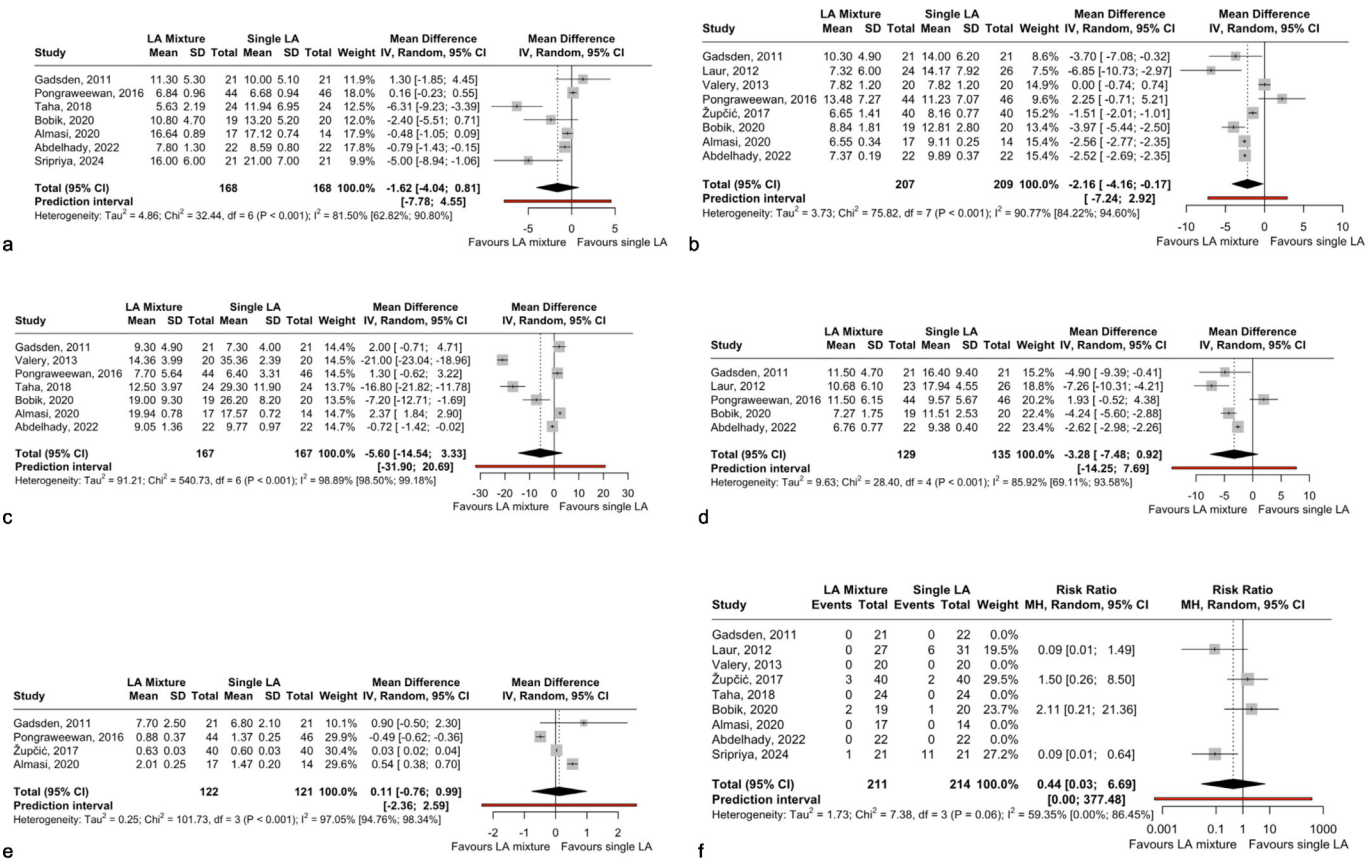

Figure 3 Forest plots. (a) time to sensory block onset; (b) duration of sensory block; (c) motor block onset; (d) duration of motor block; (e) mean pain score in 24 hours; (f) block failure. IV, inverse variance; LA, local anesthetic; MH, Mantel-Haenszel.

pH of 5.4, the final pH recently demonstrated in vitro was 6.5.[42] Such pH should make the non-ionized portion of LA more available to penetrate the neural membranes and block sodium channels. However, this reduction was not observed in our analysis, proposing that there is more to it than dilution and pH. Perhaps protein binding, lipid solubility, vasoreactivity[43] and crystallization[42] of LA mixtures could prevent the LA availability. Future in vivo studies may provide a more in-depth understanding of the underlying mechanisms of LA combinations.

Our analysis suggests a reduction in the duration of the sensory block when an LA mixture is used over a single LA. A similar, and even more pronounced reduction, was observed by Aguilera *et al*[44] when using an LA mixture with dexamethasone as an adjuvant. It remains unclear, however, what is the clinical impact of sensory or motor block reduction, as previous studies of LA mixture found no difference in satisfaction for patients[16 45] or surgeons.[16] In that regard, perhaps the reduction of block could be a strategy for patients undergoing ambulatory surgery. Conversely, reduction in sensory block duration could impact rebound pain, an outcome not studied in any of the included trials. Nonetheless, when evaluated, pain over 24 hours was not different between groups and the LA mixture did not alter postoperative opioid consumption when compared with the use of a single LA. Readers should also acknowledge that definitions of duration should be standardized. To improve the quality of future clinical trials, we recommend the following: (1) defining the duration of analgesia by considering the return of sensation and the onset of any pain, with block durations assessed at intervals of no more than 1 hour; (2) consistently evaluating rebound pain and opioid consumption over 24 hours; and (3) systematically including safety outcomes in the study design.

Implications for practice

Informed by the current evidence, we suggest that LA mixture should not be considered a strategy for sensory or motor onset reduction in PNB US-guided. If this strategy is employed, anesthesiologists should be mindful of the potential for a reduced duration of sensory blockade.

Strengths and potential limitations

Our study has some strengths, particularly the inclusion of randomized studies only, which minimizes potential confounding factors frequently present in observational data. In addition, the inclusion of blocks performed with ultrasound, reflecting the current practice of regional anesthesia.

This study also has important limitations. The small number of participants increases data variability and result inconsistency. Most estimates exhibited high statistical heterogeneity, identified as a source of inconsistency in the evaluation of the strength of evidence. Additionally, aggregate data meta-analyses are subject to the potential for ecological fallacy, which we acknowledge as an inherent limitation. Onset sensory block evaluation in most trials was determined by a complete sensory block for all nerves; however, two studies[16 32] only required a blockade of one dermatome. The duration of sensory and motor blocks were based on patient reports, mostly without predetermined interval evaluation. While we included studies with a high risk of bias, sensitivity analyses were performed to mitigate its impact.

Furthermore, six studies lacked a public protocol register,[30–35] raising the possibility of selective reporting. Finally, we intentionally chose not to adjust for multiple statistical tests; therefore, some statistically significant results may represent chance findings.

CONCLUSIONS

This review and meta-analysis suggests that LA mixture may have no effect on sensory and motor onsets for US-guided regional anesthesia, while it may reduce the duration of analgesic effects and motor block. The safety of the LA mixture is very uncertain.

X Vanessa Henriques Carvalho @VanessaHCarval2

Acknowledgements Partial results of this review were presented during the ASRA Spring 2024 Meeting. This manuscript presents different results from the conference abstract due to the latest search update.

Contributors Study conception and design: all authors. Data acquisition: NPdS, VdPS, GSdSO, VCM. Data analysis: NPdS, VHC. Data interpretation: all authors. Drafting the manuscript or revising it critically for important intellectual content: all authors. Final approval of the version to be published: all authors. Guarantor: NPdS.

Funding This research did not receive a specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data extracted from included studies and data used for all analyses and analytic code can be available upon reasonable request.

ORCID iDs
Natanael Pietroski dos Santos https://orcid.org/0000-0002-4640-7178
Vanessa de Paula Silva https://orcid.org/0009-0003-8971-4359
Guilherme Stéfano da Silva Oliveira https://orcid.org/0009-0000-2709-9766
Victor Cardoso Musacchio https://orcid.org/0009-0002-5244-7237
Vanessa Henriques Carvalho https://orcid.org/0000-0002-1001-1948

REFERENCES

1 Cuvillon P, Nouvellon E, Ripart J, *et al*. A comparison of the pharmacodynamics and pharmacokinetics of bupivacaine, ropivacaine (with epinephrine) and their equal volume mixtures with lidocaine used for femoral and sciatic nerve blocks: a double-blind randomized study. *Anesth Analg* 2009;108:641–9.
2 Özmen Ö, Alici HA, ÇELiK M, *et al*. The effect of addition of lidocaine to bupivacaine on anesthesia beginning time, block time, and block quality in lateral sagittal infraclavicular block. *Turk J Med Sci* 2013;43:542–7.
3 Rohan B, Singh PY, Gurjeet K. Addition of clonidine or lignocaine to ropivacaine for supraclavicular brachial plexus block: a comparative study. *Singapore Med J* 2014;55:229–32.
4 Hanks RK, Pietrobon R, Nielsen KC, *et al*. The effect of age on sciatic nerve block duration. *Anesth Analg* 2006;102:588–92.
5 Bugamelli S, Zangheri E, Montebugnoli M, *et al*. One-day surgery for acquired forefoot deformity: sciatic nerve blockade with mepivacaine vs mepivacaine+ropivacaine: a prospective, randomized study. *Minerva Anestesiol* 2007;73:57–64.
6 Gunjiyal MS, Mohammed S, Bhatia P, *et al*. Effect of combined versus sequential injection of 2% lidocaine and 0.5% bupivacaine on the onset and duration of supraclavicular brachial plexus block: A double blinded randomised controlled trial. *J Clin Anesth* 2021;72:110313.
7 Brull R, Perlas A, Chan VWS. Ultrasound-guided peripheral nerve blockade. *Curr Pain Headache Rep* 2007;11:25–32.
8 Marhofer P, Chan VWS. Ultrasound-guided regional anesthesia: current concepts and future trends. *Anesth Analg* 2007;104:1265–9.
9 Higgins JPT, Thomas J, Chandler J, eds. *Cochrane handbook for systematic reviews of interventions version 6.4*. Cochrane, 2023. Available: www.training.cochrane.org/handbook
10 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
11 Barrington MJ, D'Souza RS, Mascha EJ, *et al*. Systematic Reviews and Meta-analyses in Regional Anesthesia and Pain Medicine (Part I). *Guidelines for Preparing the Review Protocol Anesth Analg* 2024;138:379–94.
12 D'Souza RS, Barrington MJ, Sen A, *et al*. Systematic Reviews and Meta-analyses in Regional Anesthesia and Pain Medicine (Part II). *Guidelines for Performing the Systematic Review Anesth Analg* 2024;138:395–419.
13 Furuya-Kanamori L, Barendregt JJ, Doi SAR. A new improved graphical and quantitative method for detecting bias in meta-analysis. *Int J Evid Based Healthc* 2018;16:195–203.
14 Vassiliou T, Müller H-H, Ellert A, *et al*. High- versus low-stimulation current threshold for axillary plexus blocks: a prospective randomized triple-blinded noninferiority trial in 205 patients. *Anesth Analg* 2013;116:247–54.
15 Yang WT, Chui PT, Metreweli C. Anatomy of the normal brachial plexus revealed by sonography and the role of sonographic guidance in anesthesia of the brachial plexus. *Am J Roentgenol* 1998;171:1631–6.
16 Pongraweewan O, Inchua N, Kitsiripant C, *et al*. Onset time of 2% lidocaine and 0.5% bupivacaine mixture versus 0.5% bupivacaine alone using ultrasound and double nerve stimulation for infraclavicular brachial plexus anesthesia in ESRD patients undergoing arteriovenous fistula creation. *Med Assoc Thail* 2016;99:589–95.
17 Luo D, Wan X, Liu J, *et al*. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018;27:1785–805.
18 Wan X, Wang W, Liu J, *et al*. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
19 Shi J, Luo D, Wan X, *et al*. Detecting the skewness of data from the five-number summary and its application in meta-analysis. *Stat Methods Med Res* 2023;32:1338–60.
20 Bahreini M, Jalili M, Moradi-Lakeh M. A comparison of three self-report pain scales in adults with acute pain. *J Emerg Med* 2015;48:10–8.
21 Viechtbauer W. Bias and Efficiency of Meta-Analytic Variance Estimators in the Random-Effects Model. *J Educ Behav Stat* 2005;30:261–93.
22 Hartung J, Knapp G. On tests of the overall treatment effect in meta-analysis with normally distributed responses. *Stat Med* 2001;20:1771–82.
23 Greenland S, Senn SJ, Rothman KJ, *et al*. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol* 2016;31:337–50.
24 IntHout J, Ioannidis JPA, Rovers MM, *et al*. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* 2016;6:e010247.
25 Rothman KJ. No Adjustments Are Needed for Multiple Comparisons. *Epidemiology (Sunnyvale)* 1990;1:43–6.
26 Harrer M, Cuijpers P. Doing meta-analysis in R. 2019. Available: https://zenodo.org/record/2551803
27 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
28 Haddaway NR, Page MJ, Pritchard CC, *et al*. *PRISMA2020*: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Syst Rev* 2022;18:e1230.
29 Mohammed Abdelhady IS, Ahmed Ghallab MA, Mahmoud Zaki MS, *et al*. Comparative study between bupivacaine 0.5% vs. bupivacaine 0.5% plus lidocaine 2% vs. lidocaine 1.5% in ultrasound guided axillary brachial plexus block for brachiocephalic fistula formation in chronic renal failure patients. *Anaesth pain intensive care* 2022;26:743–8.
30 Valery P, Aliaksei M. A comparison of the onset time of complete blockade of the sciatic nerve in the application of ropivacaine and its equal volumes mixture with lidocaine: a double-blind randomized study. *Korean J Anesthesiol* 2013;65:42.
31 Almasi R, Rezman B, Kriszta Z, *et al*. Onset times and duration of analgesic effect of various concentrations of local anesthetic solutions in standardized volume used for brachial plexus blocks. *Heliyon* 2020;6:e04718.
32 Gadsden J, Hadzic A, Gandhi K, *et al*. The effect of mixing 1.5% mepivacaine and 0.5% bupivacaine on duration of analgesia and latency of block onset in ultrasound-guided interscalene block. *Anesth Analg* 2011;112:471–6.
33 Laur JJ, Bayman EO, Foldes PJ, *et al*. Triple-blind randomized clinical trial of time until sensory change using 1.5% mepivacaine with epinephrine, 0.5% bupivacaine, or an equal mixture of both for infraclavicular block. *Reg Anesth Pain Med* 2012;37:28–33.
34 Taha AM, Abd-Elmaksoud AM. The femoral nerve block characteristics using ropivacaine 0.2% alone, with epinephrine, or with lidocaine and epinephrine. *Am Univ Beirut* 2018;25:15–20.
35 Bobik P, Kosel J, Świrydo P, *et al*. *Comparison of the pharmacological properties of 0.375% bupivacaine with epinephrine, 0.5% ropivacaine and a mixture of bupivacaine with epinephrine and lignocaine–a randomized prospective study*. Taylor Francis Ltd, 2020:156–60.

36 Župčić M, Graf Župčić S, Duzel V, *et al*. A combination of levobupivacaine and lidocaine for paravertebral block in breast cancer patients undergoing quadrantectomy causes greater hemodynamic oscillations than levobupivacaine alone. *Croat Med J* 2017;58:270–80.
37 Sripriya R, Sivashanmugam T, Rajadurai D, *et al*. Equal mixture of 2% lidocaine with adrenaline and 0.5% bupivacaine 20 mL provided faster onset of complete conduction blockade during ultrasound-guided supraclavicular brachial plexus block than 20 mL of 0.5% bupivacaine alone: a randomized double-blinded clinical trial. *Reg Anesth Pain Med* 2024;49:104–9.
38 Moore DC, Bridenbaugh LD, Bridenbaugh PO, *et al*. Does compounding of local anesthetic agents increase their toxicity in humans? *Anesth Analg* 1972;51:579–85.
39 Nestor CC, Ng C, Sepulveda P, *et al*. Pharmacological and clinical implications of local anaesthetic mixtures: a narrative review. *Anaesthesia* 2022;77:339–50.
40 Roberman D, Arora H, Sessler DI, *et al*. Combined versus sequential injection of mepivacaine and ropivacaine for supraclavicular nerve blocks. *Reg Anesth Pain Med* 2011;36:145–50.
41 Gadsden J, Shariat A, Hadzic A, *et al*. The sequence of administration of 1.5% mepivacaine and 0.5% bupivacaine does not affect latency of block onset or duration of analgesia in ultrasound-guided interscalene block. *Anesth Analg* 2012;115:963–7.
42 Hoerner E, Stundner O, Seisl A, *et al*. Crystallization of mixtures of local anesthetics with and without select adjuvants: a semiquantitative light microscopy analysis. *Reg Anesth Pain Med* 2025;50:59–64.
43 Taylor A, McLeod G. Basic pharmacology of local anaesthetics. *BJA Educ* 2020;20:34–41.
44 Aguilera G, Tabilo C, Jara Á, *et al*. 0.25% bupivacaine-1% lidocaine vs 0.5% bupivacaine for ultrasound-guided infraclavicular brachial plexus block: a randomized controlled trial. *Reg Anesth Pain Med* 2025;50:627–34.
45 Fredrickson MJ, Wolstencroft PJ, Chinchanwala S, *et al*. Does motor block related to long-acting brachial plexus block cause patient dissatisfaction after minor wrist and hand surgery? A randomized observer-blinded trial. *Br J Anaesth* 2012;109:809–15.