Systematic Review and/or Meta-analysis

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Efficacy of perioperative dexmedetomidine in postoperative pain and neurocognitive functions in orthopedic surgery: a systematic review and meta-analysis with trial sequential analysis of randomized controlled trials

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Introduction: With an estimated 2.1 million hip and knee replacements performed annually in developed countries, orthopedic surgeries can result in complications such as postoperative pain and cognitive dysfunctions. Dexmedetomidine shows potential for reducing pain and opioid use and improving cognitive outcomes, but its efficacy in orthopedic settings needs further evaluation.

Methods: A comprehensive literature search was performed across electronic databases (e.g., PubMed) up to 1 June 2024 to identify relevant randomized controlled trials (RCTs) investigating the use of dexmedetomidine for orthopedic surgeries. The primary outcomes included visual analog scale (VAS), opioid consumption, incidence of postoperative cognitive dysfunction (POCD), and postoperative delirium (POD). Meta-analysis was conducted using RevMan 5.3 and Stata 16.0, with statistical significance set at $P < 0.05$. Sensitivity analyses, along with trial sequential analysis (TSA), were used to evaluate the robustness of the findings.

Results: The meta-analysis included 59 RCTs with 7713 participants and demonstrated that dexmedetomidine significantly reduced postoperative VAS score (mean difference [MD] –0.50, $P = 0.0003$) and opioid consumption (MD –11.91, $P < 0.0001$) and decreased the incidence of POCD (risk ratio [RR] 0.59, $P = 0.006$) and POD (RR 0.49, $P < 0.0001$). Dexmedetomidine also prolonged motor (MD: 1.70, $P < 0.0001$) and sensory block durations (MD: 1.80, $P < 0.0001$) and delayed the time to first rescue analgesics (MD: 1.51, $P < 0.0001$). TSA and sensitivity analysis confirmed the robustness and reliability of the results, whereas meta-regression revealed no significant effect of variables on primary outcomes.

Conclusion: Our study demonstrates that intravenous dexmedetomidine significantly improved postoperative pain and neurocognitive functions in orthopedic surgery patients.

Keywords: dexmedetomidine, neurocognitive function, orthopedic surgery, pain, POCD, POD

HIGHLIGHTS

- This study demonstrates that perioperative dexmedetomidine significantly decreases postoperative pain scores and reduces opioid consumption in patients undergoing orthopedic surgeries.
- The analysis indicates a notable reduction in the incidence of postoperative cognitive dysfunction and postoperative delirium with the use of dexmedetomidine in orthopedic surgeries.
- Trial sequential analysis favored dexmedetomidine in improving pain management and cognitive functions post-surgery.
- Dexmedetomidine is shown to be an effective drug within Enhanced Recovery After Surgery protocols, contributing to improved recovery outcomes.

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Introduction

Orthopedic surgeries, such as total hip arthroplasty and total knee arthroplasty (TKA), are frequently performed to alleviate pain and improve function in patients with joint disorders, with an estimated 2.1 million hip and knee replacements performed annually in developed countries[1]. Despite their effectiveness in alleviating joint disorders and improving quality of life, these surgeries are associated with significant postoperative complications, including pain, postoperative cognitive dysfunction (POCD), and postoperative delirium (POD)[2]. Inadequate pain management has been identified as a key risk factor in the development of POD and POCD[3-6], which may impede recovery, prolong hospital stays, and increase healthcare costs[7,8].

Postoperative pain management primarily involves pharmacological therapies, such as local anesthetics and opioids[9,10], alongside nonpharmacological methods such as music therapy and back massage[11]. However, the use of opioids has been linked to an increased risk of postoperative complications, including respiratory depression, sedation, postoperative nausea and vomiting, pruritus, difficulty voiding, ileus, and surgical site infections. These complications can lead to delayed hospital discharge[12-14]. Nonpharmacological methods, while beneficial as adjunct therapies, often provide insufficient pain relief when used alone. Thus, there is a critical need for analgesics that effectively manage pain with minimal postoperative complications, potentially reducing POD and POCD.

Dexmedetomidine is a potent, highly selective α2-adrenergic receptor agonist with intrinsic analgesic properties, as well as sedative, anxiolytic, and sympatholytic effects[15,16]. Previous meta-analyses have demonstrated the benefits of intravenous dexmedetomidine in mitigating postoperative pain and reducing opioid consumption in patients undergoing various surgeries, including knee or hip surgery[17,18], neurosurgery[19], and abdominal surgery[20]. The mechanisms involved are yet to be fully elucidated. At the supraspinal level, dexmedetomidine exerts analgesic effects by activating presynaptic α2 receptors in the locus coeruleus, thereby reducing the release of norepinephrine and decreasing descending noradrenergic activity[21,22]. At the spinal level, dexmedetomidine may inhibit pain transmission by activating α2-A and α2-C receptors in the spinal dorsal horn, leading to neuronal hyperpolarization via G protein-mediated potassium channel activation[21,23,24]. These mechanisms are particularly relevant in orthopedic surgery, where postoperative pain often involves both nociceptive and neuropathic components[25].

Considering the analgesic effect of intravenous dexmedetomidine during the perioperative period and the relationship between pain management and the incidence of POCD, dexmedetomidine infusion may also improve postoperative cognitive outcomes. Multiple studies have shown that dexmedetomidine administration may reduce the risk of POCD[26-28], especially in elderly individuals[29-31]. This may be related to the anti-inflammatory effects of dexmedetomidine[32,33], as POCD is thought to be associated with neuroinflammation[34,35]. Dexmedetomidine can decrease the levels of various inflammatory mediators, including interleukin 1β, tumor necrosis factor-α, and NF-κB[30,36], thereby improving memory function and reducing cognitive decline.

Despite growing evidence of the physiological benefits of dexmedetomidine, prior meta-analyses have primarily focused on mixed surgical populations or single types of surgery, such as cardiac and abdominal procedures[20], rather than comprehensively evaluating its impact in orthopedic surgery patients, who represent a high-risk group due to the prevalence of geriatric patients and the complexity of postoperative rehabilitation. Additionally, the impact of intravenous dexmedetomidine on pain relief and the incidence of POCD and POD in a diverse range of orthopedic surgeries, including both joint and spinal procedures, has not been systematically evaluated.

To address these gaps, our study focuses specifically on orthopedic surgery, incorporating a broad range of procedures (e.g., joint, limb, and spinal surgeries) to provide a more comprehensive analysis of dexmedetomidine's effects. Furthermore, we aim to evaluate not only postoperative pain, opioid consumption, POCD, and POD but also secondary outcomes such as sensory and motor block duration, time to first opioid use, and the incidence of adverse events, providing a detailed profile of dexmedetomidine's perioperative effects. By comparing dexmedetomidine to both placebo and active medications, and by including a larger number of studies than previous analyses, we aim to provide robust and clinically relevant conclusions.

Methods

Protocol and registration

This systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Supplemental Digital Contents 1, http://links.lww.com/JS9/D985 and 2, http://links.lww.com/JS9/D986)[37] and the Assessing the Methodological Quality of Systematic Reviews (Supplemental Digital Content 3, http://links.lww.com/JS9/D987)[38] guidelines, ensuring methodological rigor and comprehensive reporting standards. The study was registered in the international open-access Prospective Register of Systematic Reviews.

Literature search

A comprehensive literature search was conducted across PubMed, Embase, Web of Science, Google Scholar, and the Cochrane Library from inception to 1 June 2024 to identify all relevant randomized controlled trials (RCTs) investigating dexmedetomidine in the context of orthopedic surgeries. The search terms included both entry terms and medical descriptors/MeSH terms such as "Orthopaedic procedures," "Acetabuloplasty," "Amputation, surgical," "Arthrodesis," "Arthroplasty," "Arthroscopy," "Bone lengthening" "Bone transplantation," "Cementoplasty," "Diskectomy," "Fracture fixation," "Laminectomy," "Limb salvage," "meniscectomy," "Osteotomy," "Tenotomy," "Dexmedetomidine," and "RCT." The search strategy used in each database is summarized in Supplemental Digital Content 6, http://links.lww.com/JS9/D989.

Study selection and inclusion criteria

Studies satisfying the following criteria were included: (1) population: patients with orthopedic surgeries; (2) intervention: intravenous dexmedetomidine was administered; (3) comparison: placebos (e.g., normal saline), opioids, or standard care were deemed eligible for the control group; (4) outcomes: the visual analog scale (VAS), opioid consumption, and incidence of POCD of POD; and (5) design: RCTs.

The following studies were excluded: (1) case reports, conference abstracts, systematic reviews or meta-analyses, or consensus statements; (2) studies with insufficient data; (3) studies for which the full text was not available; and (4) studies in which dexmedetomidine was not intravenously administered.

Data extraction

Data extraction was conducted by 2 independent reviewers via a piloted and standardized data extraction form. Any disagreements were resolved by mutual consensus. The following data from each included study were retrieved: (1) study characteristics: authors' information, sample size, control drug, dexmedetomidine dose, surgery type, and anesthesia type and (2) outcomes: VAS score within the first 24 hours, opioid consumption, and incidence of POCD or POD; secondary outcomes included the duration of motor block, duration of sensory block, postoperative nausea and vomiting (PONV), time to the first postoperative opioid requirement, and surgery duration; adverse outcomes included bradycardia and hypotension.

Quality assessment

The quality and risk of bias were assessed using the Cochrane risk of bias tool[39]. This quality evaluation system encompasses 7 critical domains for assessing methodological rigor and potential bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Seven domains of bias were categorized as high, unclear, or low risk. Risk of bias graphs were generated using RevMan software (version 5.3).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was employed to systematically evaluate the methodological rigor and credibility of the evidence[40]. The quality of evidence was stratified into 4 hierarchical categories, namely, high, moderate, low, and very low, on the basis of a comprehensive assessment of multiple critical domains. Any disagreements between the 2 reviewers were discussed, and if unresolved, a third reviewer was involved in the discussion until a consensus was reached.

Data synthesis

Meta-analyses were performed using RevMan 5.3 software and Stata 16.0. The mean difference (MD) with 95% confidence intervals (CIs) was used to evaluate continuous data, and the risk ratio (RR) was used for dichotomous data. When units are consistent across studies, the weighted mean difference (WMD) with its 95% CI is recommended; however, in cases of unit heterogeneity or significant value variability, the standardized mean difference (SMD) should be utilized. The P value was calculated and recorded for each outcome measure, with statistical significance defined as $P < 0.05$. A funnel plot focusing on a specific outcome was constructed to evaluate potential publication bias. A sensitivity analysis was conducted by excluding individual studies to assess the impact of each study on the overall conclusions, thereby demonstrating the stability of the results.

Furthermore, to align with clinical needs and explore sources of heterogeneity, subgroup analyses were performed on the basis of the following 3 factors: the type of surgery, including spinal surgery (e.g., cervical or lumbar), joint surgery (e.g., knee or shoulder or hip), and limb surgery; the type of control group, categorized as either saline or non-saline; and the type of anesthesia, classified as general anesthesia or non-general anesthesia.

To mitigate the potential impact of false-positive outcomes due to multiple testing and the limited data available, trial sequential analysis (TSA) (TSA Viewer version 0.9.5.10 Beta) was carried out to assess the robustness of the cumulative evidence regarding the primary outcomes. We calculated the required information size (RIS) adjusted for our meta-analysis, along with the trial sequential monitoring boundaries (TSMBs), to assess the reliability and conclusiveness of the evidence presented in our meta-analysis[41]. The interaction between the TSA boundary and the cumulative Z-curve was systematically evaluated following the computation of sequential monitoring and requisite information size thresholds. When the cumulative Z-curve intersected the predefined TSA boundary, it signified a statistically robust level of evidence supporting the hypothesized intervention effect, thereby rendering additional investigative efforts potentially superfluous. Alternatively, if the cumulative Z-curve failed to cross the TSA boundary, it indicated an inadequate evidential foundation to formulate definitive conclusions with sufficient scientific confidence. We conducted TSA calculations with a type-1 error α of 5% and a predefined power $(1 - \beta)$ of 80%, while other data were derived from the average incidence in all included studies or those with a low risk of bias[40,42,43].

Results

Study selection

This comprehensive systematic literature search was conducted across multiple databases, including PubMed, Embase, Web of Science, Google Scholar, and the Cochrane Library, initially identifying 1429 potentially relevant articles (Fig. 1). Following the removal of 371 duplicate entries, screening of the remaining 958 titles and abstracts revealed 99 potentially eligible articles. Subsequent full-text review of these articles led to the exclusion of 40 studies on the basis of predefined criteria: insufficient data accessibility (n = 18), review articles (n = 12), non-intravenous administration routes (n = 4), conference abstracts (n = 4), and case reports (n = 2). Ultimately, a total of 59 RCTs with 7713 participants were included in this systematic review and meta-analysis[44-102].

Characteristics of the studies

The characteristics of the 59 RCTs included in our meta-analysis are presented in Table 1. The included RCTs demonstrated substantial variability in participant counts, encompassing a spectrum from 30 to 732 individuals. The control drugs included clonidine, saline, placebo, fentanyl, ketorolac, midazolam, morphine, propofol, ketamine, lidocaine, acetaminophen, and propacetamol. Across all the RCTs, the loading dose varied between 0.2 and 2 μg/kg, while the infusion rate ranged from 0.1 to 0.7 μg/kg/h. A total of 27 of the 59 RCTs applied general anesthesia[46,53,54,57-59,62,63,65-68,70,71,73-75,79-81,83,90-92,94,95,99], and the remaining RCTs employed non-general anesthesia, including spinal anesthesia[47-50,52,56,64,69,72,77,78,82,85,87,100-102], peripheral neural block[93], lumbosacral plexus block[76], paravertebral block[76], brachial plexus block[60,61,88], quadruple nerve block[51], interscalene blocks[86], sciatic nerve block[96,97], femoral nerve block[55,96,97], and local infiltration[84,98]. Several RCTs have explored the use of

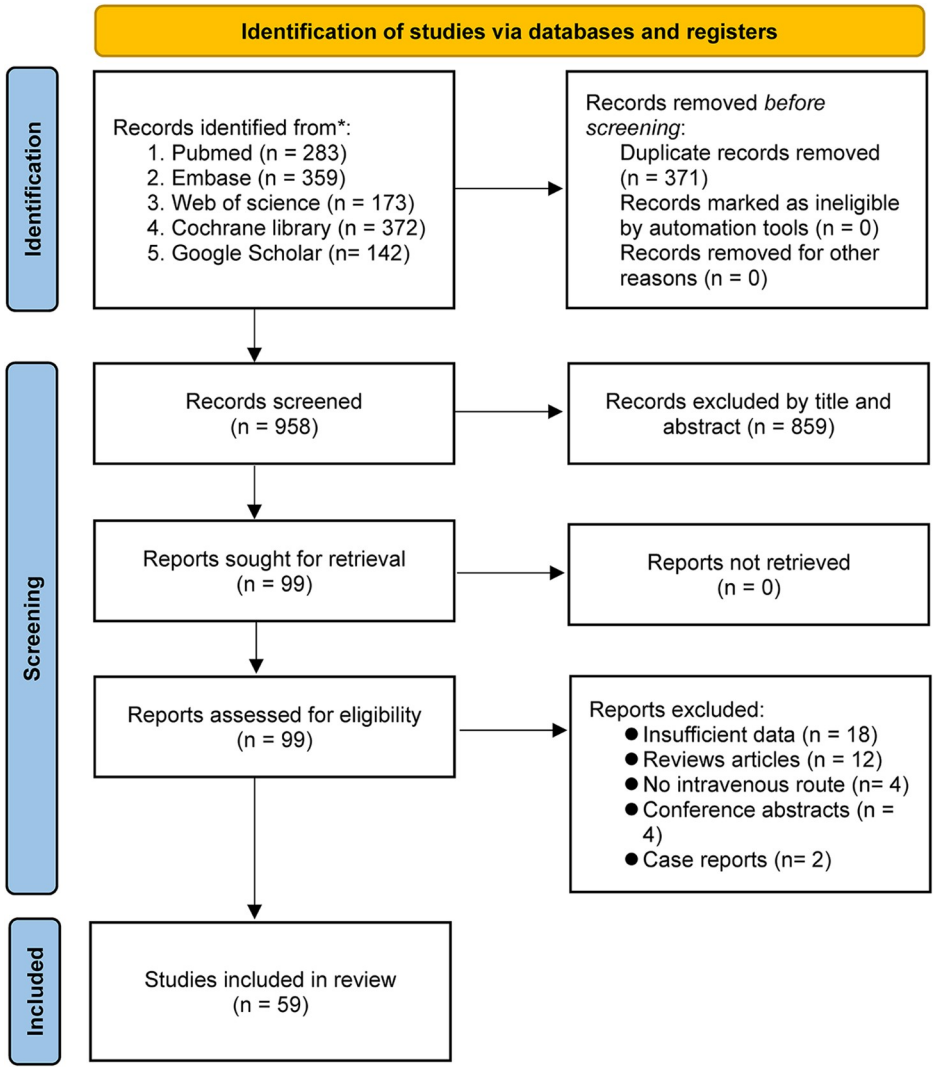


Figure 1. Flowchart for inclusion and exclusion of studies.

dexmedetomidine in spine surgeries, such as laminectomy[57,79,92], vertebral osteotomy[58], anterior cervical discectomy and fusion[63,90], lumbar discectomy[81,84,98], and other spinal procedures[80,91]. Additionally, other RCTs have investigated its application in knee[47,49-51,55,56,65, 72,73,77,82,94,95,100], shoulder[46,59,66,67,70,71,74,86], and hip surgeries[48, 72,75,76,101], as well as in surgeries involving the lower limbs[44,45,64,68,78,85,87,89,93,96,97], upper extremities[53,60,61,83,88], ankles[69], and mixed surgery[52,54,62,99,102].

Risk of bias assessment

The comprehensive bias risk assessment of the included studies revealed an overall low risk (Figs 2 and 3). The randomization process demonstrated robust methodology, with 56 out of 59 studies exhibiting a low risk of bias, whereas the remaining studies were categorized as unclear due to insufficient documentation of random sequence generation[53,88,91]. Allocation concealment analysis indicated that 43 RCTs demonstrated low bias risk, with 15 RCTs presenting an unclear risk[49,56,57,61,62,64,68,70,71,78-80,98,99,102] and 1 RCT classified as high risk due to suboptimal allocation concealment protocols[82]. The performance bias evaluation revealed that 50 RCTs had a low risk of bias, whereas 9 RCTs were deemed unclear secondary to incomplete blinding procedure documentation[46-48,53,64,70,76,95,100]. Detection bias assessment revealed minimal uncertainty, with only 2 of 59 RCTs exhibiting an unclear risk of bias related to outcome assessment blinding[72,79]. Attrition bias analysis indicated that 7 RCTs had an unclear risk due to ambiguous missing data handling[56,57,59,66,73,76,97], whereas 52 RCTs maintained a low bias risk. With respect to reporting bias, 22 RCTs demonstrated low risk, whereas 37 RCTs were classified as unclear, primarily stemming from insufficient elaboration on selective outcome reporting evaluation methodologies[44-49,51-54,56-59,63-66,68,70,71,76,78-82,84-92,96].

Outcomes

Primary outcomes: VAS score within the first 24 hours, opioid consumption, incidence of POCD and POD

The meta-analysis revealed that dexmedetomidine was significantly associated with reduced VAS scores within the first 24 hours (WMD −0.50; 95% CI −0.77 to −0.23, P = 0.0003,

Table 1

Characteristics of the included studies.

Studies (year)	Country	Sample size (Dex/control)	Control drug	Dexmedetomidine dose		Surgery type	Anesthesia type
				Loading dose (μg/kg)	Infusion rate (μg/kg/h)		
Park et al (2018)[82]	Korea	20/20	Midazolam	1	0.5	TKA	Spinal anesthesia
Sirivanasandha et al (2018)[90]	Thailand	49/47	Saline	0.5	0.5	ACDF	General anesthesia
Wang et al (2023)[93]	China	88/88	Midazolam	None	1.5	Below-knee orthopedic surgery	PNB
Shin et al (2023)[87]	Korea	366/366	Propofol	1	0.1-0.5	Lower extremity surgery	Spinal anesthesia
Reddy et al (2013)[85]	India	25/25	Clonidine, saline	0.5	None	Lower limb surgery	Spinal anesthesia
Mei et al (2018)[76]	China	148/148	Propofol	0.8-1.0	0.1-0.5	Total hip arthroplasty	LSPB and PVB
Ozkose et al (2006)[81]	Turkey	20/20	Saline	1	0.2	Lumbar discectomy	General anesthesia
Li et al (2019)[72]	China	55/55/54	Propofol, midazolam	Not reported	Not reported	Hip or knee arthroplasty	Spinal anesthesia
Xuan et al (2018)[95]	China	227/226	Saline	None	0.1	Joint replacement surgery	General anesthesia
Lu et al (2017)[74]	China	75/76	Saline	None	0.06	Shoulder arthroscopy	General anesthesia
Naik et al (2016)[80]	Virginia	63/68	Saline	1	0.5	Multilevel spine surgery	General anesthesia
Zhao et al (2023)[100]	China	40/42	Saline	0.5	0.5	Joint replacement surgery	CSEA
Ying et al (2021)[97]	China	40/40	Saline	0.8	0.2	Lower extremity surgery	SNB and FNB
Zhu et al (2021)[102]	China	95/92	Saline	1	0.5	Orthopedic surgery	Epidural anesthesia
Zhang et al (2022)[98]	China	30/30	Saline	1	0.5	PELD	LI
Zhu et al (2023)[101]	China	109/110	Propofol	0.3	0.2-0.7	Hip fracture surgery	Spinal anesthesia
Peng et al (2016)[84]	China	30/30	Midazolam	0.5	0.5	Lumbar disk surgery	LI
Turgut et al (2008)[92]	Turkey	25/25	Fentanyl	0.6	0.2 increased by 0.1	Lumbar laminectomy	General anesthesia
Liu et al (2016)[73]	China	39/40, 60/58	Saline	None	0.2-0.4	Joint replacement surgery	General anesthesia
Lv et al (2022)[75]	China	152/157	Saline	None	0.1	Total hip joint replacement	General anesthesia
Xiao et al (2022)[94]	China	44/43	Saline	0.6	0.2-0.4	TKA	General anesthesia
Yekta et al (2015)[96]	Turkey	20/20	Propofol	1	0.5	Lower limb surgery	SNB and FNB
Song et al (2016)[91]	Korea	53/52	Saline	0.5	0.2	Lumbar spinal surgery	General anesthesia
Zhao et al (2016)[99]	China	26/25	Ringer solution	1	0.4	Multiple-fracture surgery	General anesthesia
Parween et al (2023)[83]	India	40/40	Paracetamol	Not reported	None	Upper limb surgery	General anesthesia
Singapura et al (2016)[88]	India	35/35	Saline	1	None	Upper limb surgery	BPB
Modir et al (2022)[78]	Iran	35/35/35/35	Keta, Lido, Aceta	Not reported	Not reported	Tibia fracture surgery	Spinal anesthesia
Mei et al (2020)[77]	China	183/183	Propofol	0.8-1.0	0.1-0.5	Total knee hip arthroplasty	Spinal anesthesia
Singhal et al (2024)[89]	India	45/45	Saline	0.7	None	Lower limb surgery	Subarachnoid block
Mottaghi et al (2021)[79]	Iran	25/26	Saline	0.6	0.4	Lumbar laminectomy	General anesthesia
Rodrigues et al (2021)[86]	Canada	66/65	Saline	Not reported	Not reported	AASS	ISB
Abhishek et al (2020)[44]	Indian	50/50	Saline	1	0.3	Lower limb surgery	Subarachnoid block
Agrawal et al (2016)[45]	Indian	40/40/40	Clonidine, saline	1	0.3	Lower limb surgery	Spinal anesthesia
Albrecht et al (2023)[46]	France	60/62	Saline	1	None	ARCR	General anesthesia
AlOweidi et al (2011)[47]	Amman	25/25/25	Propofol, saline	1	0.2-0.5	Total knee replacement	Spinal anesthesia
Alshawadfy et al (2022)[48]	Egypt	30/30	Saline	0.5	None	Hip arthroplasty	Spinal anesthesia
Breebaart et al (2021)[49]	Belgium	43/43	Saline	0.5	None	Knee arthroscopy	Spinal anesthesia
Chan et al (2016)[50]	Canada	20/20	Saline	0.5	0.5	TKA	Spinal anesthesia
Chassery et al (2021)[51]	France	45/45	Saline	2	None	TKA	QNB
Contractor et al (2016)[52]	Indian	50/50	Saline	1	0.5	Orthopedic surgery	Spinal anesthesia
Dolatabadi et al (2018)[53]	Iran	40/40	Midazolam	1	None	DRFR	General anesthesia
Dong Jun et al (2015)[54]	Korean	30/30	Saline	None	0.4	Orthopedic surgery	General anesthesia
Gao et al (2022)[55]	China	47/48	Saline	1	0.4	TKA	LI and FNB
Gómez-Vázquez et al (2007)[56]	Mexico	15/15	Propacetamol	1	0.3	Arthroscopic knee surgery	Spinal anesthesia
Gunes et al (2008)[57]	Turkey	32/32	Morphine	Not reported	Not reported	Laminectomy	General anesthesia
He et al (2018)[58]	China	30/30/30	Midazolam, saline	0.5	0.4	Vertebral osteotomy	General anesthesia
Helwa et al (2024)[59]	Egypt	70/70	Saline	None	0.6	Arthroscopic shoulder surgery	General anesthesia
Hong et al (2019)[60]	Korea	49/47	Midazolam	1	0.6	Upper extremity surgery	BPB
Hong et al (2021)[61]	Korea	29/27, 29/26	Midazolam	1	0.4	Upper extremity surgery	BPB
Hong et al (2021)[62]	China	351/347	Saline	Not reported	Not reported	Orthopedic surgery	General anesthesia
Jain et al (2019)[63]	India	32/32	Saline	1	0.2	ACDF	General anesthesia

(*Continues*)

Table 1
(Continued).

Studies (year)	Country	Sample size (Dex/control)	Control drug	Dexmedetomidine dose		Surgery type	Anesthesia type
				Loading dose (μg/kg)	Infusion rate (μg/kg/h)		
Javahertalab et al (2020)[64]	Iran	40/40/40	Clonidine, saline	0.2	0.1	Lower limb surgery	Spinal anesthesia
Jin et al (2021)[65]	China	31/30	Saline	0.5	None	TKA	General anesthesia
Kang et al (2017)[66]	Korea	18, 18, 18/18	Saline	0.5, 1, 2	None	Arthroscopic shoulder surgery	General anesthesia
Kang et al (2019)[67]	Korea	22/22	Saline	1	None	Arthroscopic shoulder surgery	General anesthesia
Kaur et al (2016)[68]	India	50/50	Ketorolac	0.5	None	Lower limb surgery	General anesthesia
Kim et al (2019)[69]	Korea	22/21	Propofol	1	0.2–0.7	Ankle surgery	Spinal anesthesia
Kim et al (2022)[70]	Korea	40/38	Saline	None	0.6	Arthroscopic shoulder surgery	General anesthesia
Lee et al (2024)[71]	Korea	45/45	Saline	2	0.5	Arthroscopic shoulder surgery	General anesthesia

Abbreviations: AASS, ambulatory arthroscopic shoulder surgery; ACDF, anterior cervical discectomy and fusion surgery; Aceta, acetaminophen; ARCR, arthroscopic rotator cuff repair; BPB, brachial plexus block; CSEA, combined spinal-epidural anesthesia; DRFR, Distal Radius Fractures Reduction; FNB, femoral nerve block; ISB, Interscalene blocks; Keta: ketamine; LI, local infiltration; Lido, lidocaine; LSPB, lumbosacral plexus block; PELD, percutaneous endoscopic lumbar discectomy; PNB, peripheral neural block; PVB, paravertebral block; QNB, quadruple nerve block; SNB, sciatic nerve block; TKA, total knee arthroplasty.

2881 participants, I^2 = 92%; Fig. 4a). Additionally, patients receiving dexmedetomidine exhibited a significant decrease in opioid consumption (WMD −11.91; 95% CI −16.73 to −7.09; P < 0.00001, I^2 = 97%, 2667 participants; Fig. 5a). Dexmedetomidine significantly decreased the incidence of POCD (RR 0.59; 95% CI 0.41 to 0.86, P = 0.006, I^2 = 39%, 742 participants; Fig. 6a). Furthermore, with respect to the incidence of POD, dexmedetomidine showed a pronounced benefit (RR 0.49; 95% CI 0.41 to 0.59, P < 0.00001, I^2 = 0%, 3486 participants; Fig. 7a). Encouragingly, in relation to the TSA results for all primary outcomes, the Z-curves of the TSA models reached the RIS and crossed the TSMB, thereby indicating robust evidence for the anticipated intervention effect (Figs 4b, 5b, 6b, and 7b). Regarding publication bias, the funnel plot for evaluating publication bias regarding VAS score within the first 24 hours (P = 0.398), opioid consumption (P = 0.877), incidence of POCD (P = 0.188), and incidence of POD (P = 0.987) appeared nearly symmetrical, indicating a low level of publication bias (Supplementary Fig. 1, http://links.lww.com/JS9/D988; Supplemental Digital Content 4. http://links.lww.com/JS9/D988).

The secondary outcomes included the duration of motor block, duration of sensory block, PONV, time to the first postoperative opioid requirement, and surgery duration

Participants administered intravenous dexmedetomidine demonstrated significantly prolonged motor block duration compared to the control group (SMD: 1.70, 95% CI: 1.11 to 2.29, P < 0.0001, I^2 = 95%, 1361 participants) (Supplementary Fig. 2, http://links.lww.com/JS9/D988; Supplemental Digital Content 4, http://links.lww.com/JS9/D988). Correspondingly, the sensory block duration was also substantially extended in the dexmedetomidine group (SMD: 1.80, 95% CI: 1.08 to 2.52, P < 0.0001, I^2 = 96%, 1239 participants) (Supplementary Fig. 3, http://links.lww.com/JS9/D988; Supplemental Digital Content 4, http://links.lww.com/JS9/D988). Moreover, dexmedetomidine administration was associated with a reduced incidence of PONV (RR 0.70; 95% CI 0.57 to 0.86, P < 0.0001, I^2 = 8%, 451 participants) (Supplementary Fig. 4, http://links.lww.com/JS9/D988; Supplemental Digital Content 4. http://links.lww.com/JS9/D988). The dexmedetomidine group additionally exhibited a delayed time to first postoperative opioid requirement (SMD: 1.51, 95% CI: 0.88 to 2.14,

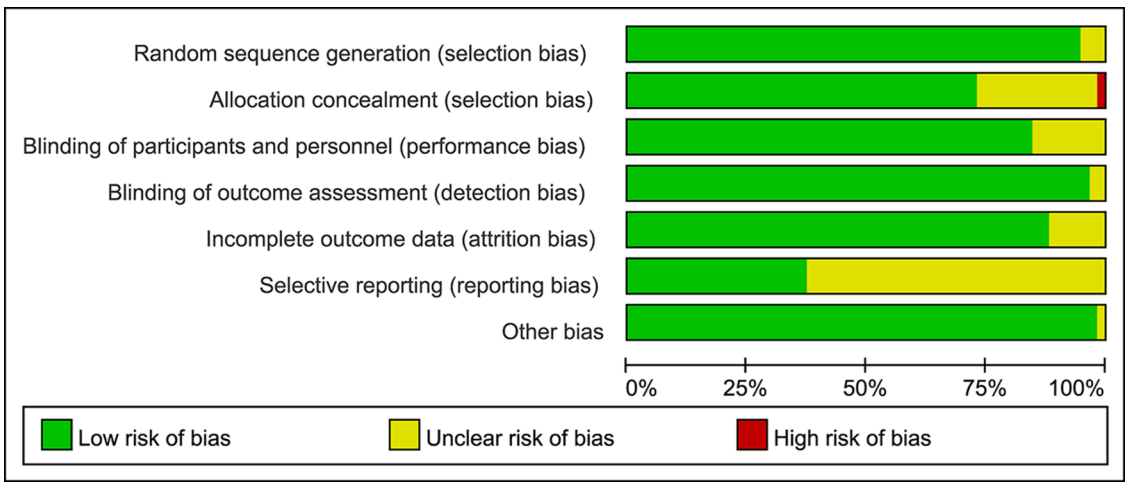


Figure 2. Risk of bias summary.

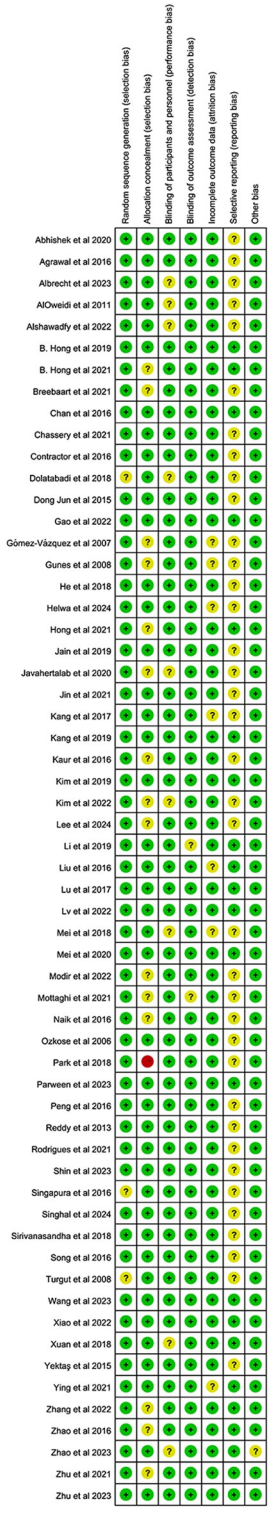


Figure 3. Risk of bias graph.

$P < 0.00001$, $I^2 = 96\%$, 1582 participants) (Supplementary Fig. 5, http://links.lww.com/JS9/D988; Supplemental Digital Content 4. http://links.lww.com/JS9/D988). No statistically significant differences were observed in surgical procedure duration (SMD: 0.04, 95% CI: −0.04 to 0.11, $P = 0.33$, $I^2 = 48\%$, 6687 participants) (Supplementary Fig. 6, http://links.lww.com/JS9/D988; Supplemental Digital Content 4, http://links.lww.com/JS9/D988).

Adverse outcomes: bradycardia and hypotension

The participants who were administered intravenous dexmedetomidine presented a greater incidence of bradycardia than did those who did not receive it (RR 1.59; 95% CI 1.22 to 2.07, $P = 0.0006$, $I^2 = 2\%$, 2520 participants) (Supplementary Fig. 7, http://links.lww.com/JS9/D988; Supplemental Digital Content 4, http://links.lww.com/JS9/D988). In addition, intravenous administration of dexmedetomidine was associated with a significantly greater incidence of hypotension (RR 1.44; 95% CI 1.09 to 1.92, $P = 0.001$, $I^2 = 56\%$, 2863 participants) (Supplementary Fig. 8, http://links.lww.com/JS9/D988; Supplemental Digital Content 4, http://links.lww.com/JS9/D988).

Sensitivity analysis

The sensitivity analysis revealed that omitting any study had a relatively low influence on the overall combined estimates (Supplementary Tables 1-11, http://links.lww.com/JS9/D989; Supplemental Digital Content 5, http://links.lww.com/JS9/D989), which increased the reliability of the conclusion.

Meta-regression analysis

The meta-regression analysis indicated that there was no significant association between the dosage of intravenous dexmedetomidine infusion and its positive impact on the VAS score within the first 24 hours (coefficient: −0.65, $P = 0.523$), opioid consumption (coefficient: −1.18, $P = 0.258$), the incidence of POCD (coefficient: 0.06, $P = 0.953$), or POD (coefficient: 0.37, $P = 0.723$); Fig. 8

Subgroup analysis

The subgroup analysis of the primary outcome is presented in Table 2. Given the scarcity of literature on the incidence of POCD, with only 7 studies available, we refrained from conducting a subgroup analysis on this particular metric. Subgroup analysis on the basis of the type of surgery (spinal surgery vs. joint surgery vs. limb surgery), type of control group (saline vs. non-saline), and type of anesthesia (general anesthesia vs. non-general anesthesia) demonstrated that these variables had no significant effect on the heterogeneity of the VAS score, opioid consumption, or incidence of POD.

Certainty of evidence

Table 3 presents a summary of the evidence quality assessed via the GRADE methodology. The quality of evidence for primary outcomes ranged from moderate to high, thereby strengthening the robustness and reliability of the conclusions.

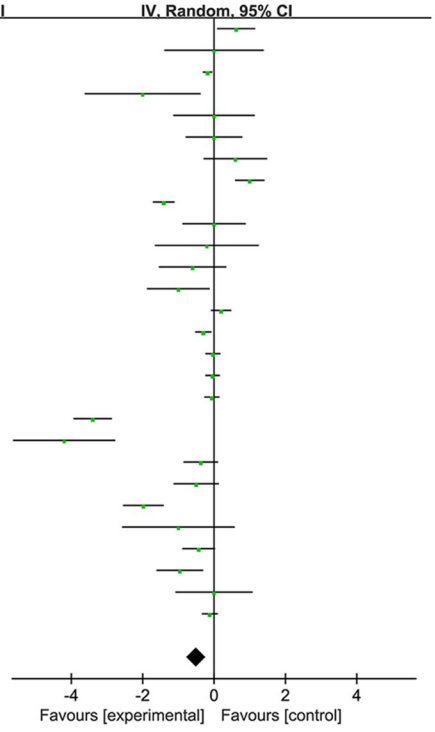
Discussion

This systematic review and meta-analysis, focusing on 59 studies with a total of 7713 patients, demonstrated that perioperative intravenous dexmedetomidine significantly reduced postoperative pain scores, opioid consumption, and the incidence of

A

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
A. A. Dolatabadi 2018	3.47	1.37	40	2.85	1.05	40	4.0%	0.62 [0.09, 1.15]
A. Alshawadfy 2022	4	2.75	30	4	2.75	30	2.1%	0.00 [-1.39, 1.39]
A. M. Helwa 2024	1.63	0.46	70	1.81	0.37	70	4.7%	-0.18 [-0.32, -0.04]
B. Hong 2019	3	2.75	49	5	5	47	1.8%	-2.00 [-3.62, -0.38]
B. Hong 2021	3	2.25	29	3	2.1	27	2.6%	0.00 [-1.14, 1.14]
B. Hong 2021 (2)	1.5	1.5	29	1.5	1.5	26	3.4%	0.00 [-0.79, 0.79]
B. Lee 2024	5	2	45	4.4	2.3	45	3.2%	0.60 [-0.29, 1.49]
C. Chassery 2021	3	1	45	2	1	45	4.3%	1.00 [0.59, 1.41]
C. Gao 2022	3.15	0.59	47	4.56	0.9	48	4.5%	-1.41 [-1.72, -1.10]
E. Albrecht 2023	3	2.5	60	3	2.5	62	3.2%	0.00 [-0.89, 0.89]
I. A. Chan 2016	4.8	2.4	20	5	2.3	20	2.0%	-0.20 [-1.66, 1.26]
K. Dong Jun 2015	5.1	1.6	30	5.7	2.1	30	3.0%	-0.60 [-1.54, 0.34]
Lu, J. 2017	3	2.75	75	4	2.75	76	3.2%	-1.00 [-1.88, -0.12]
Mei, B. 2018	1.9	1.3	148	1.7	1.2	148	4.5%	0.20 [-0.09, 0.49]
Mei, B. 2020	1.9	0.9	183	2.2	1.3	183	4.6%	-0.30 [-0.53, -0.07]
Modir, H. 2022	2.25	0.44	35	2.28	0.45	35	4.6%	-0.03 [-0.24, 0.18]
Modir, H. 2022 (2)	2.25	0.44	35	2.29	0.43	35	4.6%	-0.04 [-0.24, 0.16]
Modir, H. 2024 (3)	2.25	0.44	35	2.31	0.47	35	4.6%	-0.06 [-0.27, 0.15]
Mottaghi, K. 2021	2.4	0.96	25	5.8	1	26	4.0%	-3.40 [-3.94, -2.86]
Ozkose, Z. 2006	1.4	2.1	20	5.6	2.5	20	2.1%	-4.20 [-5.63, -2.77]
Parween, J. 2023	1.23	0.62	40	1.6	1.43	40	4.1%	-0.37 [-0.85, 0.11]
Peng, Ke 2016	1.5	1.25	30	2	1.25	30	3.8%	-0.50 [-1.13, 0.13]
Wang, X. 2023	0.28	0.86	88	2.26	2.59	88	3.9%	-1.98 [-2.55, -1.41]
Xiao, R. 2022	5	3.75	44	6	3.75	43	1.8%	-1.00 [-2.58, 0.58]
Zhang, X. 2022	1.7	0.84	30	2.13	0.97	30	4.2%	-0.43 [-0.89, 0.03]
Zhao, J. N. 2016	1.54	1.19	26	2.5	1.19	25	3.7%	-0.96 [-1.61, -0.31]
Zhao, W. 2023	3	2.5	40	3	2.5	42	2.7%	0.00 [-1.08, 1.08]
Zhu, Y. 2021	3.9	0.74	95	4.02	0.81	92	4.6%	-0.12 [-0.34, 0.10]
Total (95% CI)			**1443**			**1438**	**100.0%**	**-0.50 [-0.77, -0.23]**

Heterogeneity: Tau² = 0.41; Chi² = 339.86, df = 27 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.58 (P = 0.0003)



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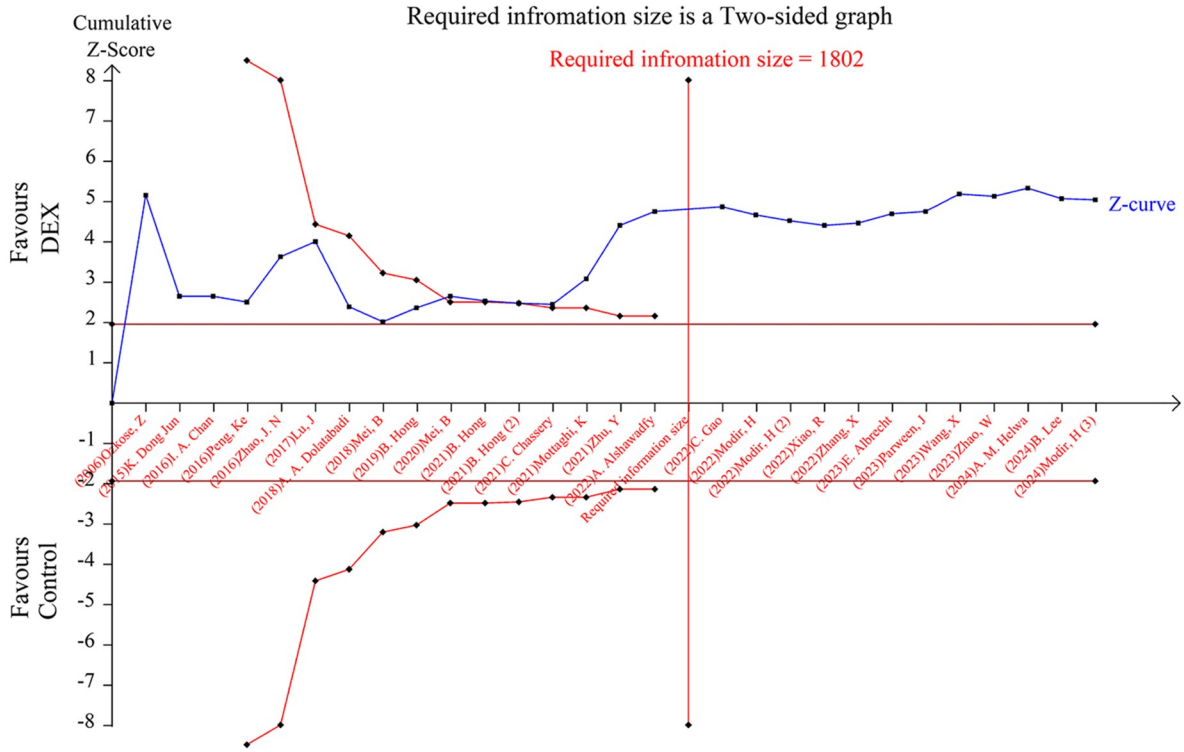

Figure 4. Forest plot showing the association of dexmedetomidine use with VAS score within the first 24 hours. (A) Forest plot showing the association of dexmedetomidine use with VAS score. (B) Trial sequential analysis supporting the substantial evidence regarding intravenous dexmedetomidine's impact on the reduction of VAS. Abbreviation: VAS, visual analog scale.

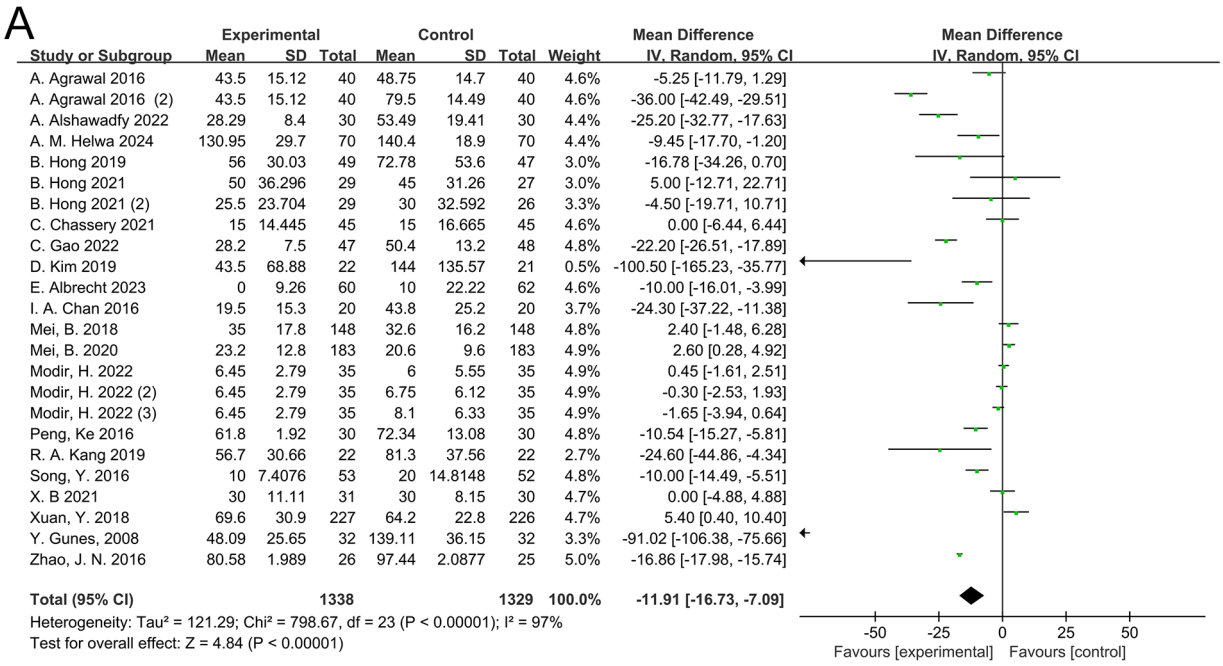

Figure 5. Forest plot showing the association of dexmedetomidine use with opioid consumption. (A) Forest plot showing the association of dexmedetomidine use with opioid consumption. (B) Trial sequential analysis supporting the substantial evidence regarding intravenous dexmedetomidine's impact on the reduction of opioid consumption.

POCD and POD in orthopedic surgery patients. Additionally, dexmedetomidine prolonged the time to first rescue opioid use and the duration of sensory and motor block, while reducing PONV. However, it increased the risk of bradycardia and hypotension.

This study employed TSA to evaluate 4 primary outcomes, including postoperative VAS scores, opioid consumption, POD incidence, and POCD incidence. The TSA results indicated that the cumulative data for all primary outcomes exceeded the RIS, confirming sufficient data to support reliable conclusions.

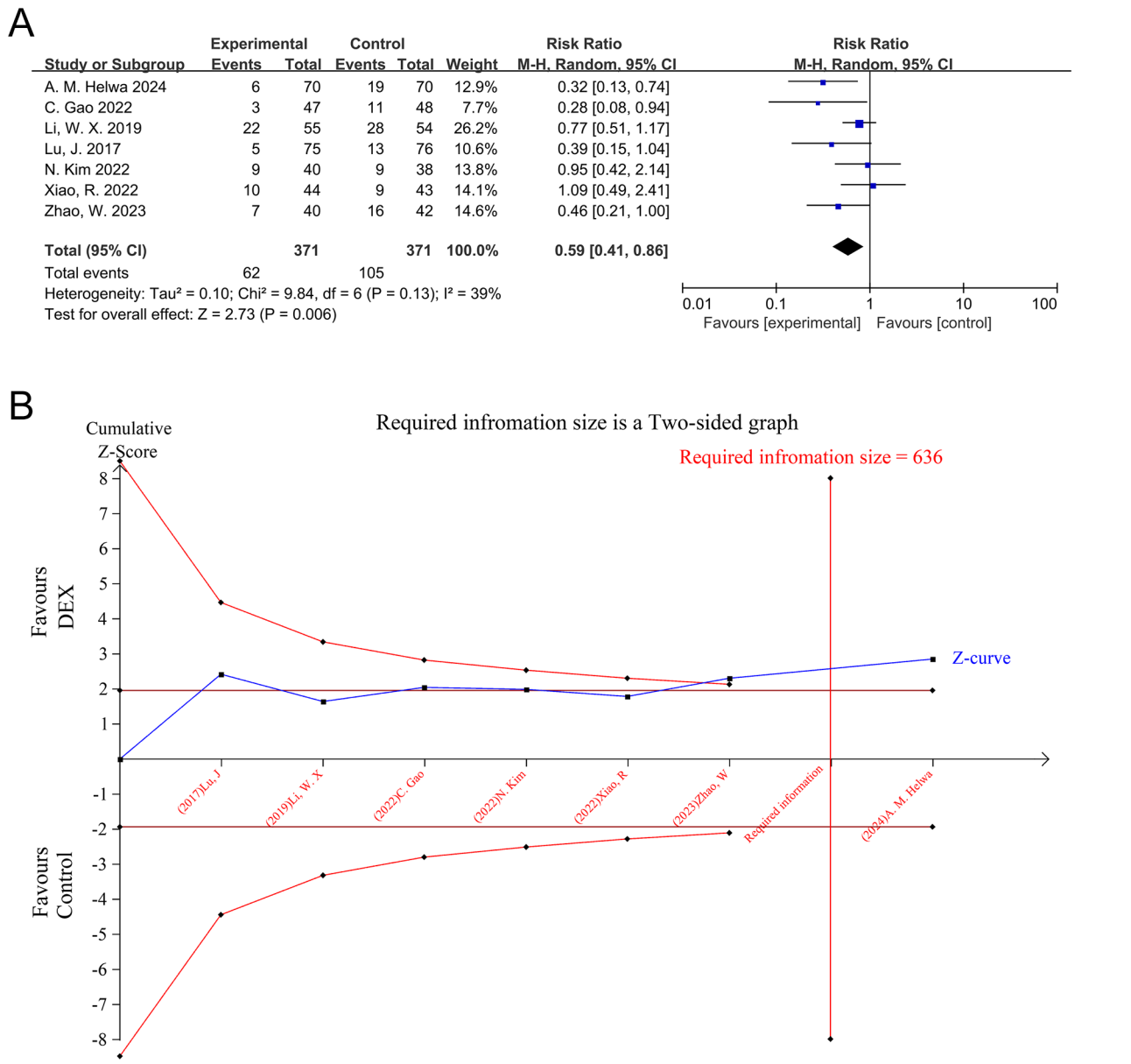

Figure 6. Forest plot showing the association of dexmedetomidine use with incidence of POCD. (A) Forest plot showing the association of dexmedetomidine use with the incidence of POCD. (B) Trial sequential analysis supporting the substantial evidence regarding intravenous dexmedetomidine's impact on the reduction of incidence of POCD. Abbreviation: POCD, postoperative cognitive dysfunction.

Although we performed a meta-regression analysis to assess the effects of the loading dose on the primary outcomes, we did not find a significant dose-dependent relationship, indicating that increasing the loading dose may not lead to better treatment outcomes.

Our findings align with previous meta-analyses showing that intravenous dexmedetomidine reduces postoperative pain scores and opioid consumption in orthopedic surgery patients[17,18]. However, unlike prior studies that were limited to knee or hip arthroplasty, our analysis incorporates various types of orthopedic surgeries, including spinal, joint, and limb procedures, thus broadening the generalizability of our findings. Furthermore, we evaluated not only primary pain-related outcomes but also secondary end points such as sensory and motor block duration, time to first opioid request, and the incidence of adverse events, providing a more comprehensive assessment of dexmedetomidine's perioperative effects. One meta-analysis[103] demonstrated that dexmedetomidine infusion during general anesthesia improved short-term postoperative pain, but the study had high heterogeneity, and subgroup analysis had insufficient studies in some subgroups, potentially compromising the reliability of the conclusions. Another meta-analysis[104] examining the impact of dexmedetomidine on postoperative chronic pain revealed borderline statistical significance, but the study quality was low, and the single-outcome assessment method made the conclusions less robust. Our

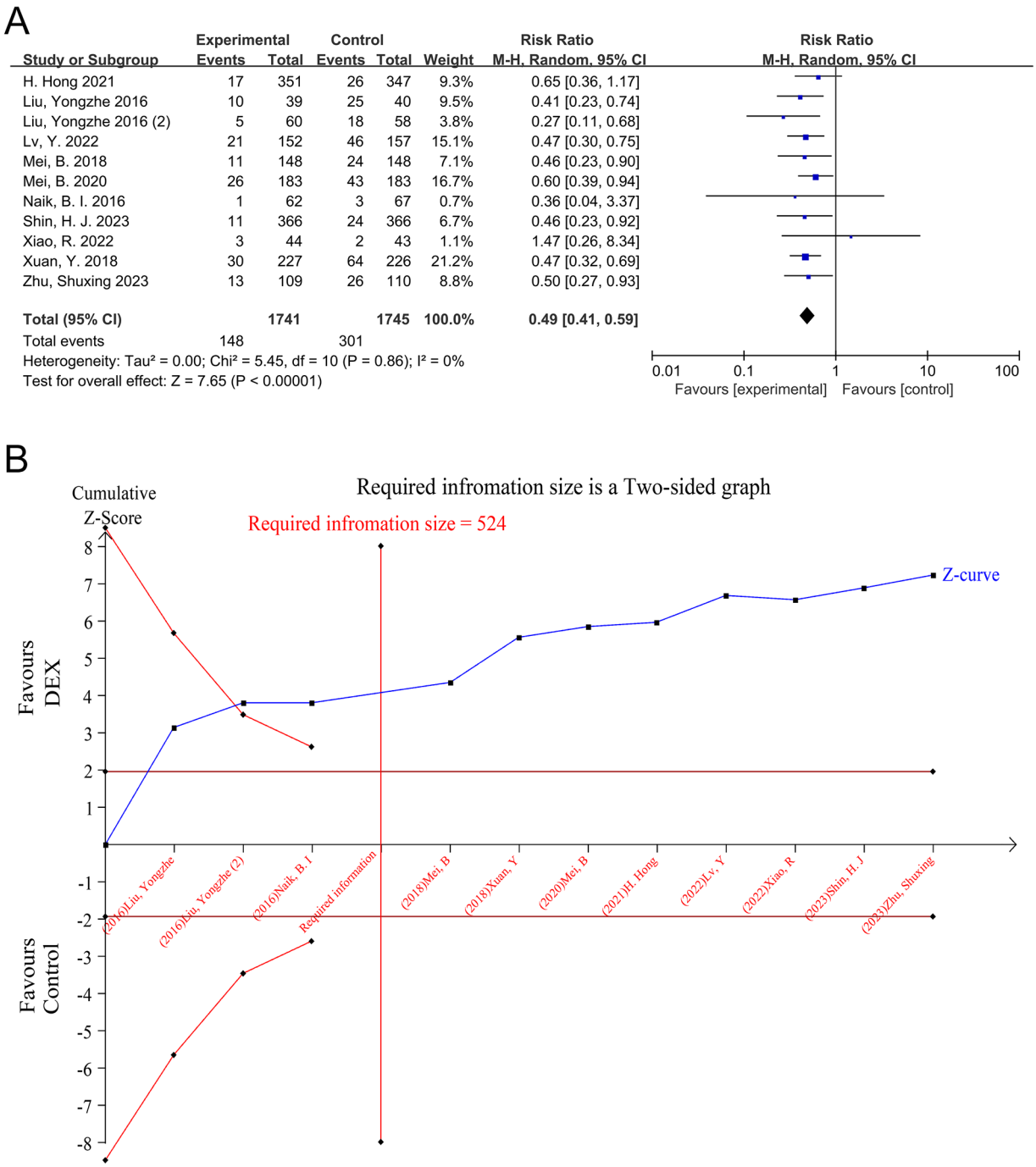

Figure 7. Forest plot showing the association of dexmedetomidine use with incidence of POD. (A) Forest plot showing the association of dexmedetomidine use with incidence of POD. (B) Trial sequential analysis supporting the substantial evidence regarding intravenous dexmedetomidine's impact on the reduction of incidence of POD. Abbreviation: POD, postoperative delirium.

study evaluated the impact of intravenous dexmedetomidine on perioperative pain in orthopedic surgeries, including postoperative VAS scores, opioid consumption, duration of motor and sensory block, and time to first opioid request. These results suggested a positive effect of dexmedetomidine on perioperative pain management. We included almost all types of orthopedic surgeries to incorporate as many studies as possible, which may have increased heterogeneity. However, both the sensitivity analysis and the TSA confirmed the robustness of our conclusions. Furthermore, we conducted subgroup analyses for different types of orthopedic surgeries, including spinal, joint, and limb surgeries, all of which revealed that dexmedetomidine improved postoperative pain outcomes. Notably, when the use of saline as a control was compared,

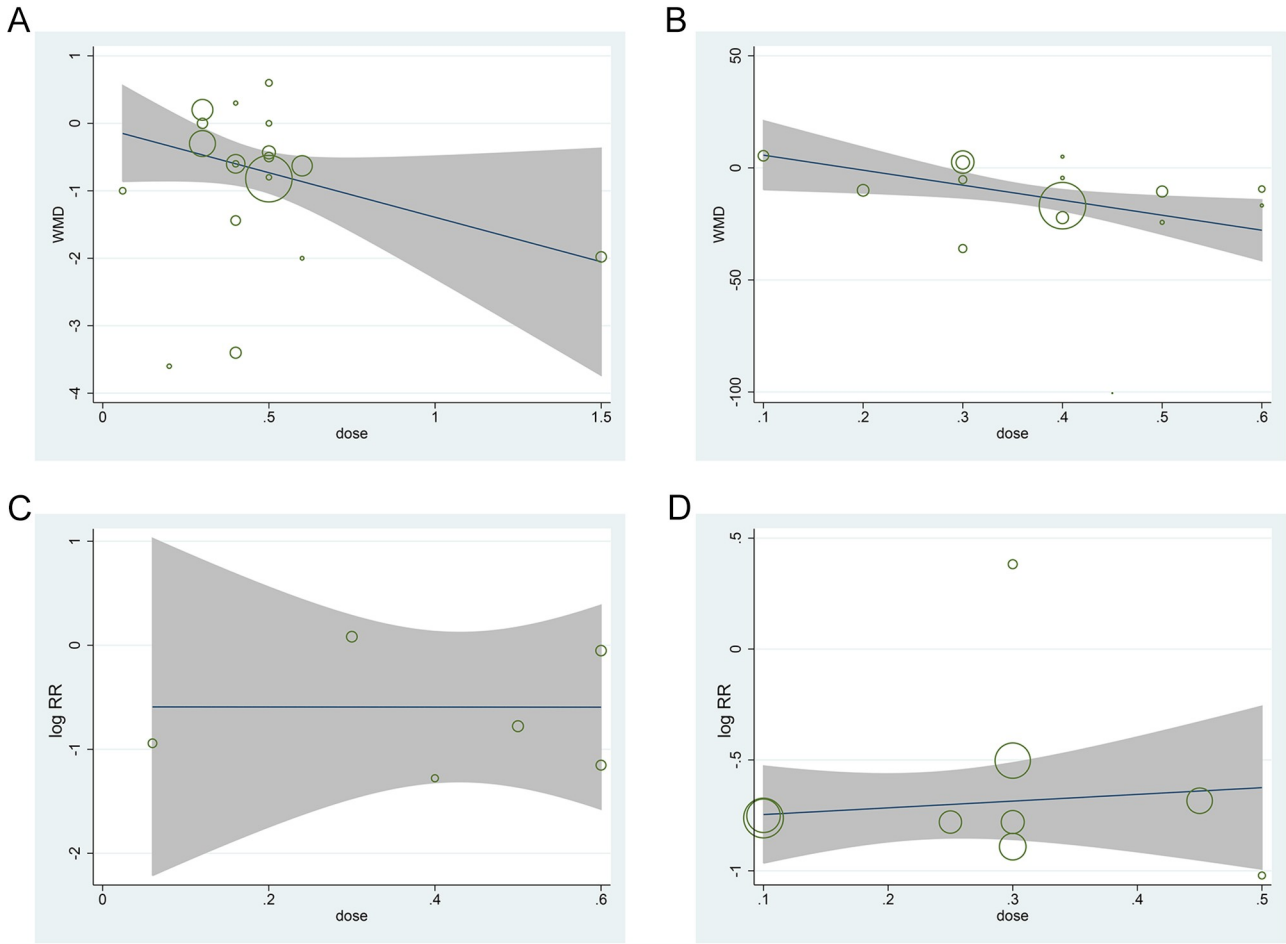

Figure 8. Meta-regression indicating a lack of correlation between infusion dosage and the beneficial effects of intravenous dexmedetomidine on (A) VAS score within the first 24 hours (coefficient: –0.65, $P = 0.523$); (B) opioid consumption (coefficient: –1.18, $P = 0.258$); (C) incidence of POCD (coefficient: 0.06, $P = 0.953$); (D) incidence of POD (coefficient: 0.37, $P = 0.723$). Abbreviations: POCD, postoperative cognitive dysfunction; POD, postoperative delirium; VAS, visual analog scale.

dexmedetomidine demonstrated superior opioid effects, possibly due to its synergistic analgesic interaction with other medications.

POCD and POD were common postoperative cognitive disorders, but their onset and manifestations differ. POD typically occurred within a few days after surgery, with acute, transient cognitive fluctuations, whereas POCD appeared weeks to months after surgery, with more persistent symptoms, including memory and attention deficits[105]. Despite these differences, POD is believed to increase the risk of POCD[106], highlighting the importance of their prevention in perioperative care, particularly in elderly orthopedic surgery patients. Our study demonstrated that intravenous dexmedetomidine could significantly reduce the incidence of both POD and POCD, thereby contributing to rapid recovery and demonstrating the great potential of dexmedetomidine in orthopedic surgery.

Previous studies have shown that dexmedetomidine significantly reduces the incidence of POD and POCD in cardiac and noncardiac surgery patients, especially in elderly patients[26,30,31,107-111]. Orthopedic surgery, which is a major trauma surgery with longer recovery times, places considerable importance on pain management and postoperative care for cognitive function. Our study confirms that intravenous dexmedetomidine improves the incidence of POD and POCD, supported by TSA and sensitivity analyses. While numerous studies have explored dexmedetomidine's neuroprotective effects in non-orthopedic surgeries, fewer have specifically addressed its impact in orthopedic populations, where the incidence of postoperative cognitive complications is especially high, particularly among elderly patients. A previous study[112] reported that dexmedetomidine improved emergence agitation but had no significant effect on POD. This could be due to differences in postoperative management, drug usage protocols, and the complexity of postoperative cognitive disorders. In orthopedic surgery patients, dexmedetomidine may play a crucial role in preventing POD and POCD through its unique analgesic, sedative, anti-inflammatory, and neuroprotective effects. Furthermore, the small sample size in that study and the relatively low POD incidence may have led to insufficient statistical power to detect the effect of dexmedetomidine. Duan et al.[40] performed a comprehensive meta-analysis of dexmedetomidine for POD, but the quality of evidence was not high enough to draw conclusions for all types of surgeries. Moreover, this study did not address the relationship between dexmedetomidine dosage and cognitive function. In our study, we conducted a meta-regression to investigate

Table 2

Results of subgroup analysis based on different standards.

Primary outcome or subgroup	Data sets	Participants	Effect estimate	*P* value	I^2
VAS	28	2881	−0.50 (−0.77, −0.23)[a]	0.0003	92%
Saline	16	1411	−0.65 (−1.15, −0.14)[a]	0.01	94%
Non-saline	12	1470	−0.30 (−0.57, −0.04)[a]	0.03	84%
General anesthesia	12	1318	−0.81 (−1.36, −0.26)[a]	0.004	94%
Non-general anesthesia	16	1563	−0.30 (−0.62, 0.02)[a]	0.07	90%
Spine	6	458	−1.46 (−2.63, −0.29)[a]	0.01	97%
Knee, hip, shoulder	12	1619	−0.17 (−0.57, 0.23)[a]	0.41	90%
Limb	10	804	−0.36 (−0.70, −0.01)[a]	0.04	92%
Opioid consumption	24	2667	−11.91 (−16.73, −7.09)[a]	<0.0001	97%
Saline	13	1410	−17.87 (−27.01, −8.74)[a]	0.0001	96%
Non-saline	11	1257	−5.38 (−11.87, 1.10)[a]	0.10	98%
General anesthesia	8	1040	−17.08 (−26.64, −7.52)[a]	0.0005	97%
Non-general anesthesia	16	1627	−9.24 (−14.13, −4.35)[a]	0.0002	95%
Spine	3	229	−35.30 (−60.90, −9.70)[a]	0.007	98%
Knee, hip, shoulder	11	1767	−8.42 (−15.11, −1.73)[a]	0.01	94%
Limb	10	671	−9.79 (−17.41, −2.18)[a]	0.01	98%
POD	11	3486	0.49 (0.41, 0.59)[b]	<0.0001	0%
Saline	6	1744	0.48 (0.38, 0.60)[b]	<0.0001	0%
Non-saline	5	1742	0.52 (0.39, 0.70)[b]	<0.0001	0%
General anesthesia	6	1744	0.48 (0.38, 0.60)[b]	<0.0001	0%
Non-general anesthesia	5	1742	0.52 (0.39, 0.70)[b]	<0.0001	0%
Spine	1	698	0.65 (0.36, 1.17)[b]	0.15	0%
Knee, hip, shoulder	9	2056	0.48 (0.40, 0.59)[b]	<0.0001	0%
Limb	1	732	0.46 (0.23, 0.92)[b]	0.03	0%

Abbreviations: VAS, visual analog scale; POD, postoperative delirium.
[a]Weighted mean difference.
[b]Risk ratio.

the relationship between the loading dose and outcome measures but did not find a significant dose-response relationship. This suggests that increasing the dose may not lead to more significant effects and could even increase the risk of side effects.

Adverse effects, including bradycardia and hypotension, were more frequent with dexmedetomidine, consistent with previous meta-analyses[108,110]. Our meta-regression results suggest that low doses of dexmedetomidine can achieve adequate analgesic effects and prevent POD and POCD while minimizing the risk of side effects.

There are several limitations in our study. First, the inclusion of diverse orthopedic surgeries contributed to high heterogeneity, particularly in VAS scores (I^2 = 91%) and opioid consumption (I^2 = 97%). While subgroup analyses were performed to mitigate this variability, differences in surgical type, patient characteristics, dosage, timing of administration, and outcome evaluations likely contributed to the heterogeneity. Standardized protocols in future research could address these issues. More precise subgroup analyses and standardized outcome evaluations will help reduce heterogeneity and improve the reliability of the results. Second, while meta-regression did not find a significant dose-response relationship, our study could not comprehensively evaluate the correlation between total infusion doses, blood concentrations, and outcomes. This highlights the need for further research to determine the optimal dosing regimen for balancing efficacy and safety.

Future studies should focus on increasing the sample size and conducting multicenter studies to increase the statistical power and reduce biases associated with small sample sizes. To reduce heterogeneity, research should standardize surgical types, patient characteristics, drug dosages, and outcome evaluation time points, with more detailed subgroup analyses. Additionally, future studies should explore the optimal dosage and administration scheme of dexmedetomidine, using blood drug concentration monitoring to optimize therapeutic efficacy and minimize side effects. Long-term follow-up studies should also assess the sustained impact of POCD to provide more comprehensive guidance for clinical practice. Moreover, individualized treatment strategies should be developed on the basis of patient-specific factors (such as age and comorbidities) to improve treatment efficacy and minimize adverse effects.

Conclusion

In conclusion, this systematic review and meta-analysis demonstrated that intravenous dexmedetomidine significantly reduces postoperative pain scores, opioid consumption, and the incidence of POCD and POD in orthopedic surgery patients. It also prolongs the time to first analgesic request and sensory and motor block durations and reduces the incidence of PONV. Although no significant dose-response relationship was found and the study has some bias and heterogeneity, the sensitivity analysis and TSA results support the robustness of the conclusions. This study's comprehensive scope and robust methodology, including a large sample size and TSA, distinguish it from prior research and provide significant clinical implications for improving postoperative outcomes in orthopedic surgery. Future studies should further explore the optimal dose and administration regimen of dexmedetomidine and conduct

Table 3

Quality of the evidence and recommendation strengths.

Certainty assessment							Number of patients		Effect			
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dex	Control	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Certainty assessment number of patients effect VAS												
25	Randomized trials	Not serious	Serious	Not serious	Not serious	None	1443	1436	–	MD 0.5 fewer (0.77 fewer to 0.23 fewer)	⊕⊕⊕◯ Moderate	Critical
Opioid consumption												
20	Randomized trials	Not serious	Serious	Not serious	Not serious	None	1338	1329	–	MD 11.91 mg fewer (16.73 fewer to 7.09 fewer)	⊕⊕⊕◯ Moderate	Critical
Incidence of POCD												
7	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	62/371 (16.7%)	105/371 (28.3%)	RR 0.59 (0.41 to 0.86)	116 fewer per 1000 (from 167 fewer to 40 fewer)	⊕⊕⊕⊕ High	Critical
Incidence of POD												
10	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	148/1741 (8.5%)	301/1745 (17.2%)	RR 0.49 (0.41 to 0.59)	88 fewer per 1000 (from 102 fewer to 71 fewer)	⊕⊕⊕⊕ High	Critical

Abbreviations: Dex, dexmedetomidine; MD, mean difference; POCD, postoperative cognitive dysfunction; POD, postoperative delirium; RR, risk ratio; VAS, visual analog scale.

multicenter research to reduce heterogeneity, ensuring the reliability and wide applicability of the findings.

Ethical approval

Not applicable.

Consent

Not applicable.

Sources of funding

Not applicable.

Author contributions

C.Z. and H.L. conceived and designed the study; X.Z., Y.L. X.R. Y. and YXY collected and analyzed the data; all authors contributed to data analysis and interpretation; X.Z., Y.L. wrote the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Guarantor

Cheng Zhou and Hao Liu.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

Presentation

Not applicable.

Acknowledgements

Not applicable.

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