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Comparative efficacy of local anaesthetic adjuvants for the erector spinae plane block on postoperative analgesia: a systematic review and dose-stratified network meta-analysis

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Abstract

Background

The erector spinae plane block (ESPB) provides opioid-sparing analgesia, but single-injection blocks are short-lived, prompting the addition of local-anaesthetic adjuvants. Their comparative effectiveness is undefined, and existing syntheses are single-agent, pairwise and disregard dose. We compared and ranked ESPB adjuvants and characterised the dexmedetomidine dose-response.

Methods

We searched PubMed, Embase, the Cochrane Library and Web of Science to 1 June 2026 for randomised trials of adults receiving an ESPB with local anaesthetic plus an adjuvant. A frequentist network meta-analysis used the ratio of means (ROM) for time to first rescue analgesia (primary outcome) and 24-hour opioid consumption, and odds ratios for postoperative nausea and vomiting (PONV). The dexmedetomidine node was split by dose (0.5 versus 1.0 μg/kg).

Results

Fifteen trials (1,127 participants) evaluated dexmedetomidine, dexamethasone, ketamine, magnesium sulfate and nalbuphine. Magnesium sulfate, 1.0 μg/kg dexmedetomidine, ketamine and nalbuphine each prolonged analgesia and reduced opioid consumption versus plain local anaesthetic, whereas dexamethasone and 0.5 μg/kg dexmedetomidine did not. Nalbuphine ranked first for opioid sparing. A coherent dexmedetomidine dose-response was found: 1.0 μg/kg was superior to 0.5 μg/kg for time to first rescue (ROM 1.75, 95% CI 1.04–2.97), and only the higher dose separated from plain local anaesthetic. Pooled dexmedetomidine reduced PONV, but this benefit dissolved on dose stratification.

Conclusions

Local-anaesthetic adjuvants differ substantially in ESPB efficacy. Magnesium sulfate, ketamine, nalbuphine and 1.0 μg/kg dexmedetomidine prolonged analgesia and spared opioids, nalbuphine ranking first for opioid sparing, whereas perineural dexamethasone was ineffective and dexmedetomidine's effect was dose-dependent. Several rankings, from sparse data, need head-to-head confirmation.

Background

Postoperative pain remains a major determinant of surgical recovery, and its inadequate control prolongs hospitalisation, delays mobilisation and increases the risk of chronic post-surgical pain. Because reliance on systemic opioids carries well-recognised adverse effects (nausea and vomiting, sedation, ileus and respiratory depression), regional and fascial-plane techniques have become central to multimodal, opioid-sparing analgesia [1]. The erector spinae plane block (ESPB), first described by Forero and colleagues in 2016 for the management of thoracic neuropathic pain, is an ultrasound-guided interfascial technique in which local anaesthetic is deposited in the plane between the erector spinae muscle and the vertebral transverse process [2]. Cadaveric studies indicate that the injectate spreads cranio-caudally over several vertebral levels and, at least in part, anteriorly towards the paravertebral and epidural spaces, although the magnitude of anterior spread and the precise contribution of each pathway remain debated [3]. Whatever the exact mechanism, the block produces extensive truncal analgesia while avoiding the pleural puncture risk of paravertebral techniques and the haemodynamic and neuraxial hazards of epidural analgesia. These practical advantages (technical simplicity, a favourable safety profile and anatomical versatility) have driven rapid adoption, and randomised trials and meta-analyses now support its opioid-sparing efficacy across breast, thoracic, abdominal, spinal and paediatric surgery [4–6]. The ESPB has consequently become a widely used component of enhanced-recovery pathways across a broad range of surgical settings.

A recognised limitation of the single-injection ESPB is that plain local anaesthetic provides only a few hours of analgesia, so that its benefit often wanes before the period of maximal postoperative pain has passed, and its regression may be followed by abrupt rebound pain that undermines early recovery [7]. To prolong and intensify the block without resorting to indwelling catheters (which

add cost, complexity and their own risks), a range of pharmacological adjuvants has been added to the local anaesthetic, mirroring their established use in peripheral and neuraxial blockade [8, 9]. The most extensively studied agents act through distinct and complementary mechanisms: dexmedetomidine, a selective α2-adrenoceptor agonist that also blocks the hyperpolarisation-activated cation (Ih) current in peripheral nerves [10, 11]; dexamethasone, a potent glucocorticoid that attenuates nociceptive C-fibre activity and slows local-anaesthetic absorption [12, 13]; magnesium sulfate and ketamine, both N-methyl-D-aspartate receptor antagonists that limit central sensitization [8, 14]; and nalbuphine, a mixed κ-agonist/μ-antagonist opioid with a comparatively favourable side-effect profile [15]. By extending analgesic duration and reducing opioid requirements, these adjuvants have become a focus of intense clinical interest in regional anaesthesia.

Despite this interest, the comparative effectiveness of the available adjuvants for the ESPB remains poorly defined, and the existing evidence has three important limitations. First, the randomised trials are individually small, use heterogeneous local anaesthetics and surgical populations, and typically compare a single adjuvant with plain local anaesthetic, so that head-to-head data for most adjuvant pairs simply do not exist. Second, the published syntheses are narrow in scope: the available ESPB meta-analyses have each been confined to a single agent, almost invariably dexmedetomidine, and have relied on conventional pairwise comparison, which cannot rank several competing adjuvants simultaneously [16]. Indirect comparisons and network meta-analyses in the wider peripheral-nerve-block literature have begun to contrast agents, but they are largely restricted to brachial plexus blockade and consistently examine only one or two drugs at a time [17–19]. No network meta-analysis has yet integrated the full range of ESPB adjuvants into a single coherent framework. Third, and most importantly, dose has been largely ignored. Dexmedetomidine in particular is administered across a several-fold range of weight-based doses, yet trials and reviews routinely collapse these doses into one node; the single ESPB synthesis that has considered dose did so by anaesthetic concentration rather than by administered dose, and still within a pairwise design [20]. Because a dose that is genuinely effective may be obscured when averaged with an ineffective one, these pooling risks both diluting real effects and masking a dose-response relationship of direct clinical relevance.

We therefore performed a systematic review and frequentist network meta-analysis of local-anaesthetic adjuvants for the ESPB, with two principal objectives. The first was to compare and rank dexmedetomidine, dexamethasone, ketamine, magnesium sulfate and nalbuphine for their effects on the time to first rescue analgesia, 24-hour opioid consumption and postoperative nausea and vomiting (PONV). The second, a pre-specified methodological innovation, was to split the dexmedetomidine node by administered dose (0.5 versus 1.0 μg/kg) so as to characterise its dose-response and to test whether dose is a driver of the heterogeneity that has hampered previous work. By simultaneously synthesising direct and indirect evidence and interrogating dose explicitly, the analysis aims to provide a clinically actionable ranking of adjuvants and to clarify the effective dose of the most widely used agent.

Methods

This systematic review and network meta-analysis (NMA) was prospectively registered with PROSPERO (registration number CRD420261462208) and is reported in accordance with the PRISMA extension statement for network meta-analyses (PRISMA-NMA).

Inclusion and exclusion criteria

Eligibility was defined using the PICOS framework. Population: adults (≥ 18 years) undergoing surgery who received an erector spinae plane block (ESPB) for perioperative analgesia, irrespective of surgical site. Intervention: ESPB performed with a local anaesthetic combined with a pharmacological adjuvant (dexmedetomidine, dexamethasone, ketamine, magnesium sulfate or nalbuphine). Comparator: ESPB with plain local anaesthetic, a saline or sham injection, or a different adjuvant, so that a connected network could be formed. Outcomes: the primary outcome was the time to first rescue analgesia; secondary outcomes were 24-hour opioid consumption (converted to intravenous morphine equivalents) and postoperative nausea and vomiting (PONV). Study design: randomised controlled trials (RCTs). Studies were excluded if they reported none of the outcomes of interest, lacked an extractable comparator arm, enrolled paediatric patients, were non-randomised, or were conference abstracts, protocols, reviews or animal studies, or embedded the dexmedetomidine dose comparison within a non-comparable co-analgesic framework (a fixed second adjuvant or a mandatory continuous opioid background).

Search strategy

PubMed, Embase, the Cochrane Library (CENTRAL) and Web of Science were searched from inception to 1 June 2026, with Embase and the Cochrane Library searched together on the Ovid platform. The search combined controlled vocabulary and free-text terms for three concepts, namely the erector spinae plane block, local-anaesthetic adjuvants, and a randomised-trial filter, joined with the Boolean operator AND. No language restriction was applied, and the reference lists of eligible studies and relevant reviews were hand-searched for additional records. The full line-by-line strategy for each database is provided in Supplementary Appendix S1.

Study selection and data extraction

After de-duplication, two reviewers independently screened titles and abstracts and then full texts against the eligibility criteria, with disagreements resolved by discussion or a third reviewer. Two reviewers independently extracted study, patient and block characteristics, intervention details and doses, and outcome data. Because dexmedetomidine was administered at two distinct doses, its node was stratified a priori into 0.5 and 1.0 μg/kg to preserve transitivity and to permit a dose-response comparison.

Risk of bias assessment

Methodological quality was assessed using the Cochrane Risk of Bias (RoB 1) tool across seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain was rated as low, unclear, or high risk of bias, and an overall judgment was assigned for each study.

Statistical analysis

Analyses were performed in R version 4.5.2 within a frequentist framework using the netmeta package (version 3.6.1), which implements the graph-theoretical (Rücker) random-effects model, together with the meta (8.5.0) and metafor (4.4.0) packages. Continuous outcomes were analysed as the ratio of means (ROM) and PONV as the odds ratio (OR); the ROM was preferred over the standardised mean difference because it accommodates the differing scales and units of the included trials and yielded substantially lower heterogeneity. A single heterogeneity variance was assumed across comparisons and estimated by the method of moments, and heterogeneity was summarised with I^2 and τ^2. The relative ranking of treatments was expressed as P-scores. Transitivity was appraised by inspecting the distribution of potential effect modifiers across comparisons. Global consistency was evaluated with the design-by-treatment interaction model, which decomposes the Q statistic into within- and between-design components, and local consistency with node-splitting (the separate indirect-from-direct evidence method). Sources of heterogeneity for the primary outcome were explored by univariable random-effects meta-regression (restricted maximum likelihood) on the dexmedetomidine-versus-plain contrast, with each candidate moderator's marginal contribution expressed as R^2. Robustness was tested by leave-one-study-out analysis and by removing single-study closed loops, and the effect measure was varied across the mean difference, standardised mean difference and ratio of means. Small-study effects were assessed using comparison-adjusted funnel plots and an Egger-type regression of the comparison-adjusted effects. A two-sided P value below 0.05 was considered significant and estimates are reported with 95% confidence intervals.

Results

Characteristics of the included studies

The study selection process is detailed in the PRISMA flow diagram (Fig. 1). Fifteen studies (1,127 randomised participants) met the inclusion criteria. The trials were conducted in Egypt, China, India and Greece and covered breast/modified radical mastectomy, thoracic, spine, urological, abdominal and shoulder surgery. All administered an erector spinae plane block (ESPB); comparators were plain local anaesthetic or local anaesthetic combined with dexmedetomidine, dexamethasone, ketamine, magnesium sulfate or nalbuphine, or a saline/sham injection. Because dexmedetomidine was given at two distinct doses, its node was stratified a priori into 0.5 μg/kg (four studies) and 1.0 μg/kg (seven studies), giving seven to eight treatment nodes per outcome. The main characteristics of the 15 included RCTs are presented in Table 1.

Figure 1. PRISMA diagram of search results and selections.

Identification of studies via databases

Table 1
Characteristics of the included randomized controlled trials.

Study	Country	Surgery	n	Block level	Side	Timing	ESPB arms (adjuvant; DEX µg/kg)	Local anaesthetic	Rescue threshold	Outcomes
Abu El Hassan 2024[41]	Egypt	Spine	90	L3	Bi	Pre-ind.	DEX 0.5; Plain; Saline	Bupiv. 0.25%, 20 mL	VAS > 6	P
Ahmed 2023[42]	Egypt	Breast	90	T5	Uni	Pre-ind.	DEX 1.0; DEXA; Plain	Levobupiv. 0.25%, 30 mL	VAS ≥ 4	T, O, P
Basing 2021[43]	India	Breast	60	T5	Uni	Pre-ind.	DEX 0.5; DEXA	Ropiv. 0.2%, 20 mL	VAS > 4	T, O
El Sherif 2022[44]	Egypt	Breast	60	T5 & T7	Uni	Pre-ind.	KET; MgSO4; Plain	Levobupiv. 0.25%, 20 mL	VAS ≥ 3	T, O, P
Feltaoos 2026[45]	Egypt	Breast	60	T5*	Uni	Postop	DEX 1.0; Plain	Bupiv. 0.5%, 20 mL	VAS > 4	T, O, P
Gao 2019[33]	China	Thoracic	90	T5	Uni	Pre-ind.	DEX 1.0; DEXA; Plain	Ropiv. 0.5%, 30 mL	VAS > 3	T, P
Gundlakunta 2024[46]	India	Urology	100	T8	Uni	Postop	NLB; DEXA	Levobupiv. 0.25%, 20 mL	VAS ≥ 4	T, O
Hamed 2023[47]	Egypt	Shoulder	60	T2	Uni	Pre-ind.	DEX 0.5; Plain	Bupiv. 0.25%, 20 mL	NRS ≥ 4	T, P
Rao 2021[48]	China	Thoracic	95	T5	Uni	Pre-ind.	DEX 1.0; NLB; Plain	Ropiv. 0.5%, 30 mL	VAS > 3	T, P
Shaker 2024[49]	Egypt	Breast	75	T4	Uni	Post-ind.	DEX 1.0; KET; Plain	Bupiv. 0.25%, 30 mL	VAS > 3	T, O, P
Sifaki 2022[34]	Greece	Abdominal	60	T7	Bi	Pre-ind.	DEX 1.0; Plain; Saline	Ropiv. 0.375%, 20 mL	PCA demand	O, P
Sun 2023[15]	China	Urology	110	T10	Uni	Post-ind.	NLB (20/10 mg); Plain	Ropiv. 0.33%, 30 mL	VAS > 3	T, O, P
Wang 2021[50]	China	Breast	60	T3	Uni	Pre-ind.	DEX 1.0; Plain	Ropiv. 0.33%, 30 mL	VAS > 3	O, P
Wang 2022[51]	China	Thoracic	60	T5	Uni	Pre-ind.	DEX 0.5; Plain	Ropiv. 0.5%, 28 mL	NRS ≥ 4	T, O, P
Zhang 2025[52]	China	Spine	57	L2	Bi	Post-ind.	NLB; Plain	Ropiv. 0.375%, 20 mL	NRS ≥ 4	T, P

*n, total randomised participants. Block level: T/L, thoracic/lumbar transverse-process level. Side: Bi, bilateral; Uni, unilateral. Timing: Pre-ind., before induction; post-ind., after induction/intubation; Postop, postoperative. DEX, dexmedetomidine (µg/kg); DEXA, dexamethasone; KET, ketamine; MgSO4, magnesium sulfate; NLB, nalbuphine; Plain, plain local anaesthetic; Saline, saline/sham. Bupiv., bupivacaine; Levobupiv., levobupivacaine; Ropiv., ropivacaine (concentration and volume per side). Rescue threshold: pain score triggering the first rescue analgesic; VAS, visual analogue scale; NRS, numerical rating scale; PCA demand, patient-controlled analgesia without a fixed score threshold. Outcomes contributed to the network: T, time to first rescue; O, 24-hour opioid; P, PONV. **

Risk of bias in studies

Based on the rigorous assessment using the Cochrane Risk of Bias (RoB-1) tool across all seven domains, the methodological quality of the 15 included randomized controlled trials was systematically evaluated. Among these, only four studies were rated as low risk of bias across all domains, demonstrating robust randomization, adequate allocation concealment, complete blinding of both personnel and outcome assessors, and comprehensive reporting. Conversely, the majority of trials exhibited unclear or high risk primarily due to insufficient descriptions of blinding procedures, inadequate allocation concealment (e.g., unsealed or non-sequentially numbered envelopes), and significant attrition without intention-to-treat analysis.(Fig. 2).

Network Geometry

The evidence networks were connected for all three outcomes and contained closed loops permitting incoherence assessment (Fig. 3). For time to first rescue analgesia, twelve studies informed seven nodes (Fig. 3A); plain local anaesthetic was the best-connected comparator and the 1.0 μg/kg dexmedetomidine node carried the most direct evidence, whereas magnesium sulfate and ketamine were each informed by a single three-arm trial. The 24-hour opioid network comprised eight nodes from ten studies (Fig. 3B) and the PONV network eight nodes from thirteen studies (Fig. 3C). The two dexmedetomidine dose nodes were never compared head-to-head, so the 0.5-versus-1.0 μg/kg contrast rested on indirect evidence.

A

Figure 3. Network geometry of the dose-stratified comparisons.

Primary and secondary outcomes

Time to first rescue analgesia (Fig. 4A). Relative to plain local anaesthetic, magnesium sulfate produced the largest prolongation (ROM 3.30, 95% CI 1.69–6.44), followed by 1.0 μg/kg dexmedetomidine (2.09, 1.50–2.90), ketamine (2.13, 1.31–3.46) and nalbuphine (1.92, 1.32–2.79); dexamethasone (1.26, 0.82–1.93) and 0.5 μg/kg dexmedetomidine (1.19, 0.77–1.84) did not differ significantly from plain LA. P-scores ranked magnesium sulfate first (0.95), ahead of 1.0 μg/kg dexmedetomidine and ketamine (both 0.70) and nalbuphine (0.62), with 0.5 μg/kg dexmedetomidine (0.22) near the bottom (Figure S1). The leading position of magnesium sulfate rested on a single small trial with a wide interval; 1.0 μg/kg dexmedetomidine, supported by seven trials, provided the most robust evidence of benefit.

24-hour opioid consumption (Fig. 4B). All active adjuvants except dexamethasone and 0.5 μg/kg dexmedetomidine significantly reduced opioid consumption: nalbuphine (ROM 0.47, 0.26–0.84), magnesium sulfate (0.50, 0.26–0.97), ketamine (0.55, 0.33–0.92) and 1.0 μg/kg dexmedetomidine (0.61, 0.42–0.89). The saline/sham comparator was associated with higher consumption (3.60, 1.44–8.99). Nalbuphine ranked first (P-score 0.83) (Figure S1).

PONV (Fig. 4C). This network was statistically homogeneous (I^2 = 5.6%). After dose stratification no single adjuvant reached significance, although all point estimates favoured the adjuvants (magnesium sulfate OR 0.29, 0.07–1.32; 0.5 μg/kg dexmedetomidine 0.43, 0.16–1.16; 1.0 μg/kg dexmedetomidine 0.63, 0.34–1.16); the saline/sham comparator increased the odds of PONV (2.96, 1.12–7.87). When the two dexmedetomidine doses were pooled, dexmedetomidine significantly reduced PONV (OR 0.58, 0.35–0.96); the loss of significance after stratification reflects the reduced number of patients per node.

Figure 4. Network estimates for each adjuvant versus plain local anaesthetic (random-effects).

A

Dexmedetomidine dose–response (effect-modifier analysis)

Analgesic efficacy followed a coherent dose–response (Fig. 5; Table 2). For the primary outcome, 1.0 μg/kg was significantly superior to 0.5 μg/kg (ROM 1.75, 95% CI 1.04–2.97; P = 0.037), and only the 1.0 μg/kg node separated from plain local anaesthetic — for both time to first rescue (ROM 2.08, 1.50–2.90) and 24-hour opioid consumption (0.61, 0.42–0.89) — whereas 0.5 μg/kg was statistically indistinguishable from plain LA for every efficacy outcome (time 1.19, 0.77–1.84; opioid 0.69, 0.33–1.43). The direction again favoured the higher dose for opioid consumption (1.0 vs 0.5 μg/kg ROM 0.89, 0.39–2.01), although this contrast was imprecise.

The antiemetic effect did not track this gradient. The lower dose carried the numerically smaller PONV odds (0.5 μg/kg OR 0.43, 0.16–1.16 vs plain; 1.0 μg/kg OR 0.63, 0.34–1.16), and the 1.0-versus-0.5 μg/kg odds ratio was 1.47 (0.46–4.74; *P* = 0.52), pointing to a possible dissociation between the analgesic and antiemetic dose–responses that warrants dedicated confirmation. Taken together, these data indicate that 0.5 μg/kg confers no detectable analgesic advantage over plain local anaesthetic while 1.0 μg/kg is the analgesically effective dose.

Effect estimate (95% CI) for the 0.5 and 1.0 μg/kg nodes across the three outcomes; the dashed line marks no effect. The higher dose is superior for time to first rescue (1.0 vs 0.5 μg/kg: ROM 1.75, 95% CI 1.04–2.97) and is the only dose that separated from plain local anaesthetic for the efficacy outcomes; for PONV the gradient reverses (0.5 μg/kg carries the lower odds), indicating a possible dissociation between the analgesic and antiemetic dose–responses.

Table 2
Dexmedetomidine dose–response across the three outcomes (random-effects network estimates, 95% CI).

Outcome (effect measure)	0.5 μg/kg vs plain LA	1.0 μg/kg vs plain LA	1.0 vs 0.5 μg/kg
Time to first rescue (ROM)	1.19 (0.77–1.84)	2.08 (1.50–2.90)	1.75 (1.04–2.97)
24-h opioid consumption (ROM)	0.69 (0.33–1.43)	0.61 (0.42–0.89)	0.89 (0.39–2.01)
PONV (OR)	0.43 (0.16–1.16)	0.63 (0.34–1.16)	1.47 (0.46–4.74)

ROM, ratio of means; OR, odds ratio. Bold indicates statistical significance (95% CI excluding 1). For time to first rescue a value > 1 favours the higher dose (or dexmedetomidine over plain LA); for 24-hour opioid consumption and PONV a value < 1 favours the higher dose (or dexmedetomidine). The two analgesic outcomes show a consistent dose–response (1.0 > 0.5 μg/kg) and only the 1.0 μg/kg dose separates from plain LA, whereas for PONV the point estimate favours the lower dose (1.0 vs 0.5 μg/kg OR 1.47).

Sensitivity Analysis and Heterogeneity Assessment

Heterogeneity of the two continuous outcomes was very high, and its sources were investigated systematically. Throughout we distinguish network-level heterogeneity (the whole network) from backbone heterogeneity (the dexmedetomidine-versus-plain contrast alone), because the two differ and behave oppositely across outcomes.

Choice of effect measure. At the network level, the standardised mean difference inflated heterogeneity (time I^2 96.0%; opioid 96.8%) relative to the mean difference (92.3%; 91.7%), whereas the ratio of means was comparable for time (93.0%) and appreciably lower for opioid (82.6%); the standardised mean difference also generated implausibly large effects. The ratio of means was therefore adopted.

Where the heterogeneity resides. For time, network heterogeneity (I^2 91.5% after dose stratification) exceeded that of the dexmedetomidine-versus-plain backbone (82.8%), indicating that most heterogeneity lies outside the dexmedetomidine contrast. For opioid the relationship was reversed (network 84.8% vs backbone 95.4%): heterogeneity was concentrated within the dexmedetomidine contrast and diluted by more homogeneous comparisons elsewhere.

Which factors explain the primary-outcome heterogeneity. On the dexmedetomidine-versus-plain backbone (seven trials; base I^2 82.8%), univariable random-effects meta-regression quantified each candidate moderator's marginal contribution (Fig. 6). Dexmedetomidine dose was the only mechanistic, non-aliased source, explaining 74.5% of the between-study variance (residual I^2 51.7%; Q_M *P* = 0.008) and corroborated by the stratified-node analysis. Block timing (marginal R^2 72.7%) and rescue-analgesia threshold (58.9%) also showed high R^2, but each of their levels was defined by the single outlying trial (Shaker 2024) and was thus completely aliased with that study; surgery category (45.3%), sample size (21.4%) and total LA volume (17.4%) were non-significant, and publication year, country and outcome definition explained none of the variance. Because these moderators were mutually confounded and only seven to twelve studies were available, their independent contributions could not be estimated in a multivariable model, and the marginal R^2 values are not additive.

Inconsistency and influence. Design-by-treatment decomposition of the dose-stratified time network attributed almost all residual heterogeneity to between-design inconsistency (Q_between = 117.5, *P* < 0.001) rather than within-design heterogeneity (Q_within = 12.6); node-splitting is shown in Figure S2. Leave-one-study-out analysis kept network I^2 between 84.9% and 92.8%, and removing

both single-study loops (El Sherif 2022 and Shaker 2024) lowered it only from 91.5% to 89.0% — no single study or loop accounted for the heterogeneity. Primary-outcome heterogeneity is therefore genuine and distributed, reflecting true clinical diversity (multiple adjuvants, two dexmedetomidine doses, and heterogeneous surgery and anaesthetic regimens) rather than an artefact of individual studies.

For 24-hour opioid consumption the opposite held: excluding Shaker 2024 alone reduced network I^2 from 84.8% to 54.1%, collapsed between-design inconsistency ($Q_{between}$ 37.4→6.6; P 5×10^{-7}→0.087, non-significant) and rendered every node-split non-significant, identifying this trial as a single dominant outlier. A sensitivity analysis excluding it is accordingly reported for the opioid outcome.

Publication bias

Small-study effects were examined with comparison-adjusted funnel plots (Figure S3) and an Egger-type regression of the comparison-adjusted effects. Funnel asymmetry was significant for time to first rescue (intercept $P = 0.021$), the smaller trials tending to report larger benefits, but not for opioid consumption ($P = 0.280$) or PONV ($P = 0.170$). Because fewer than ten studies informed most pairwise comparisons, these tests are underpowered and were interpreted qualitatively; the asymmetry for the primary outcome reinforces a cautious reading of the absolute effect magnitudes.

Discussion

In this dose-stratified network meta-analysis of 15 randomised trials (1,127 participants), every active adjuvant except dexamethasone prolonged the time to first rescue analgesia and reduced 24-hour opioid consumption relative to plain local anaesthetic, but the magnitude of benefit differed markedly between agents and, for dexmedetomidine, between doses. Magnesium sulfate, 1.0 µg/kg dexmedetomidine, ketamine and nalbuphine each produced clinically meaningful prolongation of analgesia and opioid sparing, whereas dexamethasone and 0.5 µg/kg dexmedetomidine were statistically indistinguishable from plain local anaesthetic for every efficacy outcome. The central and novel finding was a coherent dexmedetomidine dose-response: 1.0 µg/kg was superior to 0.5 µg/kg for the primary outcome and was the only dose to separate from plain local anaesthetic, while the antiemetic effect did not track this analgesic gradient.

The biological plausibility of these findings rests on the distinct pharmacology of each adjuvant. Dexmedetomidine's prolongation of block is mediated chiefly by blockade of the hyperpolarisation-activated cation (I_h) current rather than by α2-adrenoceptor agonism alone, and this action is dose-dependent in experimental models [11, 21], providing a direct correlate for the clinical dose-response we observed and for the superiority of 1.0 over 0.5 µg/kg; perineural administration enhances sensory and motor blockade without histological evidence of neurotoxicity [22], whereas its sedative and antiemetic effects appear predominantly central and systemically mediated, consistent with the antiemetic benefit not tracking the analgesic dose-response [10]. The remaining agents act through complementary pathways. Dexamethasone, a glucocorticoid, suppresses nociceptive C-fibre transmission, reduces potassium conductance and slows local-anaesthetic clearance through a local vasoconstrictive effect [12]. Magnesium sulfate and ketamine are non-competitive N-methyl-D-aspartate receptor antagonists that limit the central sensitisation underlying postoperative hyperalgesia, magnesium additionally modulating trans-membrane calcium influx [8]. Nalbuphine, a κ-agonist/µ-antagonist, engages peripheral, dorsal-root-ganglion and, through limited systemic absorption, spinal opioid receptors [15]. That these mechanisms are largely non-overlapping is consistent with the divergent effects we observed and offers a rationale for combining agents in future multimodal regimens.

These mechanistic differences translate into divergent clinical behaviour. Although dexamethasone reliably prolongs peripheral blocks, a large body of evidence shows that much of its benefit is achieved equally by the intravenous route, with only a modest perineural advantage at best [13, 23–25]; our finding that perineural dexamethasone did not outperform plain local anaesthetic within the ESPB is congruent with this route-independence and suggests that, in a well-vascularised interfascial plane with rapid systemic absorption, its locally mediated component is small. Among the NMDA antagonists, head-to-head trials suggest that magnesium is the more effective of the two, prolonging analgesia with fewer adverse effects [26, 27], consistent with the strong analgesic signal for magnesium in our network, although its perineural safety and optimal dosing remain less well characterised than those of dexmedetomidine. Nalbuphine ranked first for opioid sparing [15, 28], an outcome that follows directly from its opioid pharmacology and that may make it attractive where minimising systemic opioid exposure is the priority.

Our results both corroborate and extend the existing literature. For dexmedetomidine, the only agent previously meta-analysed within the ESPB, earlier pairwise syntheses concluded that it prolongs analgesia and reduces PONV when doses are pooled [16, 20], and our pooled estimate reproduces this; the added value here is to show that the average conceals a threshold, with benefit carried almost entirely by the 1.0 μg/kg dose. This gradient is corroborated by direct evidence: two randomised trials compared 0.5 and 1.0 μg/kg dexmedetomidine head-to-head within the ESPB and independently found the higher dose superior for quality of recovery and analgesia [29, 30], in close agreement with our network estimate. Neither, however, was eligible for quantitative synthesis. In Gao and colleagues [30] all three arms co-administered fixed dexamethasone (0.1 mg/kg), leaving no plain-local-anaesthetic reference and confounding every arm with a second adjuvant; in Guo and colleagues [29] analgesia was reported as the QoR-15 score rather than our pre-specified time to first rescue, and rescue was a non-opioid delivered against a mandatory continuous opioid background, precluding a comparable 24-hour opioid requirement. Because each dose contrast was embedded within a co-analgesic framework that could not be mapped onto the network nodes under a defensible transitivity assumption, both were retained as external head-to-head confirmation rather than internal evidence—agreement that indicates the observed dose-response is not an artefact of indirect estimation. Beyond the ESPB, prior network meta-analyses of adjuvants in brachial plexus blockade have consistently ranked dexamethasone and dexmedetomidine among the most effective agents, frequently placing dexamethasone first [20, 31, 32], and indirect comparisons have likewise favoured dexamethasone over dexmedetomidine [17, 18]. Our ESPB-specific network diverges sharply on this point, finding perineural dexamethasone ineffective, a discrepancy that reinforces the principle that adjuvant performance is block-type specific and cannot be transported wholesale from the brachial plexus to a fascial-plane block with different pharmacokinetics. At the level of individual trials, the agents that topped our ranking correspond to the positive single studies in the network: for example, the dexmedetomidine-versus-dexamethasone thoracic trial of Gao and colleagues [33], the dose-ranging nalbuphine trial of Sun and colleagues [15], and the dexmedetomidine abdominal trial of Sifaki and colleagues [34]. A recent trial combining a paravertebral block with an ESPB also reached concordant conclusions about the analgesic value of dexmedetomidine [35]. That perineural dexmedetomidine reliably prolongs peripheral blocks is well established in the broader literature [36, 37], making its dose-dependence, rather than its efficacy per se, the salient question this analysis addresses.

The dose-response we describe sits within a broader, and clinically important, recognition that the effects of perineural adjuvants are dose-dependent rather than all-or-none. For dexamethasone, dedicated dose-finding and dose-ranging randomised trials have demonstrated a graded, saturable relationship between dose and duration of analgesia [38, 39], and model-based analyses have formalised this as a plateau beyond which further dose increases add little. Our data extend this dose-aware paradigm to dexmedetomidine within the ESPB and, in doing so, expose a practical hazard of ignoring dose: because 0.5 and 1.0 μg/kg differ materially in efficacy, pooling them, as most meta-analyses and guideline-oriented reviews have done, simultaneously dilutes the true effect of the higher dose and manufactures an illusory, modest average effect for the node as a whole. Making dose an explicit analytical variable, rather than a nuisance to be averaged away, is therefore not a statistical nicety but a prerequisite for valid inference and for actionable dosing guidance [40]; we would argue that future syntheses of perineural adjuvants should pre-specify dose-stratified nodes as a matter of routine.

Two analytical features underpin these conclusions. First, the pre-specified dexmedetomidine dose split was not merely descriptive: it was the principal, and the only mechanistically interpretable, source of heterogeneity for the primary outcome, explaining roughly three-quarters of the between-study variance on the dexmedetomidine-versus-plain backbone. Other high-R^2 moderators, block timing and rescue-analgesia threshold, were completely aliased with a single outlying trial and therefore could not be distinguished from a study effect, underscoring that apparent moderators must be judged against their confounding structure rather than their R^2 alone. Second, we deliberately separated network-level from backbone-level heterogeneity, because the two behaved oppositely: for the primary outcome, heterogeneity lay largely outside the dexmedetomidine contrast and was genuine and distributed (no single study or closed loop accounted for it), whereas for opioid consumption it was concentrated within one dominant outlier, whose removal collapsed both the between-design inconsistency and every node-split. Substantial inconsistency is a recurring feature of adjuvant networks [31], and this explicit, dose-aware decomposition, rather than the common practice of reporting a single pooled estimate beneath a high I^2 with little explanation, offers a more honest account of where uncertainty resides and how far each ranking can be trusted.

For clinical practice, several inferences follow, offered with due caution. Where dexmedetomidine is chosen as an ESPB adjuvant, 1.0 μg/kg, not 0.5 μg/kg, appears to be the analgesically effective dose, weighed against the dose-related risks of bradycardia and hypotension; using the lower dose may confer little pain-related advantage over plain local anaesthetic. Magnesium sulfate,

ketamine and nalbuphine emerged as effective alternatives that merit fuller evaluation, with nalbuphine particularly promising for opioid sparing, although the leading rank of magnesium sulfate rested on a single small trial and should be treated as hypothesis-generating. Perineural dexamethasone did not demonstrate benefit within the ESPB and, given the route-independence of its effect, intravenous administration may be the more rational default pending dedicated trials. Because the informative comparisons were few and the primary-outcome estimates showed small-study effects, absolute magnitudes should be read conservatively and the rankings interpreted as relative rather than definitive. Priorities for future research are adequately powered, head-to-head trials (especially direct 0.5-versus-1.0 μg/kg dexmedetomidine comparisons and trials of magnesium sulfate, ketamine and nalbuphine against active comparators) that standardise the local anaesthetic, surgical population and outcome definitions and report doses explicitly.

This study has several limitations. The evidence base was modest, comprising 15 small trials, with several nodes informed by only one study, so that some comparisons, notably those involving magnesium sulfate and ketamine, rest on sparse data and wide intervals. Heterogeneity in the two continuous outcomes was high and, for the primary outcome, genuine and only partly explained; although the ratio of means mitigated the differing scales and units of the trials, residual clinical diversity in surgery, anaesthetic regimen and outcome ascertainment remains. The pivotal dexmedetomidine dose-response was derived from indirect evidence, because the two doses were never compared head-to-head within our network; it is mechanistically supported and concordant with external head-to-head trials but still warrants direct confirmation in this setting. Means and standard deviations were reconstructed from medians for some trials, and multi-arm and multi-dose trials required node-handling decisions that, although pre-specified, introduce assumptions. The included trials originated predominantly from a small number of countries, which may limit generalisability, and small-study effects were evident for the primary outcome. Finally, as with any network meta-analysis, the validity of the indirect estimates depends on the transitivity assumption, which we supported by inspecting effect modifiers but cannot guarantee. These considerations temper the strength of the conclusions but do not overturn the central, mechanistically and clinically corroborated finding that the analgesic benefit of dexmedetomidine in the ESPB is dose-dependent.

Conclusions

In this dose-stratified network meta-analysis, local-anaesthetic adjuvants for the erector spinae plane block differed substantially in efficacy. Magnesium sulfate, 1.0 μg/kg dexmedetomidine, ketamine and nalbuphine prolonged analgesia and reduced opioid consumption, with nalbuphine ranking highest for opioid sparing, whereas perineural dexamethasone and 0.5 μg/kg dexmedetomidine were no better than plain local anaesthetic for pain-related outcomes. The defining result is a coherent, mechanistically supported dexmedetomidine dose-response: 1.0 μg/kg is the analgesically effective dose, 0.5 μg/kg confers little pain-related advantage, and the analgesic gradient is not mirrored by the antiemetic effect. Dose is therefore a decisive and previously overlooked determinant of adjuvant efficacy in the ESPB, and pooling doses can both dilute and disguise true effects. Because the evidence rests on a modest number of small trials with distributed heterogeneity and indirect dose comparisons, these rankings should be regarded as the best current estimate rather than a definitive hierarchy, and they require confirmation in adequately powered, dose-explicit, head-to-head randomised trials that standardise the local anaesthetic, surgical setting and outcome definitions.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Clinical trial number

Not applicable.

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Author Contribution

YZ and JD performed data collection, statistical analysis and manuscript writing. ZQ designed the study and manuscript revision. All authors critically reviewed the manuscript. All authors read and approved the final manuscript.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

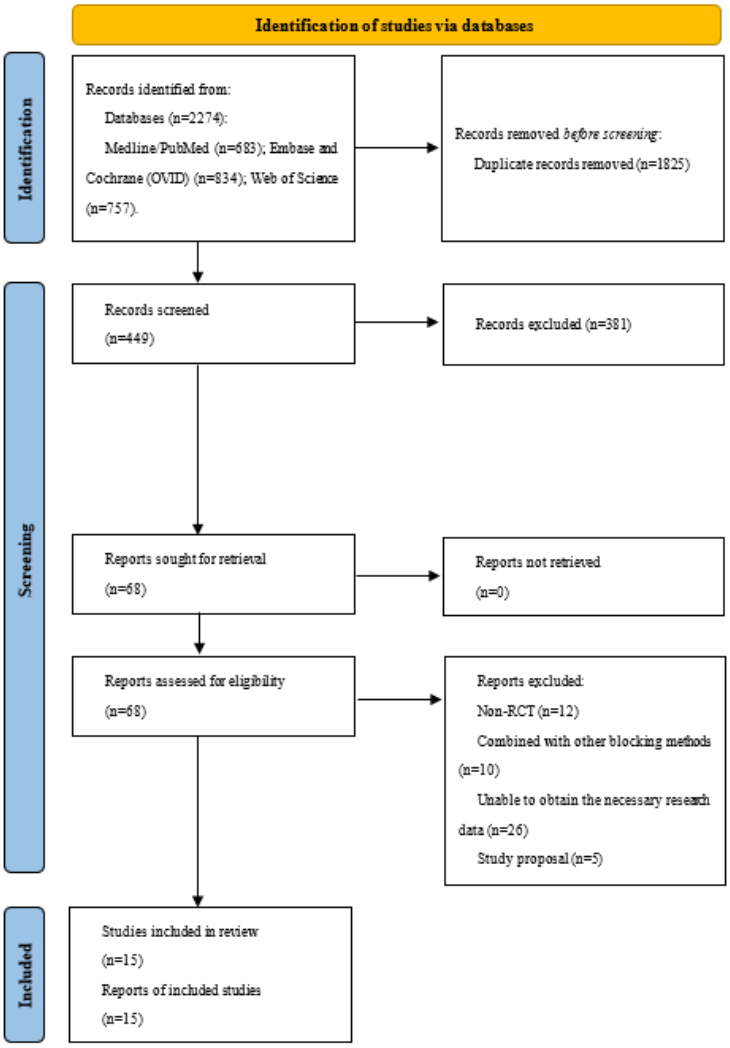


Figure 1

PRISMA diagram of search results and selections.

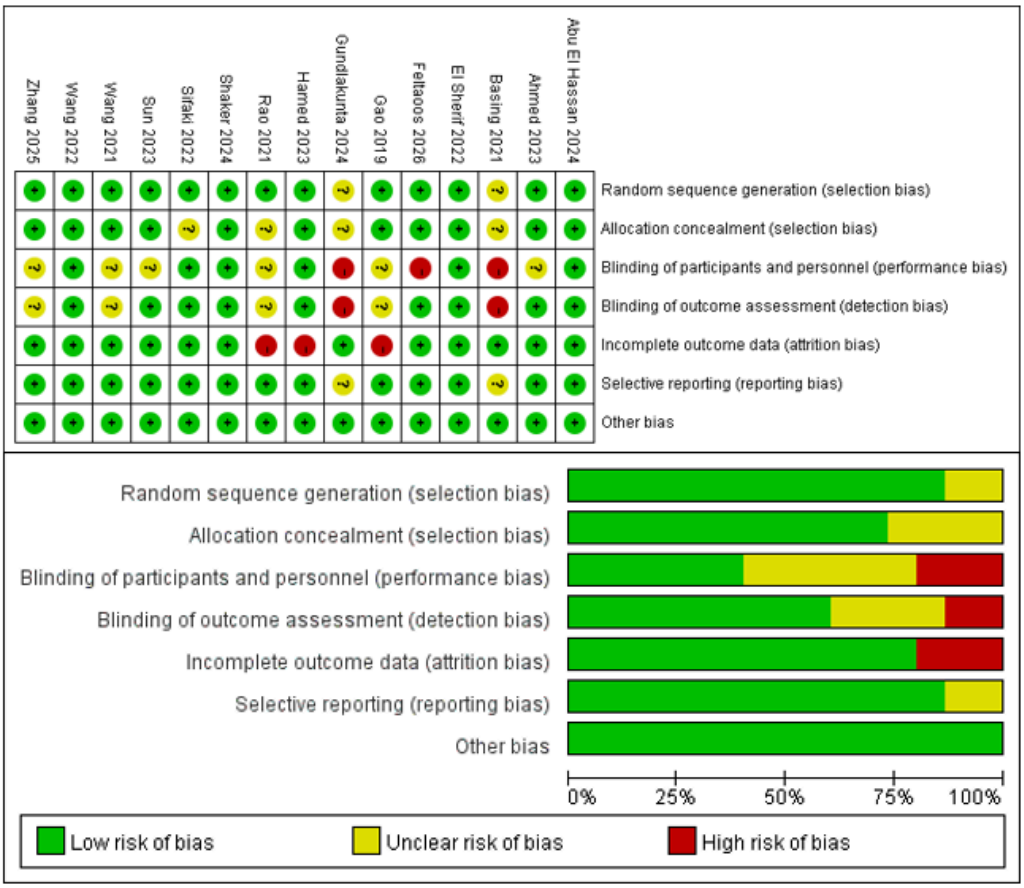


Figure 2

Risk of bias assessment in individual studies and across the included studies.

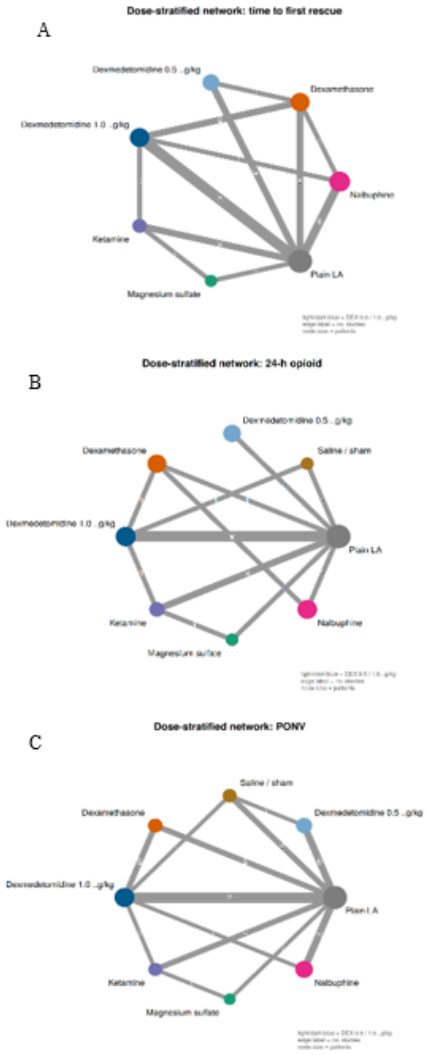


Figure 3

Network geometry of the dose-stratified comparisons.

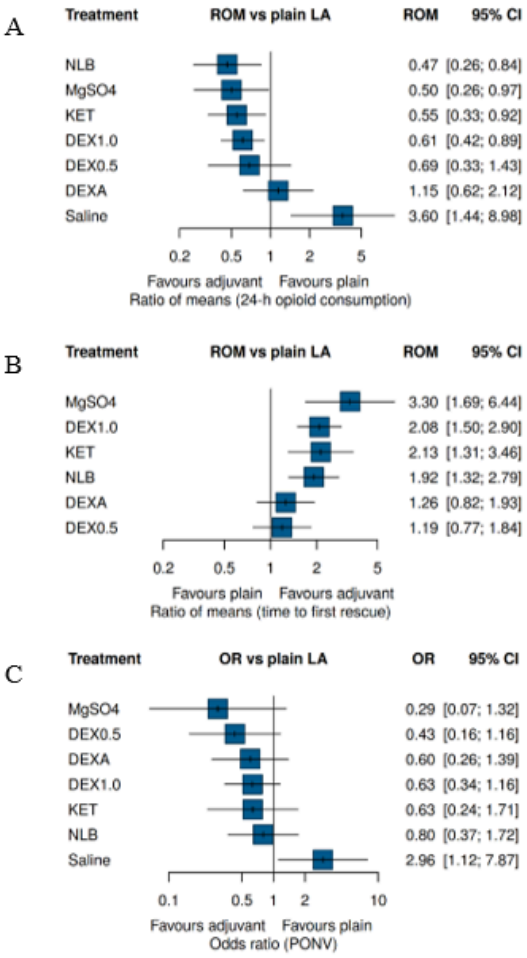


Figure 4

Network estimates for each adjuvant versus plain local anaesthetic (random-effects).

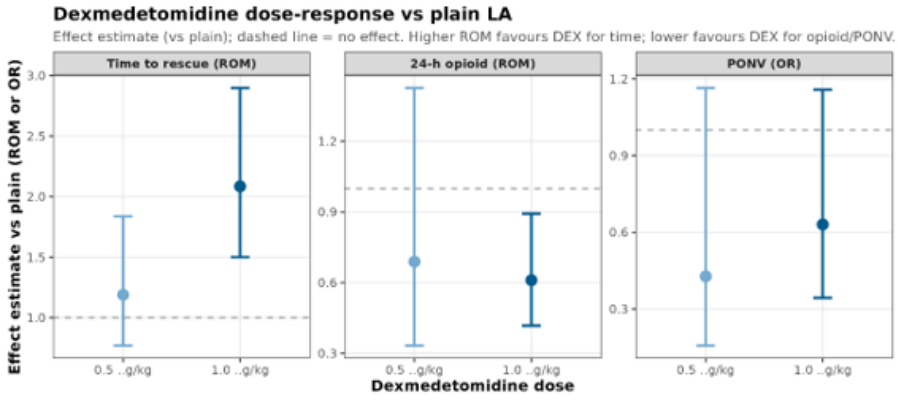


Figure 5

Dexmedetomidine dose–response versus plain local anaesthetic.

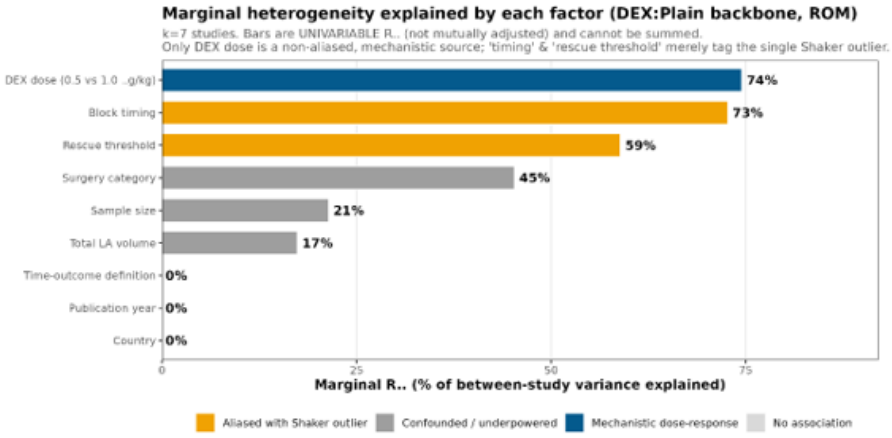


Figure 6

Marginal heterogeneity explained by each factor (dexmedetomidine-versus-plain backbone, ratio of means).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryfile.docx