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TITLE PAGE

Efficacy and Safety of Intrathecal Adjuvants in Lower Limb Orthopaedic Surgery: A Systematic Review and Network Meta-Analysis of Randomised Controlled Trials

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Short title: A network meta-analysis of intrathecal adjuvants in lower limb orthopaedic surgery

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Keywords

Intrathecal; lower limb surgery; meta-analysis; opioid; orthopaedic; pain; spinal

Abbreviations

RCTs, randomised controlled trials; LA, local anaesthetic; ERAS, Enhanced Recovery After Surgery; PROSPERO, International Prospective Register of Systematic Reviews; FDA, Food and Drug Administration; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; MME, morphine milligram equivalents; CINeMa, Confidence in Network Meta-Analysis; SUCRA, surface under the cumulative ranking curve; MD, mean difference; RR, risk ratio; MCID, minimal clinically important difference; PONV, postoperative nausea and vomiting; ISMP, Institute for Safe Medication Practices;

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Abstract

Background

Intrathecal adjuvants are frequently used in spinal anaesthesia for lower-limb surgery to enhance block quality and prolong postoperative analgesia. However, evidence remains fragmented across individual agents. This systematic review with frequentist network meta-analysis aimed to compare the efficacy and safety of intrathecal adjuvants in patients undergoing lower-limb orthopaedic surgery to evaluate the effectiveness and safety of intrathecal adjuvants combined with long-acting local anaesthetics for lower limb orthopaedic surgery.

Methods

A systematic search of PubMed, CENTRAL, and Embase was conducted to retrieve English-language RCTs involving adult patients undergoing lower-limb orthopaedic surgery under single-shot spinal anaesthesia. We included trials evaluating any intrathecal drug or placebo added to a long-acting local anaesthetic. Our primary outcome was the duration of effective analgesia, defined as the time to the first analgesic requirement, in hours. We selected randomised controlled trials (RCTs) reported in English.

Results

We included 183 RCTs, for a total of 14431 patients and 27 interventions. Morphine combined with ketorolac, morphine alone followed by diamorphine, clonidine combined with morphine and ketamine combined with midazolam provided the greatest prolongation of effective analgesia. Morphine also significantly reduced pain at 12 hours and postoperative opioid consumption with no impact on motor block duration. Dexmedetomidine reduced pain intensity at 12 hours but substantially prolonged motor block duration and increased the incidence of bradycardia. Morphine and neostigmine showed an increased risk of postoperative nausea and vomiting, while several interventions increased the risk of pruritus. The certainty of evidence ranged from low to very low due to within-study bias, reporting bias, high heterogeneity, imprecision and incoherence.

Conclusions

Considering the body of evidence in an NMA framework, intrathecal morphine appears to offer a potentially favourable efficacy-safety balance. Dexmedetomidine may prolong motor block and increase the risk of bradycardia. The certainty of the evidence was low to very low and need caution interpretation.

Registration

CRD42024557751

Strengths and limitations of this study

- Broad, systematic search strategy and predefined eligibility criteria covering a wide spectrum of intrathecal adjuvants
- Frequentist network meta-analysis framework to integrate direct and indirect evidence
- Nodes defined qualitatively by the adjuvant component alone, without modelling the differences in local anaesthetic regimens

- High heterogeneity in dosing regimens, limiting comparability across pooled studies
- Reliance on aggregate trial data from predominantly small RCTs, increasing vulnerability to small-study effects and within-study bias.

Introduction

Orthopaedic surgery is one of the most rapidly growing surgical specialities in the world, with annual procedures forecasted to increase by approximately 4.9% each year. [1]

Lower limb surgery constitutes the majority of orthopaedic procedures. This is mainly related to demographic shifts that are contributing to a substantial increase in geriatric fractures, particularly hip and femur fractures. [2] In parallel, lower limb arthroplasty, including hip or knee replacement, has become one of the most common non-cardiac surgeries in countries with higher economic income. [3]

Spinal anaesthesia is now widely preferred for many orthopaedic procedures due to advantages over general anaesthesia, including avoidance of hypnosis and neuromuscular block, reduced respiratory and myocardial depression, minimal coagulation disorders, lower incidence of nausea and vomiting, and prolonged postoperative analgesia. [4,5] However, the duration of action of local anaesthetics (LA) and their dose-dependent adverse effects on the cardiac and central nervous system limit their use. [6]

Effective postoperative pain management is crucial in this patient population, as inadequate analgesia delays mobilisation, prolongs hospital stay, and increases the risk of complications. [7] Furthermore, reducing opioid consumption in orthopaedic surgery is essential to enhance recovery and reduce opioid-related risks, as emphasised by ERAS (Enhanced Recovery After Surgery) protocols. [8]

Intrathecal adjuvants are commonly added to local anaesthetics during spinal anaesthesia to improve the duration and density of the spinal block, reduce the local anaesthetic dose and its dose-dependent adverse effects. [9]

Given the multitude of adjuvants available, a network meta-analysis represents the most effective statistical approach for summarising the effects of multiple interventions on the same outcomes.

While previous systematic reviews and meta-analyses have addressed this topic, evidence remains fragmented. The available meta-analyses mostly focused on a single adjuvant, included heterogeneous surgical populations or incorporated a limited number of trials. [10–24]

This study aimed to address these gaps by conducting a systematic review with a network meta-analysis to evaluate the efficacy and safety of intrathecal adjuvants in patients undergoing lower limb orthopaedic surgery under spinal anaesthesia. The primary outcome was the duration of effective analgesia, defined as the time to the first analgesic requirement, in hours. Secondary outcomes included postoperative pain intensity at 12 hours, postoperative opioid consumption, duration of motor block in hours and incidence of adverse events.

Methods

Protocol registration

The protocol of this review was prospectively registered on PROSPERO (International Prospective Register of Systematic Reviews, CRD42024557751) (Supplementary Material 4).

Eligibility criteria

We identified and included RCTs allocating adult patients undergoing orthopaedic lower limb surgery under single-shot spinal anaesthesia and comparing intrathecal adjuvants administered in combination with one of the following local anaesthetics: levobupivacaine, bupivacaine, ropivacaine. The common comparator was the local anaesthetic alone, with or without placebo. We investigated both FDA (Food and Drug Administration) approved and off-label agents, considering the following interventions: opioids, alpha-agonists, benzodiazepines, ketamine, neostigmine, atropine, glucocorticoids, catecholamines, and their combinations. The association with other regional techniques was an exclusion criterion.

Our primary outcome was the duration of effective analgesia, defined as the time to the first analgesic requirement, in hours. Secondary outcomes included postoperative pain intensity at 12 hours, measured on an 11-point numerical rating scale or a 100-mm visual analogue scale, converted to an 11-point score; postoperative opioid consumption, measured as oral morphine equivalents (mg); duration of motor block in hours; and incidence of adverse events as reported by the authors, including bradycardia, hypotension, postoperative nausea and vomiting (PONV), pruritus and respiratory depression.

Search strategy

We conducted a literature search through PubMed, the Cochrane Library for Clinical Trials (CENTRAL), and Embase via Elsevier. Databases were searched from inception until 06 September 2025 (Supplementary Material 1). We searched the reference lists of the included articles using the snowballing method. We included only studies in the English language.

Study screening and selection

Two authors (SS and MO) identified duplicates using Zotero and manually removed them. [25] At least two of the authors, CC, RD, DF, and MO, independently screened the references

against the eligibility criteria and reviewed the full texts of the selected studies to determine whether they should be included. Discrepancies were resolved by discussion with a third author. The Rayyan webapp was used to support the authors in the title-abstract screening phase. [26] The inclusion and exclusion process were summarised in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram (S1 Figure 1), and a list of excluded full-text studies with reasons for exclusion was provided in the Supplementary Material 2 (S2 Table 2). [27,28]

Data extraction

Data extraction was conducted using an electronic standardised form designed by SS using REDCap. [29] The authors (CC, RD, DF, MO, VFT) extracted data, including the study's first author, year, treatments, dosages, primary outcome, number of participants, and any reported outcomes of interest (S2 Table 1). Data from graphs were extracted using WebPlotDigitizer, and the median and interquartile ranges were converted to mean and standard deviation according to the formula suggested by the Cochrane Handbook. [30,31]

The reported perioperative opioid consumption was converted into oral morphine milligram equivalents (MME) using the opioid equianalgesic calculator from the Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists. [32]

Risk of bias assessment

The risk of bias was assessed using the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2) and plotted with the “robvis” shinyapp. [33–35] Two authors (MO, SS, VFT) independently assessed the risk of bias.

The overall risk was determined according to the suggested algorithms by the Cochrane RoB2 Development Group (S2 Figures 8, 15, 23, and 31).

The evidence for the primary and selected secondary outcomes was graded in the Confidence in Network Meta-Analysis (CINeMA) framework, and the grading results were plotted with the "gt" R package (Figure 2; S2 Figures 16, 24, and 32). [36,37]

Data analysis

We performed a frequentist random-effects network meta-analysis. In case of multi-arm trials, each arm was treated as a standalone intervention within the network meta-analysis framework. [38] The distribution of treatment ranks was established based on the desirability of each outcome and the effect size estimates obtained from the network meta-analysis. To summarise the hierarchy of interventions, we calculated the surface under the cumulative ranking curve (SUCRA), which reflects the probability that a treatment outperforms all other comparators. [39] Heterogeneity was assessed using the I^2 statistic, and publication bias was assessed visually with a funnel plot. In the case of arms with zero events, a 0.5 continuity correction was applied. We assessed the structural indirectness of the evidence network following the approach proposed by Konig et al., combining three complementary measures: the direct evidence proportion, the mean path length and the index of parallelism. (S2 Table 4) [40] Comparisons simultaneously meeting the three criteria: direct evidence proportion <0.2, mean path length >2, and index of parallelism close to 1, should be considered potentially unreliable. [40]

The PRISMA flowchart was plotted with the R package PRISMA 2020. [28]

Effect sizes for continuous outcomes were reported as mean differences (MD), whereas those for dichotomous outcomes were reported as risk ratios (RRs). The precision of these effect sizes was presented using 95% confidence intervals (CIs). Regarding adverse effects, we extracted data as reported by the original authors. We conducted a quantitative synthesis only for events with consistent reporting across studies (bradycardia, hypotension, nausea, vomiting, PONV, pruritus and respiratory depression) (S2 Table 3).

The clinical relevance was evaluated considering each outcome's minimal clinically important difference (MCID). Regarding effective analgesia and motor block duration, we selected an MD of 0.5 SD from the mean duration reported by the control group, resulting in values of 0.8 and 0.3 hours, respectively. [41] An MD of 1.2 points in pain scores was considered clinically relevant.[42] For postoperative opioid consumption, a difference exceeding 30 mg of oral morphine equivalents was deemed significant. [43] The analysis was conducted by SS using the netmeta R package. [44]

The plausibility of the transitivity assumption was assessed by evaluating the distribution of key potential effect modifiers across treatment comparisons, including patient characteristics (e.g., age and comorbidities), surgical procedures, local anaesthetic regimens (agent and dose), adjuvant dosing, and study setting. This assessment was conducted qualitatively by comparing the similarity of these variables across treatment nodes.

We conducted subgroup analyses based on surgical procedure (arthroscopy only versus mixed limb surgery), country of conduction (India), and Risk of Bias (studies classified as low risk versus high risk or with some concerns according to RoB 2). Additionally, we performed a model-based network meta-analysis using an Emax dose–response function within a random-effects framework to investigate the relationship between dose and treatment effect for morphine and dexmedetomidine (Supplementary Material 3 Figure 18, S3 Figure 36, S3 Figure 48, S3 Figure 66). [45]

Reporting of the Meta-analysis

A comprehensive PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions checklist was included in the online supplemental material. (Supplementary Material 1) [46]

Results

We retrieved a total of 2137 records. After removing duplicates and the title and abstract screening, 279 records were selected as relevant. Full text screening led to the exclusion of 96 records. The main reasons for exclusion were non-relevant population (n=41), outcome (n=14), design (n=4), intervention (n=26), publication type (n=7), and language other than English (n=4). We finally included a total of 183 RTCs, for a total of 14431 patients [47–229] (S1 Figure 1). Detailed characteristics of included studies are reported in Supplementary 2 Table 1.

The surgical setting predominantly involved all types of lower limb procedures (n=114), followed by knee arthroscopy (n=15), general knee procedures (n=8), open reduction of femoral fractures (n=8), general hip procedures (n=7), and hip joint with a synthetic prosthesis (n=7). Bupivacaine was the most frequently used local anaesthetic (n=157). (S2 Table 1)

The geographical distribution of the included studies spanned 25 countries across four continents. The largest contribution came from Asia, particularly India (n=101), representing more than half of all trials, followed by Iran (n=18), Turkey (n=9), China (n=5), South Korea (n=4), Japan (n=2), Pakistan (n=2), and Iraq (n=1). Nineteen trials originated from Europe: Ireland (n=4), Finland (n=3), France (n=3), Spain (n=2), Germany (n=2), Latvia (n=2), Switzerland (n=1), Sweden (n=1), and the Netherlands (n=1). Thirteen trials were included from Africa: Egypt (n=9), Tunisia (n=2), Zimbabwe (n=1), and Kenya (n=1). Additional contributions came from North America, particularly the United States (n=4), and Canada (n=1), as well as from South America, particularly Brazil (n=3), and Oceania (n=2). Four studies were multicentric, involving collaborations between Iraq, Sudan and the United Arab

Emirates; France, Tunisia and the United States; Canada and India; and Australia, Croatia and Germany. (S2 Table 1- S2 Figure 1)

The evidence profile of our findings was reported in Table 1.

THE DURATION OF EFFECTIVE ANALGESIA	Limitations	Inconsistency/ Heterogeneity	Indirectness	Imprecision	Publication bias	Mean difference [95% Confidence Interval]	Number of participants (studies)	Conclusions	Quality or certainty of the evidence (GRADE)
BUPRENORPHINE	Bias arising from the randomisation process in one study and the selection of the reported result in 3 studies	I^2 Test for Heterogeneity 99.4%.	No detected	Not detected	Potential publication bias	3.65 (2.52; 4.79)	350 (5 studies)	Effect of buprenorphine statistically and clinically significant compared to control	⊕⊕◯◯ LOW
BUTORPHANOL	Only 1 study. Bias arising from the randomisation process and the selection of the reported result	Signs of heterogeneity	No detected	Potential imprecision	Potential publication bias	1.09 (-0.87; 3.06)	60 (1 study)	Effect of butorphanol no significant compared to control	⊕◯◯◯ VERY LOW
CALCITONIN	Only 1 study. Bias arising from the randomisation process and the selection of the reported result	Signs of heterogeneity	No detected	Not detected	Potential publication bias	2.43 (-0.45; 5.30)	60 (1 study)	Effect of calcitonin no significant compared to control	⊕◯◯◯ VERY LOW
CLONIDINE	Bias arising from the randomisation process in 8 studies and the selection of the reported result in 13 studies	I^2 Test for Heterogeneity 96.6%.	No detected	Not detected	Potential publication bias	2.56 (1.85; 3.28)	1128 (16 studies)	Effect of clonidine statistically and clinically significant compared to control	⊕⊕◯◯ LOW
CLONIDINE_FENTANYL	Only 1 study. Bias arising from the selection of the reported result	No detected	No detected	Not detected	Potential publication bias	3.17 (1.25; 5.09)	50 (1 study)	Effect of clonidine_fentanyl statistically and clinically significant compared to control	⊕◯◯◯ VERY LOW
CLONIDINE_MIDAZOLAM	Only indirect estimates.	Signs of heterogeneity	No detected	Not detected	Potential publication bias	2.70 (-0.92; 6.32)	0	Effect of clonidine_midazolam no significant compared to control	⊕◯◯◯ VERY LOW
CLONIDINE_MORPHINE	Only 1 study. Bias arising from the randomisation process and the selection of the reported result	No detected	No detected	No detected	Potential publication bias	7.20 (3.77; 10.62)	60 (1 study)	Effect of clonidine_morphine statistically and clinically significant compared to control	⊕⊕◯◯ LOW
DEXAMETHASONE	Bias arising from the randomisation process and the selection of the reported result in 1 study	No detected	No detected	Not detected	Potential publication bias	3.13 (0.81;5.44)	110 (2 studies)	Effect of dexamethasone statistically and clinically significant compared to control	⊕⊕◯◯ LOW
DEXMEDETOMIDINE	Bias arising from the randomisation process in 5 studies and the selection of the reported result in 11 studies	I^2 Test for Heterogeneity 98.2%.	No detected	Not detected	Potential publication bias	3.56 (2.89; 4.24)	1146 (17 studies)	Effect of dexmedetomidine statistically and clinically significant compared to control	⊕⊕◯◯ LOW
DEXMEDETOMIDINE_EPINEPHRINE	Only indirect estimates	No detected	No detected	No detected	Potential publication bias	4.62 (1.05; 8.18)	0	Effect of dexmedetomidine_epinephrine statistically and clinically significant compared to control	⊕◯◯◯ VERY LOW
DEXMEDETOMIDINE_MAGNESIUM	Only indirect estimate.	No detected	No detected	No detected	Potential publication bias	5.88 (2.34; 9.42)	0	Effect of dexmedetomidine_magnesium sulfate statistically and clinically significant compared to control	⊕◯◯◯ VERY LOW
DIAMORPHINE	Only 1 study. Bias arising from the randomisation process and the selection of the reported result	No detected	No detected	Not detected	Potential publication bias	7.40 (4.51; 10.28)	60 (1 study)	Effect of diamorphine statistically and clinically significant compared to control	⊕⊕◯◯ LOW
FENTANYL	Bias arising from the randomisation process in 9 studies and the selection of the reported result in 14 studies	I^2 Test for Heterogeneity 98.5%.	No detected	Not detected	Potential publication bias	1.57 (0.98; 2.17)	1245 (21 studies)	Effect of fentanyl statistically and clinically significant compared to control	⊕◯◯◯ VERY LOW
FENTANYL_MAGNESIUM	Only indirect estimates.	Signs of heterogeneity	No detected	Not detected	Potential publication bias	2.49 (-0.12; 5.10)	0	Effect of fentanyl_magnesium no significant compared to control	⊕◯◯◯ VERY LOW
FENTANYL_MIDAZOLAM	Only 1 study. Bias arising from the randomisation process and the selection of the reported result	No detected	No detected	Not detected	Potential publication bias	3.36 (0.33; 6.40)	50 (1 study)	Effect of fentanyl_midazolam no significant compared to control	⊕◯◯◯ VERY LOW
KETAMINE	Only 1 study. Bias arising from the selection of the reported result	Signs of heterogeneity	No detected	Potential imprecision	Potential publication bias	1.19 (-1.61; 3.99)	40 (1 study)	Effect of ketamine no significant compared to control	⊕◯◯◯ VERY LOW
KETAMINE_MIDAZOLAM	Only 1 study. Bias arising from the selection of the reported result	No detected	No detected	No detected	Potential publication bias	6.92 (3.52; 10.32)	40 (1 study)	Effect of ketamine_midazolam statistically and clinically significant compared to control	⊕⊕◯◯ LOW
KETOROLAC	Only 1 study. No serious limitations	No detected	No detected	Not detected	Potential publication bias	4.69 (1.61; 7.77)	40 (1 study)	Effect of ketorolac statistically and clinically significant compared to control	⊕⊕⊕◯ MODERATE
MAGNESIUM SULFATE	Bias arising from the randomisation process in 1 study and the selection of the reported result in 4 studies	I^2 Test for Heterogeneity 98.4%.	No detected	Not detected	Potential publication bias	0.88 (-0.43; 2.18)	499 (6 studies)	Effect of magnesium no significant compared to control	⊕◯◯◯ VERY LOW
MIDAZOLAM	Bias arising from the randomisation process in 3 studies, measurements of outcome in 1 study and the selection of the reported result in 6 studies	I^2 Test for Heterogeneity 75.0%.	No detected	Not detected	Potential publication bias	1.92 (0.66, 3.18)	390 (5 studies)	Effect of midazolam no significant compared to control	⊕◯◯◯ VERY LOW
MORPHINE	Bias arising from the randomisation process in 5 studies and the selection of the reported result in 9 studies	I^2 Test for Heterogeneity 99.5%. Sign of local inconsistency (difference 2.49, z = 2.02, p = 0.0435)	No detected	Not detected	Potential publication bias	6.86 (5.78; 7.94)	467 (9 studies)	Effect of morphine statistically and clinically significant compared to control	⊕⊕◯◯ LOW
NALBUPHINE	Bias arising from the randomisation process in 2 studies and the selection of the reported result in 6 studies	I^2 Test for Heterogeneity 98.6%.	No detected	Not detected	Potential publication bias	1.98 (1.11, 2.86)	525 (8 studies)	Effect of nalbuphine statistically and clinically significant compared to control	⊕◯◯◯ VERY LOW
NEOSTIGMINE	Bias arising from the randomisation process in 2 studies and the selection of the reported result in 5 studies	I^2 Test for Heterogeneity 95.5%.	No detected	Not detected	Potential publication bias	1.77 (0.28; 3.25)	310 (5 studies)	Effect of neostigmine no significant compared to control	⊕◯◯◯ VERY LOW
SUFENTANIL	Only 1 study. Bias arising from the selection of the reported result	Signs of heterogeneity	No detected	Potential imprecision	Potential publication bias	1.78 (-1.25; 4.81)	60 (1 study)	Effect of sufentanil no significant compared to control	⊕◯◯◯ VERY LOW
SUFENTANIL_DEXAMETHASONE	Only indirect estimates.	No detected	No detected	Not detected	Potential publication bias	3.80 (-0.82; 8.42)	0	Effect of sufentanil_dexamethasone no significant compared to control	⊕◯◯◯ VERY LOW
TRAMADOL	Only indirect estimates.	Signs of heterogeneity	No detected	Potential imprecision	Potential publication bias	1.44 (-1.20; 4.08)	0	Effect of tramadol no significant compared to control	⊕◯◯◯ VERY LOW

PAIN INTENSITY AT 12 HOURS	Limitations	Inconsistency/ Heterogeneity	Indirectness	Imprecision	Publication bias	Mean difference [95% Confidence Interval]	Number of participants (studies)		Quality or certainty of the evidence (GRADE)
DEXMEDETOMIDINE_MORPHINE	Only indirect estimates. Major concerns regarding incoherence	Only indirect estimate	No detected	No detected	Potential publication bias	-3.26 (-5.04, -1.47)	0	Effect of dexmedetomidine_morphine statistically and clinically significant compared to control	⊕◯◯◯ VERY LOW
MORPHINE	Bias arising from the randomisation process in 4 studies and the selection of the reported result in 6 studies	I^2 Test for Heterogeneity 90.2%. Sign of local inconsistency (difference 0.89, z = 4.29, p ≤0.0001)	No detected	No detected	Potential publication bias	-1.55 (-2.17, -0.92)	447 (9 studies)	Effect of morphine statistically significant compared to control	⊕⊕◯◯ LOW
POSTPERATIVE OPIOID CONSUMPTION	Limitations	Inconsistency/ Heterogeneity	Indirectness	Imprecision	Publication bias	Mean difference [95% Confidence Interval]	Number of participants (studies)		Quality or certainty of the evidence (GRADE)
CLONIDINE_ MORPHINE	Only 1 study. Bias arising from the randomisation process and the selection of the reported result	No detected	No detected	No detected	Potential publication bias	-62.82 (-85.11, -40.53)	60 (1 study)	Effect of clonidine_morphine statistically and clinically significant compared to control	⊕⊕◯◯ LOW
KETOROLAC	Only 1 study. Major concerns regarding incoherence	No detected	No detected	No detected	Potential publication bias	-32.16 (-53.73, -10.60)	40 (1 study)	Effect of ketorolac statistically and clinically significant compared to control	⊕◯◯◯ VERY LOW
MORPHINE	Bias arising from the randomisation process in 3 studies and the selection of the reported result in 4 studies. At least one study was at high risk of bias.	I^2 Test for Heterogeneity 95.4%. Sign of local inconsistency (difference 53.75, z = 2.10, p = 0.0361)	No detected	No detected	Potential publication bias	-29.37 (-39.15, -19.59)	499 (9 studies)	Effect of morphine statistically significant compared to control	⊕⊕◯◯ LOW
DIAMORPHINE	Only 1 study. Bias arising from the randomisation process and the selection of the reported result. Major concerns regarding incoherence	Sign of local inconsistency (difference -53.75, z = -2.10, p = 0.0361)	No detected	No detected	Potential publication bias	-26.35 (-47.94, -4.53)	60 (1 study)	Effect of diamorphine statistically significant compared to control	⊕◯◯◯ VERY LOW
DURATION OF MOTOR BLOCK	Limitations	Inconsistency/ Heterogeneity	Indirectness	Imprecision	Publication bias	Mean difference [95% Confidence Interval]	Number of participants (studies)		Quality or certainty of the evidence (GRADE)
MORPHINE	Only one study. Bias arising from the randomisation process and the selection of the reported result.	Signs of heterogeneity	No detected	Potential imprecision	Potential publication bias	-0.66 (-1.74, 0.43)	40 (1 study)	Effect of morphine no significant compared to control	⊕◯◯◯ VERY LOW
SUFENTANIL	Major concerns in imprecision	I^2 Test for Heterogeneity 93.5%	No detected	Major concerns	Potential publication bias	-0.19 (-1.01, 0.64)	357 (4 studies)	Effect of sufentanil no significant compared to control	⊕◯◯◯ VERY LOW

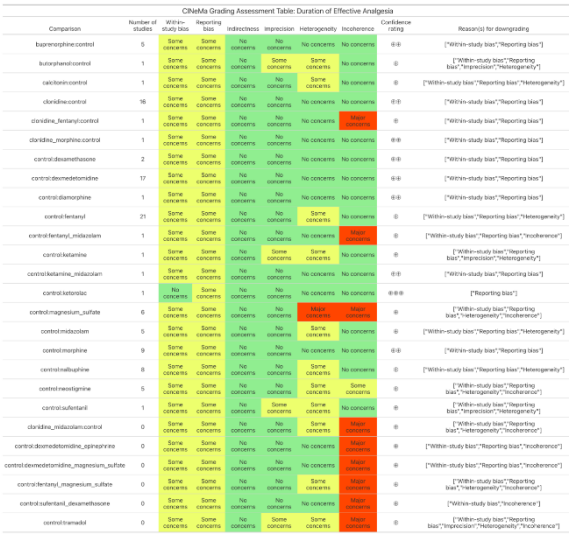
Table 1. Evidence Profile: intrathecal adjuvants for spinal anaesthesia in lower limb surgery

Risk of Bias

Regarding risk of bias, among the studies evaluating the primary outcome, nineteen trials were judged to be at low risk, whereas all others raised some concerns. Specifically, forty-eight of the trials had concerns related to the randomisation process, and ninety-two raised some concerns about selective reporting (S2 Figure 8). In particular, the most frequent pattern was absence of prospective trial registration combined with incomplete or inconsistent reporting of pre-specified secondary outcomes, which limited confidence in the completeness and transparency of outcome reporting.

According to the CINeMA assessment, the overall confidence in the results for the primary

outcome was rated as low to very low, primarily due to within-study bias, reporting bias, high heterogeneity, imprecision of the estimations, and incoherence. Only one comparison was



CINeMa Grading Assessment Table: Duration of Effective Analgesia

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
buprenorphine:control	5	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕	["Within-study bias","Reporting bias"]
butorphanol:control	1	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	⊕	["Within-study bias","Reporting bias","Imprecision","Heterogeneity"]
calcitonin:control	1	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	⊕	["Within-study bias","Reporting bias","Heterogeneity"]
clonidine:control	16	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕	["Within-study bias","Reporting bias"]
clonidine_fentanyl:control	1	Some concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	⊕	["Within-study bias","Reporting bias"]
clonidine_morphine:control	1	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕	["Within-study bias","Reporting bias"]
control:dexamethasone	2	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕	["Within-study bias","Reporting bias"]
control:dexmedetomidine	17	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕	["Within-study bias","Reporting bias"]
control:diamorphine	1	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕	["Within-study bias","Reporting bias"]
control:fentanyl	21	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	⊕	["Within-study bias","Reporting bias","Heterogeneity"]
control:fentanyl_midazolam	1	Some concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	⊕	["Within-study bias","Reporting bias","Incoherence"]
control:ketamine	1	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	⊕	["Within-study bias","Reporting bias","Imprecision","Heterogeneity"]
control:ketamine_midazolam	1	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕	["Within-study bias","Reporting bias"]
control:ketorolac	1	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕⊕	["Reporting bias"]
control:magnesium_sulfate	6	Some concerns	Some concerns	No concerns	No concerns	Major concerns	Major concerns	⊕	["Within-study bias","Reporting bias","Heterogeneity","Incoherence"]
control:midazolam	5	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	⊕	["Within-study bias","Reporting bias","Heterogeneity"]
control:morphine	9	Some concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	⊕⊕	["Within-study bias","Reporting bias"]
control:nalbuphine	8	Some concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	⊕	["Within-study bias","Reporting bias","Heterogeneity"]
control:neostigmine	5	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Some concerns	⊕	["Within-study bias","Reporting bias","Heterogeneity","Incoherence"]
control:sufentanil	1	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	⊕	["Within-study bias","Reporting bias","Imprecision","Heterogeneity"]
clonidine_midazolam:control	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Major concerns	⊕	["Within-study bias","Reporting bias","Heterogeneity","Incoherence"]
control:dexmedetomidine_epinephrine	0	Some concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	⊕	["Within-study bias","Reporting bias","Incoherence"]
control:dexmedetomidine_magnesium_sulfate	0	Some concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	⊕	["Within-study bias","Reporting bias","Incoherence"]
control:fentanyl_magnesium_sulfate	0	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Major concerns	⊕	["Within-study bias","Reporting bias","Heterogeneity","Incoherence"]
control:sufentanil_dexamethasone	0	Some concerns	Some concerns	No concerns	No concerns	No concerns	Major concerns	⊕	["Within-study bias","Incoherence"]
control:tramadol	0	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Major concerns	⊕	["Within-study bias","Reporting bias","Imprecision","Heterogeneity","Incoherence"]

rated with moderate confidence (Figure 1).

Figure 1. Grade assessment table: the primary outcome analysis, the duration of effective analgesia, was assessed using the Confidence in Network Meta-Analysis approach.

The Risk of Bias and CINeMa assessment for the secondary outcomes were reported in the Supplementary Material. (S2 Figures 15,16,23,24,31 and 32)

Primary outcome: duration of effective analgesia

The analysis of the primary outcome analysis included 8701 patients across 116 studies, examining 28 interventions. [48–51,56,57,59,60,62,64,66–68,70,71,74,79,82–84,86–92,94,97,98,100,102–104,106–109,111–116,118–126,129,130,136–139,141,143,146–154,158,159,161–165,172,177–179,184–190,192–196,198–204,207–213,215–217,220–222,225,227] Out of the 378 possible comparisons, only 185 were directly evaluated in head-to-head comparisons. (S2 Figure 2) The included intervention formed a connected network (Figure 2).

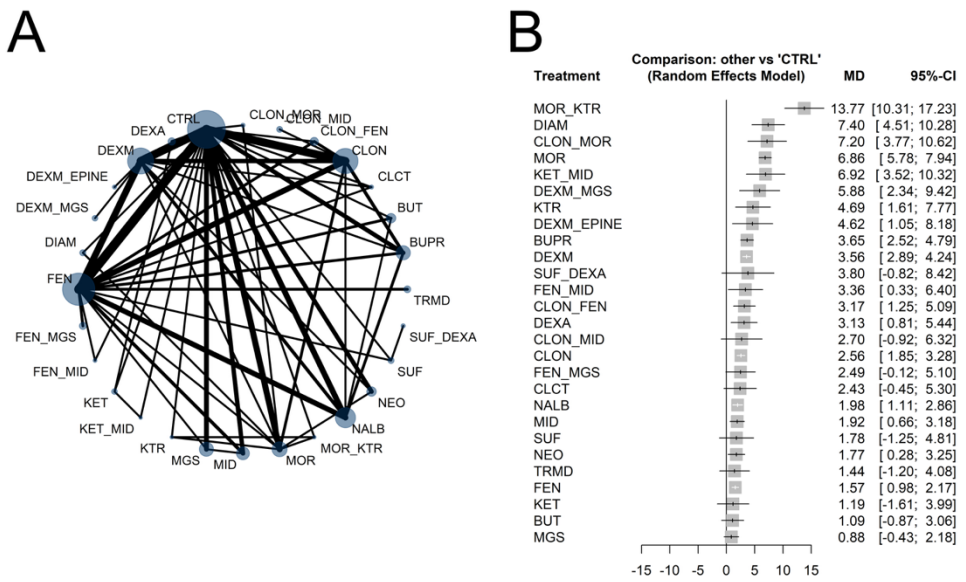


Figure 2. Network of interventions (A) and Forest plot (B) of included interventions versus placebo of the meta-analysis of duration of effective analgesia in hours.

According to SUCRA values, morphine combined with ketorolac (SUCRA 99.96), diamorphine (SUCRA 89.12), clonidine combined with morphine (SUCRA 87.56), morphine (SUCRA 87.46), and ketamine combined with midazolam (SUCRA 86.29) had higher probabilities of ranking among the most effective treatments for prolonging the duration of effective analgesia (S2 Figure 4). However, SUCRA does not account for certainty of evidence and may be affected by heterogeneity and inconsistency. Eighteen treatments showed a statistically significant effect compared with the control group. Considering a minimal clinically important difference of 0.8 hours in the duration of effective analgesia, derived as 0.5 standard deviations from the mean duration reported in the control groups, fifteen of these treatments also reached clinical significance. Morphine combined with ketorolac (MD 13.77; CI 10.31, 17.23), diamorphine (MD 7.40; CI 4.51, 10.28), clonidine combined with morphine (MD 7.20; CI 3.77, 10.62), morphine alone (MD 6.86; CI 5.78, 7.94), and ketamine combined with midazolam (MD 6.92; CI 3.52, 10.32) exhibited the most pronounced effect in prolonging the duration of effective analgesia, showing both clinical and statistical significance. Compared with other top-ranked interventions, morphine combined

with ketorolac had the most conspicuous effect (Figure 2). Dexmedetomidine (MD 3.56; CI 2.89, 4.24), and fentanyl alone (MD 1.57; CI 0.98, 2.17) also reached both statistical and clinical significance, though with a smaller effect. In contrast, sufentanil (MD 1.78; CI -1.25, 4.81), and ketamine alone (MD 1.19; CI -1.61, 3.99) did not show a significant effect.

The Egger's test regression detected evidence of funnel plot asymmetry ($t = 3.33$, $p = 0.0012$), suggesting the presence of small-study effects, which may reflect publication bias (S2 Figure 5). The heterogeneity across studies was extremely high ($I^2 = 98.8\%$; $\tau^2 = 3.14$), indicating substantial variability in effect estimates. The node-split analysis under the random-effects model identified a sign of local inconsistency for dexmedetomidine vs. fentanyl (difference 1.29, $z = 2.00$, $p = 0.0457$) (S2 Figure 6).

The network showed an overall satisfactory balance between direct and indirect evidence. The treatments comparisons supported by the most robust evidence were buprenorphine vs control (evidence direct proportion 0.52, mean path length 1.68 and minimal parallelism 3.75), clonidine vs control (evidence direct proportion 0.65, mean path length 1.50 and minimal parallelism 4.05), dexmedetomidine vs control (evidence direct proportion 0.63, mean path length 1.49 and minimal parallelism 3.82), fentanyl vs control (evidence direct proportion 0.58, mean path length 1.49 and minimal parallelism 5.68), morphine vs control (evidence direct proportion 0.72, mean path length 1.40 and minimal parallelism 3.39), and nalbuphine vs control (evidence direct proportion 0.50, mean path length 1.69 and minimal parallelism 4.09). These comparisons were characterised by relatively high contributions from direct evidence, short mean path lengths, and multiple independent evidence paths, indicating strong structural support within the network.

Sub-analysis: India country only

We performed a subgroup analysis including only studies conducted in India. Morphine (SUCRA 95.25), and ketamine combined with midazolam (SUCRA 94.09) had higher

probabilities of ranking among the most effective treatments for prolonging the duration of effective analgesia with an estimated effect comparable with the main analysis: morphine (MD 6.92; CI 4.06, 9.79), and ketamine combined with midazolam (MD 6.65; CI 3.74, 9.56). (S3 Figures 1-4)

Sub-analysis: arthroscopy only

We performed a subgroup analysis including studies with only arthroscopy procedures. The analysis included only three treatments (dexmedetomidine, midazolam and fentanyl). Dexmedetomidine (SUCRA 89.02), and midazolam (SUCRA 77.62) had the higher probabilities of ranking among the most effective treatments for prolonging the duration of effective analgesia in this surgical population. Dexmedetomidine demonstrated a statistically and clinically significant effect (MD 1.85, CI 1.38, 2.32), whereas midazolam (MD 1.63, CI 0.71, 2.55) did not reach clinical significance. (S3 Figures 5-6)

Sub-analysis: mixed limb surgeries

We performed a subgroup analysis including only studies that evaluated generic lower-limb surgical procedures. Morphine (SUCRA 97.94), ketamine combined with midazolam (SUCRA 96.05), dexmedetomidine combined with epinephrine (SUCRA 84.46), and dexmedetomidine alone (SUCRA 78.92) had the highest probabilities of ranking among the most effective treatments for prolonging the duration of effective analgesia in this surgical population. Fifteen interventions showed a statistically significant effect, of which ten also reached clinical significance. Morphine (MD 7.55, CI 5.19, 9.92), ketamine combined with midazolam (MD 6.92, CI 4.31, 9.52), dexmedetomidine combined with epinephrine (MD 4.68, CI 1.97, 7.38), and dexmedetomidine alone (MD 3.62, CI 3.03, 4.22) showed the largest effects. (S3 Figures 7-9)

Sub-analysis: low Rob2

We performed a subgroup analysis including only studies judged to be at low risk of bias. Morphine combined with ketorolac (SUCRA 99.99), morphine alone (SUCRA 76.65), and dexmedetomidine (SUCRA 72.04) showed the highest probabilities of being among the most effective treatments for prolonging the duration of effective analgesia. All three interventions demonstrated statistically and clinically significant effects: morphine combined with ketorolac (MD 12.60, CI 8.79, 16.41), morphine alone (MD 4.50, CI 1.04, 7.96), and dexmedetomidine (MD 3.76, CI 2.28, 5.24). (S3 Figures 10-13)

Sub-analysis: high or some concerns Rob2

We performed a subgroup analysis including only studies judged at high risk of bias or having some concerns. Diamorphine (SUCRA 93.56), morphine (SUCRA 93.27), clonidine combined with morphine (SUCRA 91.78), and ketamine combined with midazolam (SUCRA 88.08) showed the highest probabilities of ranking among the most effective treatments. Diamorphine (MD 7.58, CI 4.88, 10.28), morphine (MD 7.37, CI 6.20, 8.55), clonidine with morphine (MD 7.35, CI 4.17, 10.54), and ketamine combined with midazolam (MD 6.65, CI 3.36, 9.94) demonstrated the largest effects. (S3 Figures 14-17)

Model-based network meta-analysis dose response

The model-based network meta-analysis demonstrated a non-linear dose response pattern for both intrathecal adjuvants, morphine and dexmedetomidine, characterised by an initial increase in effect at lower doses followed by a plateau at higher doses. Dexmedetomidine exhibited a steeper increase in effect at lower dose ranges, suggesting greater potency, whereas morphine demonstrated a more gradual dose-response profile, reaching maximal effect at higher doses. (S3 Figure 18)

Secondary outcomes

Pain intensity at 12 hours

Forty-one studies reported pain intensity at 12 hours allocating 2939 patients to 18 interventions.[49,50,62,67,71,78,82,83,87,88,92,97,100,101,111,115,121–123,127,130,136,138,143,145,149,157,161,168,189,190,195,206,212,214,221,223,224,226,228]

Out of the 153 possible comparisons, 65 were direct (S2 Figure 9).

According to SUCRA estimates, dexmedetomidine combined with morphine (SUCRA 98.28), morphine alone (SUCRA 81.73), clonidine combined with morphine (SUCRA 66.60), and dexmedetomidine alone (SUCRA 61.29) showed the highest probabilities of being among the most effective treatments in reducing pain intensity at 12 hours (S2 Figure 11). Considering a MD of 1.2 in pain score as the minimal clinically relevant difference dexmedetomidine combined with morphine (MD -3.26; CI -5.04, -1.47) showed a statistically and clinically significant effect. [42]

Morphine alone (MD -1.55; CI -2.17, -0.92) and dexmedetomidine alone (MD -0.97; CI -1.69, -0.24) also showed a statistically significant effect in reducing pain intensity at 12 hours; however, their effects were not clinically significant. (Figure 3)

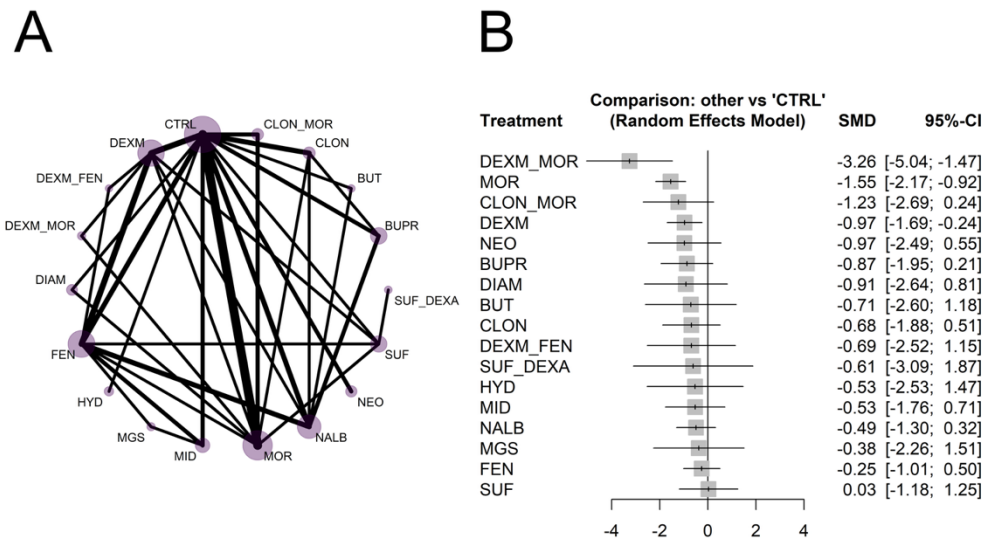


Figure 3. Network of interventions (A) and Forest plot (B) of included interventions versus placebo of the meta-analysis of duration of pain intensity at 12 hours.

The difference between these interventions was not significant. In contrast, fentanyl (MD -0.25; CI -1.01, 0.50), and sufentanil (MD 0.03; CI -1.18, 1.25) did not demonstrate significant effects.

The Egger's test regression detected evidence of funnel plot asymmetry (t = -5.94, p = 0.0001) (S2 Figure 12). The heterogeneity across studies was extremely high (I^2 = 93.6%; τ^2 = 0.99), indicating substantial variability in effect estimates. Nodesplit analysis identified local inconsistency for several comparisons: buprenorphine vs control (difference -0.78, z = -2.85, p = 0.0044), buprenorphine vs nalbuphine (difference 0.66, z = 2.38, p = 0.0174), butorphanol vs control (difference 2.69, z = 2.68, p = 0.0074), butorphanol vs nalbuphine (difference -2.27, z = -2.68, p = 0.0074), clonidine vs control (difference -0.65, z =-2.06, p = 0.0397), dexmedetomidine vs control (difference -1.35, z = -8.87, p ≤ 0.0001), dexmedetomidine vs dexmedetomidine with morphine (difference 5.86, z = 14.99, p ≤ 0.0001), dexmedetomidine vs morphine (difference 2.93, z = 14.99, p ≤ 0.0001), dexmedetomidine vs sufentanil (difference -1.88, z = -5.67, p ≤ 0.0001), dexmedetomidine with morphine vs morphine (difference 5.86, z = 14.99, p ≤ 0.0001), fentanyl vs control

(difference -0.86, z = -2.93, p = 0.0034), fentanyl vs magnesium (difference -1.52, z = -2.28, p = 0.0227), fentanyl vs midazolam (difference -0.77, z = -2.15, p = 0.0316), fentanyl vs morphine (difference 2.28, z = 4.90, p ≤ 0.0001), magnesium vs midazolam (difference -1.52, z =-2.28, p = 0.0227), midazolam vs control (difference -0.79, z = -2.29, p = 0.0222), morphine vs control (difference 1.72, z = 11.83, p ≤ 0.0001), morphine vs sufentanil (difference 0.80, z = 2.89, p = 0.0038), nalbuphine vs control (difference 0.65, z = 1.97, p = 0.0487), and sufentanil vs control (difference -3.08, z = -4.68, p ≤ 0.0001) (S2 Figure 13).

The network showed an overall satisfactory balance between direct and indirect evidence. The intervention comparisons supported by the most robust evidence were buprenorphine vs control (evidence direct proportion 0.54, mean path length 1.87, minimal parallelism 2.41), clonidine vs control (evidence direct proportion 0.81, mean path length 1.62, minimal parallelism 2.25), dexmedetomidine vs control (evidence direct proportion 0.53, mean path length 1.69, minimal parallelism 2.49), fentanyl vs control (evidence direct proportion 0.33, mean path length 1.86, minimal parallelism 4.25) and nalbuphine vs control (evidence direct proportion 0.40, mean path length 1.85, minimal parallelism 3.30). These comparisons were characterised by moderate contributions of direct evidence, moderate mean path lengths, and multiple independent evidence paths, indicating moderate structural support within the network.

Sub-analysis: India country only

We performed a subgroup analysis including only studies conducted in India. According to SUCRA estimates, dexmedetomidine (SUCRA 80.66), and midazolam (SUCRA 76.63) were the interventions with the highest probabilities of ranking among the most effective treatments for reducing pain intensity at 12 hours in this surgical population. However, no intervention demonstrated a statistically or clinically significant effect. (S3 Figures 19-22)

Sub-analysis: arthroscopy only

We performed a subgroup analysis including only studies that evaluated only arthroscopic procedures. The analysis included two interventions (dexmedetomidine and fentanyl). Dexmedetomidine showed the highest probability of ranking among the most effective treatments (SUCRA 89.31) even though its effects were not significant. (S3 Figures 23-24)

Sub-analysis: mixed limb surgeries

We performed a subgroup analysis including only studies evaluating generic lower limb surgical procedures. Morphine (SUCRA 78.09), sufentanil (SUCRA 76.58), and dexmedetomidine (SUCRA 72.38) were the interventions with the highest probabilities of ranking among the most effective treatments. All three interventions demonstrated a statistically significant effect in reducing pain intensity at 12 hours: morphine (MD -1.50, CI -2.93, -0.07), sufentanil (MD -1.41, CI -2.64, -0.18), and dexmedetomidine (MD -1.20, CI -1.76, -0.64). However, these effects did not reach clinical significance. (S3 Figures 25-27)

Sub-analysis: low Rob2

We performed a subgroup analysis including only studies judged to be at low risk of bias. Dexmedetomidine combined with morphine (SUCRA 96.37), and morphine alone (SUCRA 80.01) showed the highest probabilities of being the most effective treatments.

Dexmedetomidine combined with morphine (MD -3.55, CI -6.19, -0.91), and morphine alone (MD -2.03, CI -3.89, -0.17) demonstrated statistically significant effect in reducing pain intensity at 12 hours however, these effects did not reach clinical significance. (S3 Figures 28-31)

Sub-analysis: high or some concerns Rob2

We performed a subgroup analysis including only studies judged at high risk of bias or having some concerns. Morphine (SUCRA 81.54), and sufentanil combined with

dexamethasone (SUCRA 80.47) showed the highest probabilities of being the most effective treatments.

Morphine (MD -1.36, CI -1.95, -0.76) was the only intervention demonstrating a statistically significant effect; however, it did not reach clinical significance. (S3 Figures 32-35)

Model-based network meta-analysis dose response

The model-based network meta-analysis demonstrated a non-linear dose response pattern for both intrathecal adjuvants, morphine and dexmedetomidine. Both agents showed an initial increase in effect followed by a plateau, consistent with a saturating dose-response pattern. Morphine appeared to reach this plateau earlier, suggesting a more rapid attainment of maximal effect, whereas dexmedetomidine exhibited a more gradual and sustained increase in effect across the dose range. (S3 Figure 36)

Postoperative opioid consumption

Postoperative opioid consumption was reported by 28 studies, including 1987 patients and examining 17 interventions. [54,67,68,70,81–83,87,88,97,99,112–114,124,126,143,149,160,161,169,175,180,193,200,206,214,223,224]

Out of the 105 possible comparisons, 47 were direct (S2 Figure 17).

Morphine combined with ketorolac (SUCRA 98.73), clonidine with morphine (SUCRA 94.75), ketorolac alone (SUCRA 81.62), morphine alone (SUCRA 78.30), and diamorphine (SUCRA 75.89) showed the highest probabilities of ranking among the most effective treatments in reducing perioperative opioid consumption (S2 Figure 19). A mean difference of 10 mg of intravenous morphine equivalents was considered clinically relevant, which is equivalent to 30 mg of oral morphine [43].

Compared with control, morphine with ketorolac (MD -75.56; CI -96.06, -55.07), clonidine with morphine (MD -62.82; CI -85.11, -40.53) exhibited the largest effect with a statistically

and clinically significant effect. Ketorolac alone (MD -32.16; CI -53.73, -10.60), morphine alone (MD -26.35; CI -34.31, -18.38), and diamorphine (MD -26.24; CI -47.94, -4.53) also significantly reduced postoperative opioid consumption, even though their effects were not clinically significant (Figure 4).

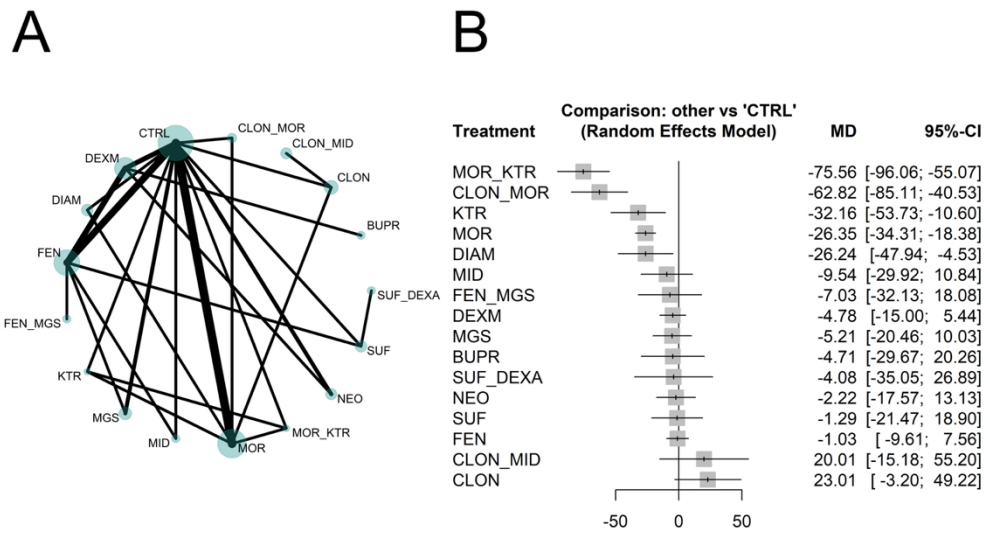


Figure 4. Network of interventions (A) and Forest plot (B) of included interventions versus placebo of the meta-analysis of postoperative opioid consumption at 24 hours.

The effect of sufentanil (MD –1.29, CI -21.47, 18.90), and fentanyl (MD –1.03, CI -9.61, 7.56) were not significant.

The Egger's regression test revealed no evidence of funnel plot asymmetry (t = 0.81, p = 0.4238) (S2 Figure 20). The heterogeneity across studies was extremely high (I^2 = 92.7%; τ^2 = 135.02), indicating substantial variability in effect estimates. Nodesplit analysis under the random effects model identified local inconsistency for several comparisons: clonidine vs control (difference -95.20, z = -3.43, p = 0.0006), clonidine vs morphine (difference -139.09, z = 3.43, p = 0.0006), diamorphine vs control (difference -56.62, z = -2.55, p = 0.0109), diamorphine vs morphine (difference 56.62, z = 2.55, p = 0.0109), and morphine vs control (difference 56.62, z = 2.55, p = 0.0109) (S2 Figure 21).

The network showed an overall satisfactory balance between direct and indirect evidence. The intervention comparisons supported by the most robust evidence were dexmedetomidine vs control (evidence direct proportion 0.59, mean path length 1.47, minimal parallelism 2.78), fentanyl vs control (evidence direct proportion 0.80, mean path length 1.25, minimal parallelism 4.13), magnesium vs control (evidence direct proportion 0.87, mean path length 1.30, minimal parallelism 1.77), morphine vs control (evidence direct proportion 0.96, mean path length 1.03, minimal parallelism 1.48), and neostigmine vs control (evidence direct proportion 0.89, mean path length 1.34, minimal parallelism 1.79). These comparisons were characterised by high contributions of direct evidence, low mean path lengths, and multiple independent evidence paths, indicating moderate structural support within the network.

Sub-analysis: India country only

We performed a subgroup analysis including only studies conducted in India. Only two interventions were evaluated (dexmedetomidine and neostigmine), and dexmedetomidine showed the highest probability of ranking among the most effective treatments (SUCRA 86.62) with a statistically significant effect (MD -2.35, CI -3.84, -0.86). (S3 Figures 37-39)

Sub-analysis: arthroscopy only

The subgroup analysis including only studies evaluating arthroscopy procedures was not performed due to insufficient data

Sub-analysis: mixed limb surgeries

The subgroup analysis including only studies evaluating generic lower limb surgical procedures was not performed due to insufficient data

Sub-analysis: low Rob2

We performed a subgroup analysis including only studies judged to be at low risk of bias. Morphine combined with ketorolac (SUCRA 99.89), ketorolac alone (SUCRA 76.02), and

morphine alone (SUCRA 68.27) showed the highest probability of ranking among the most effective treatments. Morphine combined with ketorolac (MD -73.73, CI -98.60, -48.86) showed a statistically and clinically significant effect. Ketorolac alone (MD -30.33, CI -56.08, -4.57), and morphine alone (MD -22.73, CI -38.67, -6.79) also showed a statistically significant effects, although these did not reach clinical significance. (S3 Figures 40-43)

Sub-analysis: high or some concerns Rob2

We performed a subgroup analysis including only studies judged to be at high risk of bias or with some concerns. Morphine (SUCRA 93.76) and diamorphine (SUCRA 89.29) showed the highest probabilities of ranking among the most effective treatments. Morphine (MD -32.34, CI -45.09, -16.60) showed a statistically and clinically significant effect, whereas diamorphine (MD -30.26, CI -55.25, -5.27) showed only a statistically significant effect without reaching clinical significance. (S3 Figures 44-47)

Model-based network meta-analysis dose response

The model-based network meta-analysis demonstrated a non-linear dose response pattern for both intrathecal adjuvants, morphine and dexmedetomidine. Both agents were associated with a reduction in opioid use as the dose increased, followed by a plateau, consistent with a saturating dose-response pattern. However, the dose–response curves appeared more gradual, with a less pronounced slope across the dose range, suggesting a more progressive and attenuated dose-response effect. (S3 Figure 48)

Duration of motor block

One hundred twenty-five studies allocating 10543 patients to 26 interventions examined the duration of motor block. [48–51,53,56–58,60–62,64–66,68–70,72,73,75,77–80,86,87,90,91,93,95,98–100,102–104,107–109,111–114,116,118–121,126,128,131–133,136–139,141,142,144–148,150,151,153,154,156,158–161,163–165,167,168,170–

174,176–178,182,183,185,187–191,193–205,207–217,220–222,225,229]Of the 325 possible comparisons, 219 were directed (S2 Figure 25).

The treatments with the highest likelihood of being the best for this outcome were morphine (SUCRA 91.99), and sufentanil (SUCRA 83.01) (S2 Figure 27).

We considered an MD of 0.3 hours in motor block duration as the minimal clinically relevant difference. No intervention showed a statistically or clinically significant effect compared with control. In contrast, six interventions significantly prolonged the duration of motor block, in particular dexmedetomidine (MD 1.79; CI 1.52, 2.05), dexmedetomidine combined with epinephrine (MD 2.57; CI 0.90, 4.24), and dexmedetomidine combined with magnesium sulphate (MD 2.62; CI 0.99, 4.24) showed the most conspicuous effect. Differences between these interventions were not significant (Figure 5).

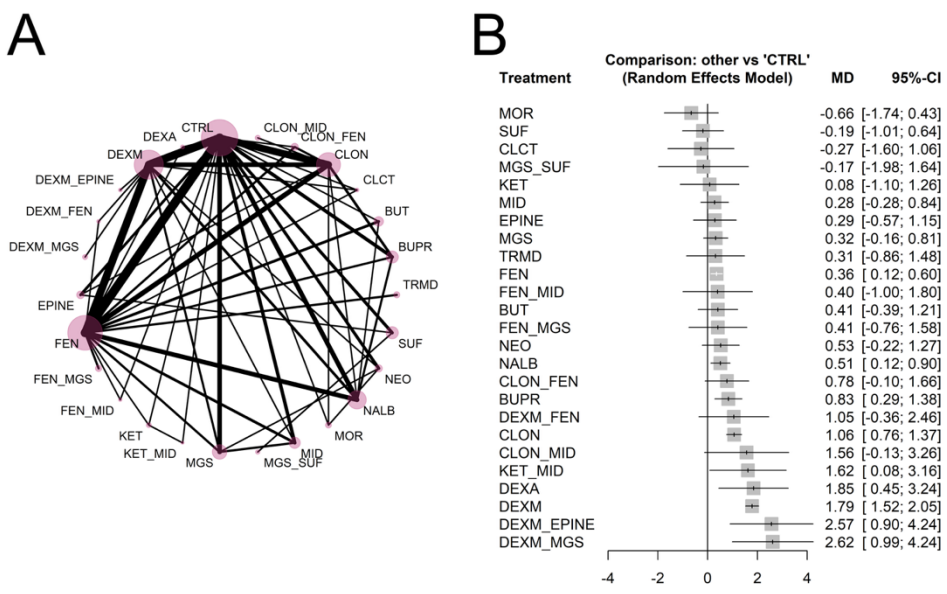


Figure 5. Network of interventions (A) and Forest plot (B) of included interventions versus placebo of the meta-analysis of duration of motor block.

The Egger's test regression detected evidence of funnel plot asymmetry ($t = 2.47$, $p = 0.0149$), suggesting the presence of small-study effects, which may reflect publication bias (S2 Figure 28). The heterogeneity across studies was extremely high ($I^2 = 99.4\%$; $\tau^2 = 0.67$), indicating substantial variability in effect estimates. Nodesplit analysis under the random-

effects model identified local inconsistency for the comparison clonidine vs dexmedetomidine (difference 0.97, z = 2.64, p = 0.0082) (S2 Figure 29).

The network showed an overall satisfactory balance between direct and indirect evidence. The intervention comparisons supported by the most robust evidence were clonidine vs control (evidence direct proportion 0.66, mean path length 1.49, minimal parallelism 4.32), dexmedetomidine vs control (evidence direct proportion 0.66, mean path length 1.47, minimal parallelism 4.46), fentanyl vs control (evidence direct proportion 0.64, mean path length 1.42, minimal parallelism 5.19), magnesium vs control (evidence direct proportion 0.72, mean path length 1.47, minimal parallelism 2.84), nalbuphine vs control (evidence direct proportion 0.47, mean path length 1.72, minimal parallelism 3.52), and neostigmine vs control (evidence direct proportion 0.84, mean path length 1.47, minimal parallelism 3.54). These comparisons were characterised by moderate-to-high contributions from direct evidence, low mean path lengths, and multiple independent evidence paths, indicating moderate structural support within the network.

Sub-analysis: India country only

We performed a subgroup analysis including only studies conducted in India. Morphine (SUCRA 93.56) calcitonin (SUCRA 84.98), and ketamine (SUCRA 74.19) had higher probabilities of ranking among the most effective treatments. No intervention showed a statistically or clinically significant effect compared with control. In contrast, nine interventions significantly prolonged the duration of motor block, with dexmedetomidine (MD 1.89; CI 1.60, 2.17), dexmedetomidine combined with epinephrine (MD 2.67; CI 1.11, 4.23), and dexmedetomidine combined with magnesium sulphate (MD 2.72; CI 1.20, 4.24) showing the most conspicuous effects. (S3 Figures 49-52)

Sub-analysis: arthroscopy only

We performed a subgroup analysis including studies evaluating only arthroscopy procedures. Fentanyl (MD -1.37, CI -2.73, -0.01) was the only treatment that showed a significant effect; however, this did not reach clinical significance. (S3 Figures 53-54)

Sub-analysis: mixed limb surgeries

We performed a subgroup analysis including only studies evaluating generic lower limb surgical procedures. Eight interventions significantly prolonged the duration of motor block, in particular dexamethasone (MD 1.88; CI 0.45, 3.31), dexmedetomidine (MD 1.78; CI 1.48, 2.09), and dexmedetomidine combined with epinephrine (MD 2.57; CI 0.86, 4.27) showed the most conspicuous effect. (S3 Figures 55-57)

Sub-analysis: low Rob2

We performed a subgroup analysis including only studies judged at low risk of bias. Sufentanil (SUCRA 77.66), and magnesium (SUCRA 71.61) had higher probabilities of ranking among the most effective treatments. No intervention demonstrated a significant effect; however, dexmedetomidine significantly prolonged its duration (MD 2.18, CI 1.41, 2.95). (S3 Figures 58-61)

Sub-analysis: high or some concerns Rob2

We performed a subgroup analysis including only studies judged at high risk of bias or having some concerns. Morphine (SUCRA 93.43), calcitonin (SUCRA 84.12), ketamine (SUCRA 73.52), and sufentanil (SUCRA 69.27) had higher probabilities of ranking among the most effective treatments. No intervention showed a significant effect, however, dexmedetomidine (MD 1.70, CI 1.42, 1.99), dexmedetomidine combined with epinephrine (MD 2.48; CI 0.90, 4.07), and dexmedetomidine combined with magnesium sulphate (MD 2.53; CI 0.99, 4.07). significantly prolonged its duration. (S3 Figures 62-65)

Model-based network meta-analysis dose response

The model-based network meta-analysis demonstrated a non-linear dose response pattern for both intrathecal adjuvants, morphine and dexmedetomidine. Dexmedetomidine was associated with an increase in motor block duration as the dose increased, whereas morphine showed a more gradual dose–response curve with a less pronounced slope across the dose range, suggesting a more progressive and attenuated dose-response effect, with a reduction in motor block duration as doses increased. (S3 Figure 66)

Adverse events

The analysis of adverse events revealed that clonidine (RR 2.90, CI 1.63, 5.17; NNH 8, CI 25, 4), dexmedetomidine (RR 5.08, CI 3.78, 6.82; NNH 4, CI 6, 3), and the combination of dexmedetomidine with magnesium (RR 8.47, CI 2.07, 34.61; NNH 2, CI 15, 1) significantly increased the risk of bradycardia compared to placebo or local anaesthetic alone, assuming a baseline risk of 6.3% (126/2008 in the control group) (S2 Figure 33). Clonidine also increased the risk of developing hypotension (RR 1.87, CI 1.28, 2.74; NNH 8, CI 26, 5) assuming a baseline risk of 13.9% (274/1965 in the control group) (S2 Figure 34).

Morphine and neostigmine were associated with a higher incidence of nausea, assuming a baseline risk of 10.2% (150/1476 in the control group), specifically morphine (RR 1.51, CI 1.06, 2.17; NNH 20, CI 164, 9), and neostigmine (RR 3.90, CI 2.28, 6.66; NNH 4, CI 8, 2). Both agents were also associated with an increased risk of vomiting, morphine (RR 1.71, CI 1.06, 2.78; NNH 29, CI 343, 12), and neostigmine (RR 4.13, CI 2.22, 7.69; NNH 7, CI 17, 4) assuming a baseline risk of 4.9% (67/1378 in the control group) (S2 Figure 35-36). Similarly, both interventions increased the risk of postoperative nausea and vomiting (PONV), assuming a baseline risk of 9.9% (86/872 in the control group): morphine (RR 2.04, CI 1.51, 2.76; NNH 10, CI 20, 6), and neostigmine (RR 4.46, CI 2.40, 8.29; NNH 3, CI 8, 2) (S2

Figure 37). Nausea was also more frequent in patients receiving sufentanil (RR 2.04, CI 1.06, 3.94; NNH 10, CI 165, 4) (S2 Figure 35).

Assuming a baseline risk of 1.4% (24/1677 in the control group), several treatments were associated with an increased risk of pruritus, particularly clonidine with morphine (RR 5.06, CI 1.58, 16.24; NNH 17, CI 121, 5), fentanyl (RR 5.22, CI 3.41, 7.99; NNH 17, CI 29, 10), tramadol (RR 5.22, CI 1.47, 18.60; NNH 17, CI 149, 4), sufentanil (RR 6.46, CI 2.77, 15.08; NNH 13, CI 40, 5), fentanyl with magnesium (RR 7.09, CI 2.85, 17.60; NNH 12, CI 38, 4), morphine (RR 7.05, CI 4.42, 11.25; NNH 12, CI 20, 7), sufentanil with dexamethasone (RR 8.08, CI 1.84, 35.49; NNH 10, CI 83, 2), magnesium with sufentanil (RR 8.62, CI 2.39, 31.09; NNH 9, CI 50, 2), and clonidine with fentanyl (RR 9.27, CI 3.55, 24.16; NNH 9, CI 28, 4) (S2 Figure 38).

No intervention showed an increased risk of shivering, urinary retention or respiratory depression (S2 Figure 39-41). Only two studies evaluated the risk of dizziness, and three assessed drowsiness.

Quantitative analysis for sedation was not performed due to insufficient data. The highest rates of sedation were observed with clonidine (48/305, 15,74%), dexmedetomidine (28/205, 13,7%), and morphine (14/153, 9,15%).

The summary of findings of adverse events was reported in Table 2.

INTERVENTIONS	ADVERSE EVENT	Risk ratio [95% Confidence Interval]	Baseline risk	Number needed to harm	Number of participants (studies)
CLONIDINE	BRADYCARDIA	2.9 (1.63, 5.17)	6.27%	8 (25,4)	649 (17 studies)
CLONIDINE	HYPOTENSION	1.87 (1.28, 2.74)	13,94%	8 (26, 5)	625 (17 study)
CLONIDINE_FENTANYL	PRURITUS	9.27 (3.55, 24.16)	1,43%	9 (28, 4)	31 (1 study)
CLONIDINE_MORPHINE	PRURITUS	5.06 (1.58, 16.24)	1,43%	17 (123, 5)	40 (1 study)
DEXMEDETOMIDINE	BRADYCARDIA	5.08 (3.78, 6.82)	6.27%	4 (6, 3)	1345 (36 studies)
DEXMEDETOMIDINE_MAGNESIUM	BRADYCARDIA	8.47 (2.07, 34.61)	6.27%	2 (15,1)	50 (1 study)
FENTANYL	PRURITUS	5.22 (3.41, 7.99)	1,43%	17 (30, 11)	1587 (47 studies)
FENTANYL_MAGNESIUM	PRURITUS	7.09 (2.85, 17.60)	1,43%	12 (38, 5)	80 (2 studies)
MORPHINE	NAUSEA	1.51 (1.06, 2.17)	10,16%	20 (197, 9)	1146 (17 studies)
MORPHINE	VOMITING	1.71 (1.06, 2.78)	4,86%	30 (515, 12)	443 (14 studies)
MORPHINE	PONV	2.03 (1.50, 2.75)	9,86%	10 (20, 6)	370 (9 studies)
MORPHINE	PRURITUS	7.05 (4.42, 11.25)	1,43%	12 (21, 7)	545 (17 studies)
NEOSTIGMINE	NAUSEA	3.9 (2.28, 6.66)	10,16%	4 (8, 2)	125 (5 studies)
NEOSTIGMINE	VOMITING	4.13 (2.22, 7.69)	4,86%	7 (18, 4)	125 (5 studies)
NEOSTIGMINE	PONV	4.45 (2.39, 8.28)	9,86%	3 (8, 2)	125 (5 studies)
SUFENTANIL	NAUSEA	2.04 (1.06, 3.94)	10,16%	10 (165, 4)	265 (4 studies)
SUFENTANIL	PRURITUS	6.46 (2.77, 15.08)	1,43%	13 (40, 5)	385 (8 studies)
SUFENTANIL_DEXAMETHASONE	PRURITUS	8.08 (1.84, 35.49)	1,43%	10 (85, 3)	30 (1 study)
SUFENTANIL_MAGNESIUM	PRURITUS	8.62 (2.39, 31.09)	1,43%	10 (51, 3)	40 (1 study)
TRAMADOL	PRURITUS	5.22 (1.47, 18.60)	1,43%	17 (152, 4)	75 (2 studies)

Table 2. Summary of Finding: the incidence of adverse events

Discussion

Our systematic review with network meta-analysis synthesised evidence from RCTs evaluating the efficacy and safety of intrathecal adjuvants in patients undergoing lower limb orthopaedic surgery. We investigated a broad range of adjuvant classes, including both FDA-

approved and off-label drugs, administered with levobupivacaine, bupivacaine, or ropivacaine to identify the most effective and safe intrathecal strategies for optimising perioperative anaesthesia in this surgical population.

Regarding the primary outcome, several interventions showed both clinically and statistically significant effects compared to control (local anaesthetic with or without placebo). The largest benefits were observed with morphine combined with ketorolac and morphine alone, and these findings were confirmed in subgroup analyses restricted to studies at low risk of bias. Other agents, including diamorphine, clonidine combined with morphine and ketamine combined with midazolam also prolonged the duration of effective analgesia with both clinical and statistical significance. However, these effects were confirmed only in subgroup analysis including studies at high risk of bias or with some concerns according to the Rob2 assessment, suggesting low certainty in these estimates. Moreover, these findings should be interpreted in light of the predefined MCDI, which was statistically derived and may not fully reflect patient-perceived benefit in all clinical contexts. Subgroup analyses restricted to studies conducted in India and to mixed lower limb surgical procedures yielded results consistent with the main analysis, indicating a substantial contribution of these studies. However, given their predominance and single-country origin, these findings suggest that the overall results are largely driven by a relatively homogeneous body of evidence, which may be more susceptible to systematic biases related to study setting, publication practices, and reporting standards, and should therefore be interpreted in light of a potential risk of publication or reporting bias. In contrast, when only arthroscopy procedures, characterised by a milder pain stimulus, were considered, dexmedetomidine emerged as the top ranked treatment, showing both statistically and clinically significant effect. Morphine also significantly reduced pain intensity at 12 hours and postoperative opioid consumption while not prolonging motor block duration. However, the certainty of evidence supporting these

findings was low to very low. As highlighted in a previous meta-analysis evaluating the use of intrathecal adjuvants for caesarean delivery, morphine's favourable performance aligns with its hydrophilic profile, which facilitates greater spinal selectivity and a prolonged residence time in the cerebrospinal fluid. [230] However, in our analysis, morphine was associated with a higher incidence of PONV and pruritus. No clear association with respiratory depression was observed (RR 1.11; CI 0.54, 2.32). These results are consistent with previous literature, for instance a systematic review with meta-analysis exploring the efficacy and safety of intrathecal morphine for analgesia after lower joint arthroplasty, including 29 trials with 1814 patients, found that morphine significantly reduced rest pain score at 8 and 12 hours and increased the incidence of PONV within 24 hours with no substantial increase in the incidence of respiratory depression. [16] Similarly, another meta-analysis of 18 trials evaluating the role of morphine for postoperative analgesia in primary total joint arthroplasty, demonstrated the efficacy of morphine in reducing 24-hour postoperative opioid consumption and prolonging the duration of analgesia. [17] This analysis also reported an increased risk of PONV, but no impact on length of hospital stay, incidence of respiratory depression or urinary retention. Overall, these findings support the efficacy of intrathecal morphine in prolonging the duration of analgesia, with no increasing in motor block. However, this should be weighed against the increased risk of PONV and pruritus.

Although dexmedetomidine significantly extended analgesia duration and reduced pain intensity at 12 hours, this benefit was offset by a marked prolongation of motor block duration, a finding that conflicts with the goal of early mobilisation, on which ERAS protocols are based. Furthermore, dexmedetomidine and the combination of dexmedetomidine with magnesium showed an increased risk of develop bradycardia, rising important concerns about safety. These potential harms should therefore be carefully

considered against the benefits. α_2-adrenergic agonists enhance block characteristics and provide postoperative analgesia by activating receptors in the dorsal horn of the spinal cord. [231] Their activation inhibits nociceptive transmission by modulating potassium and calcium channels. [232] This mechanism reduces the release of excitatory neurotransmitters, including substance P, thereby suppressing nociceptive signalling. [233] Our findings are consistent with a previous meta-analysis exploring the effect of dexmedetomidine as an adjuvant to spinal anaesthesia in orthopaedic surgeries. [13] This analysis, which included 8 trials with 510 patients, found that dexmedetomidine extended motor block duration. Similarly, a systematic review with network meta-analysis of 21 studies with 1460 patients found that dexmedetomidine prolonged postoperative analgesic duration and reduced pain intensity at 24 hours with no effects on the incidence of significant adverse effects. [20] However, our findings raise important safety concerns about these non-opioid adjuvants. The balance between efficacy, i.e. prolonged analgesia, and safety, i.e. increased risk of bradycardia, may be unfavourable for many patients typically undergoing these procedures under spinal anaesthesia, given their comorbidities and concomitant medications. Furthermore, the substantial prolongation of motor block undermines the clinical value of these adjuvants, which contrasts with their efficacy.

Safety considerations must also include the potential for direct neurotoxic effects. Due to limited cerebrospinal fluid redistribution, intrathecally administered agents may expose local tissue to high drug concentrations for prolonged period, increasing the risk of toxicity.[234] Except for morphine, all adjuvants evaluated are administered intrathecally off-label, raising concerns regarding their physicochemical and microbiological stability. [235] Formulation characteristics, including excipients, pH, osmolarity, and endotoxin content may therefore not be optimised for neuraxial use, and can increase the risk of infection, neurotoxicity, or other adverse effects.[235]

Furthermore, manual preparation of intrathecal adjuvant mixtures may result in dosing inaccuracies or contamination, particularly with disinfectants such as chlorhexidine. [236] To minimise these risks, the Institute for Safe Medication Practices (ISMP) recommends using standardised concentrations and commercially pre-prepared syringes. [237]

Our findings suggest that morphine may offer a favourable balance between analgesic efficacy and safety while dexmedetomidine alone also demonstrated significant analgesic effects. However, their safety profiles are less clearly defined, and the efficacy of dexmedetomidine is offset by a marked prolongation of motor block. The overall reliability of the evidence is constrained by several methodological limitations that hinder a clear delineation of efficacy and safety profiles. Substantial heterogeneity was observed across all analyses, indicating considerable variability in treatment effects between studies and limiting the generalisability of the pooled estimates. This level of heterogeneity may also affect the robustness and stability of treatment rankings (SUCRA values), which should therefore be interpreted with caution. This suggests that the observed benefits may vary depending on the clinical context. The heterogeneity is further compounded by the variability in administered doses across studies, which likely acts as an important effect modifier. Consistently, model-based dose-response analyses suggested a non-linear exposure-response relationship for key intrathecal adjuvants (i.e., morphine and dexmedetomidine), thereby further limiting confidence in pooled estimates. In addition, Egger's regression test indicated funnel plot asymmetry in most analyses, raising concerns about small-study effects and potential publication bias. Node-split analysis further identified multiple instances of local inconsistency across key comparisons, including morphine versus control and dexmedetomidine versus control. Collectively, these factors reduced the certainty of the

evidence and preclude strong conclusions regarding the efficacy profile of intrathecal adjuvants. The overall benefit–risk profile of each intervention is summarised in Table 3.

INTERVENTION	BENEFIT (DURATION OF EFFECTIVE ANALGESIA MD [95%CI])	CERTAINTY	RISKS	OVERALL BENEFIT-RISK JUDGMENT
MORPHINE	+ 6.86 h (5.78; 7.94)	⊕⊕◯◯ LOW	NAUSEA RR 1.51 (1.06, 2.17); NNH 20 (197, 9) VOMITING RR 1.71 (1.06, 2.78); NNH 30 (515, 12) PRURITUS RR 7.05 (4.42, 11.25); NNH 12 (21, 7)	Highly effective in prolonging analgesia, but limited by frequent opioid-related adverse events
DEXMEDETOMIDINE	+ 3.56 h (2.89; 4.24)	⊕⊕◯◯ LOW	BRADYCARDIA RR 5.08 (3.78, 6.82); NNH 4 (6, 3) INCREASE MOTOR BLOCK DURATION + 1.79 h (1.52, 2.05)	Effective in prolonging analgesia, but associated with clinically relevant bradycardia and prolonged motor block
CLONIDINE_MORPHINE	+ 7.20 h (3.77; 10.62)	⊕⊕◯◯ LOW	PRURITUS RR 5.06 (1.58, 16.24); NNH 17 (123, 5) BRADYCARDIA RR 2.9 (1.63, 5.17); NNH 8 (25,4) HYPOTENSION RR 1.87 (1.28, 2.74); NNH 8 (26, 5)	Substantial analgesic benefit, but combined cardiovascular and opioid-related adverse effects
FENTANYL	+ 1.57 h (0.98; 2.17)	⊕◯◯◯ VERY LOW	PRURITUS RR 5.22 (3.41, 7.99); NNH 17 (30, 11)	Uncertain benefit with increased risk of pruritus
SUFENTANIL	+ 1.78 h (-1.25; 4.81)	⊕◯◯◯ VERY LOW	PRURITUS RR 6.46 (2.77, 15.08); NNH 13 (40, 5) NAUSEA RR 2.04 (1.06, 3.94); NNH 10 (165, 4)	No clear analgesic benefit and potential adverse effects

Table 3. Benefit-risk: intrathecal adjuvants for spinal anaesthesia in lower limb surgery

Furthermore, our analysis is based on aggregated data encompassing a broad range of lower limb surgical procedures. Although subgroup analyses were conducted for arthroscopy and mixed lower limb surgeries, most of the included RTCs considered this population in a non-stratified manner, without accounting for differences in surgical type or nociceptive intensity. This represents a clinically relevant limitation, as the analgesic efficacy of intrathecal adjuvants may vary depending on the surgical context. In addition, postoperative pain management protocols may have differed substantially across studies, including the use of NSAIDs or paracetamol, potentially introducing performance bias and influencing the outcomes of interest. Finally, the time to first rescue analgesia, considered as primary outcome, is susceptible to variability related to rescue analgesic protocols, patient pain thresholds and institutional practices. These considerations underscore the need for further

well designed clinical and preclinical investigations to better define safe and effective protocols for the use of intrathecal adjuvants.

Strengths and limitations

Our systematic review evaluated the efficacy and safety of a broad range of intrathecal adjuvants, providing robust comparative insights relevant to perioperative practice.

The network meta-analysis approach enabled direct and indirect comparisons among interventions, thereby extending the evidence beyond pairwise comparisons. Despite comprehensive literature screening and the inclusion of numerous eligible RCTs, many studies were characterised by small sample sizes, raising concerns regarding small-study effect and and potential aggregate-data bias. Moreover, the restriction to English-language publications may have introduced a potential language bias.

Considerable heterogeneity in dosing regimens was observed, and no long-term safety data were reported. The analysis relied on aggregate data across lower limb surgeries without stratifications by type or nociceptive intensity. In addition, we did not consider differences in local anaesthetic regimens incorporated within the combinations, as nodes were qualitatively defined by the adjuvant component alone. Despite subgroup analyses and an Emax model-based approach, residual transitivity concerns remain due to variability in doses, surgical procedures, and co-interventions across studies. While the secondary outcomes yielded significant results, the certainty of evidence was generally low. Our GRADE assessment downgraded the strength of our findings, underscoring the need for cautious interpretation.

Conclusions

Overall, considering the body of evidence in a network meta-analysis framework, morphine appears to provide a potentially favourable balance between analgesic efficacy and safety in

lower limb orthopaedic surgery. Dexmedetomidine may be associated with improved analgesic outcomes but with a higher risk of bradycardia and clinically relevant prolongation of motor block. However, the certainty of the evidence is predominantly low to very low, and the estimates are affected by substantial heterogeneity and inconsistency across studies, therefore, these findings should be interpreted with caution. Moreover, clinical interpretation of such findings remains limited by the absence of a formal iterative process of consensus based on such evidence, also taking into account implementation, local feasibility, perioperative management, patients' preferences and characteristics.

Ethics declarations

Competing interests

Andrea Cortegiani is the Editor-in-Chief of the Journal of Anesthesia Analgesia and Critical Care.

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Declarations

Ethics approval and consent to participate: Not applicable. This study used only published, de-identified, aggregate trial data and was conducted in accordance with the Declaration of Helsinki.

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Figure legends

Figure 1:

The primary outcome analysis, the duration of effective analgesia, was assessed using the Confidence in Network Meta-Analysis approach. This approach takes into consideration within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Both direct and indirect evidence were examined separately. Symbols: ⊕ "very low," ⊕⊕ "low," ⊕⊕⊕ "moderate," and ⊕⊕⊕⊕ "high."

Figure 2:

Summary of the findings of the meta-analysis of duration of effective analgesia in hours.

Panel A. The network of interventions, with node sizes proportional to the number of patients allocated to the treatments.

Panel B. Forest plot for pairwise comparisons of included interventions versus placebo or local anaesthesia alone. The effect size is expressed as the mean difference with the 95% CI.

Abbreviations: DIAM, diamorphine; MOR, morphine; CLON_MOR, clonidine + morphine; KET_MID, ketamine + midazolam; DEXM_MGS, dexmedetomidine + magnesium; DEXM_EPINE, dexmedetomidine + epinephrine; BUPR, buprenorphine; DEXM, dexmedetomidine; SUF_DEXA, sufentanil + dexamethasone; FEN_MID, fentanyl + midazolam; CLON_FEN, clonidine + fentanyl; DEXA, dexamethasone; KTR, ketorolac; CLON, clonidine; CLON_MID, clonidine + midazolam; FEN_MGS, fentanyl + magnesium; CLCT, calcitonine; NALB, nalbuphine; MID, midazolam; SUF, sufentanil; NEO, neostigmine; TRDM, tramadol; FEN, fentanyl; KET, ketamine; BUT, butorphanol; MGS, magnesium

Figure 3:

Summary of the findings of the meta-analysis of pain intensity at 12 hours as 0-10 score.

Panel A. The network of interventions, with node sizes proportional to the number of patients allocated to the treatments.

Panel B. Forest plot for pairwise comparisons of included interventions versus placebo or local anaesthesia alone. The effect size is expressed as the mean difference with the 95% CI.

Abbreviations: DEXM_MOR, dexmedetomidine + morphine; MOR, morphine; CLON_MOR, clonidine + morphine; DEXM, dexmedetomidine; DIAM, diamorphine; NEO, neostigmine; BUPR, buprenorphine; SUF_DEXA, sufentanil + dexamethasone; DEXM_FEN, dexmedetomidine + fentanyl; BUT, butorphanol; MID, midazolam; HYD, hydromorphone; NALB, nalbuphine; MGS, magnesium; FEN, fentanyl; CLON, clonidine; SUF, sufentanil

Figure 4:

Summary of the findings of the meta-analysis of the postoperative opioid consumption as oral morphine equivalents.

Panel A. The network of interventions, with node sizes proportional to the number of patients allocated to the treatments.

Panel B. Forest plot for pairwise comparisons of included interventions versus placebo or local anaesthesia alone. The effect size is expressed as the mean difference with the 95% CI.

Abbreviations: CLON_MOR, clonidine + morphine; MOR, morphine; DIAM, diamorphine; KTR, ketorolac; MID, midazolam; FEN_MGS, fentanyl + magnesium; DEXM, dexmedetomidine; MGS, magnesium; BUPR, buprenorphine; SUF_DEXA, sufentanil + dexamethasone; NEO, neostigmine; SUF, sufentanil; FEN, fentanyl; CLON_MID, clonidine + midazolam; CLON, clonidine

Figure 5:

Summary of the findings of the meta-analysis of the duration of motor block in hours.

Panel A. The network of interventions, with node sizes proportional to the number of patients allocated to the treatments.

Panel B. Forest plot for pairwise comparisons of included interventions versus placebo or local anaesthesia alone. The effect size is expressed as the mean difference with the 95% CI.

Abbreviations: MOR, morphine; SUF, sufentanil; CLCT, calcitonin; MGS_SUF, magnesium + sufentanil; KET, ketamine; MID, midazolam; EPINE, epinephrine; MGS, magnesium; TRMD, tramadol; FEN, fentanyl; FEN_MID, fentanyl + midazolam; BUT, butorphanol; FEN_MGS, fentanyl + magnesium; NEO, neostigmine; NALB, nalbuphine; CLON_FEN, clonidine + fentanyl; BUPR, buprenorphine; DEXM_FEN, dexmedetomidine + fentanyl; CLON, clonidine; CLON_MID, clonidine + midazolam; KET_MID, ketamine + midazolam; DEXA, dexamethasone; DEXM, dexmedetomidine; DEXM_EPINE, dexmedetomidine + epinephrine; DEXM_MGS, dexmedetomidine + magnesium;