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RESEARCH

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Intravenous dexmedetomidine for delirium prevention in elderly patients following orthopedic surgery: a meta-analysis of randomized controlled trials

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Abstract

Objectives We conducted a meta-analysis to investigate the effect of dexmedetomidine on postoperative delirium in elderly orthopedic surgery patients.

Methods A meta-analysis was conducted to identify randomized controlled trials of dexmedetomidine in elderly patients undergoing orthopedic surgery. The data was published on October 25, 2024. PubMed, Embase, and Cochrane Library databases were searched. Outcome measures included incidence of delirium, length of hospital stay, visual analogue scale, and postoperative complications. Estimates are expressed as relative risk (RR) or mean difference (MD) with a 95% confidence interval (CI). The publications were reviewed according to the guidelines of the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Results This study was registered with INPLASY (number INPLASY2024110004). A total of 3159 patients were included in 9 randomized controlled trials. The results showed that dexmedetomidine exhibited a preventive effect on delirium compared with the control group in elderly patients after orthopedic surgery (RR: 0.55, 95% CI: 0.45–0.66, $P<0.01$, $I^2=0\%$). Subgroup analysis suggested that dexmedetomidine was significantly different from saline(RR: 0.56; 95% CI: 0.44–0.73, $P<0.01$, $I^2=31\%$) and propofol(RR: 0.52; 95% CI: 0.39–0.70, $P<0.01$, $I^2=0\%$) in reducing postoperative delirium in elderly fracture patients. No statistically significant differences were observed in length of hospital stay, visual analogue scale, and postoperative complications ($P>0.05$). Certainty of evidence for postoperative delirium was moderate.

Conclusions Dexmedetomidine has been shown to have a protective effect on postoperative delirium in elderly patients following orthopedic surgery.

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Keywords Dexmedetomidine, Delirium, Orthopedic surgery

Introduction

Postoperative delirium (POD) is a neurological disorder associated with temporary loss of consciousness and cognitive dysfunction. The exact etiology of POD remains uncertain [1]. The occurrence of POD is related to a number of factors, including the patient's age, the type of surgery, the anesthesia and sedation administered during the procedure, and the complications that arise during the surgery. Elderly patients who have undergone fracture surgery have been shown to have a number of characteristic features, including advanced age, prolonged bed rest, blood loss, and the presence of underlying comorbidities. The incidence of POD is 32–53.3% [1], which is significantly higher than in younger patients [2]. POD has been shown to increase the risk of short- and long-term complications in older patients who have sustained a fracture and undergone surgery. Additionally, it has been shown to prolong hospital stay and increase associated costs [3–4]. Therefore, it is of great clinical importance to identify effective preventive measures against delirium in this population.

Dexmedetomidine is a highly selective α-2-adrenergic receptor antagonist that can inhibit sympathetic nerve excitability [5], increase vagus nerve excitability, lower blood pressure, lower heart rate, and reduce myocardial oxygen consumption. In addition, dexmedetomidine has been observed to cause sedation, analgesia, anxiolytic effects, hypnosis, memory loss, and anesthesia-like symptoms. The drug exerts a sedative effect by inhibiting the division of neurons, thereby reducing the perception of pain and anxiety. The pharmacological properties of dexmedetomidine include rapid absorption, rapid distribution, rapid metabolism and rapid excretion. In clinical practice, dexmedetomidine is used for sedation, analgesia and sedation, as well as for intraoperative and postoperative sedation and analgesia [6]. Additionally, dexmedetomidine has been shown to inhibit central nervous system activity, thereby reducing pain in patients [7]. A number of studies have documented the neuroprotective effects of dexmedetomidine [8]. Nevertheless, the results of recent randomized controlled trials suggest that the effectiveness of dexmedetomidine in reducing the incidence and safety of POD in elderly patients undergoing orthopedic surgery is still inconclusive. The aim of this study is to conduct a meta-analysis to evaluate the potential protective effect of dexmedetomidine on the occurrence of POD in elderly patients undergoing orthopedic procedures.

Methods

The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [9]. The protocol has been registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols database (Inplasy protocol: INPLASY2024110004) and is fully available on Inplasy.com (https://inplasy.com/inplasy-2024-11-0004/). Ethical approval was not required for this study.

Search strategy

Three researchers (Jing Sun, Duo Wang, and Yue Zhao) conducted a comprehensive electronic literature search for articles published in this area before October 25, 2024. The database includes PubMed, Embase and the Cochrane database. The PubMed basic search strategy as follows: (cataclasis[Title/Abstract] OR fracture[Title/Abstract] OR joint[Title/Abstract] OR articulation[Title/Abstract] OR arthroplasty[Title/Abstract] OR limb[Title/Abstract] OR orthopedic[Title/Abstract]) AND (dexmedetomidine[Title/Abstract]) AND (delirium[Title/Abstract] OR deliriums[Title/Abstract]). Manually select relevant randomized controlled trials. The search strategy of the literature was shown in the supplement (Supplementary file: Table S1). Language is limited to English.

Study selection criteria

This systematic review and meta-analysis focused primarily on elderly patients (60 years or older) undergoing orthopedic surgery. All published full-text randomized controlled trials (RCTs) comparing the effectiveness of dexmedetomidine with other agents (such as placebo or propofol) in preventing postoperative delirium after orthopedic surgery were eligible for inclusion. The outcomes were the incidence of delirium after orthopedic surgery, the length of hospital stay, visual analog scale, and complications 30 days after surgery (defined as new-onset adverse conditions requiring therapeutic intervention according to the Clavien-Dindo classification, which included grade 2 or higher)., including acute renal failure, pulmonary infection, disease control and disease control). Heart failure, myocardial infarction, new cardiac arrhythmias, pulmonary embolism or deep vein thrombosis, and cerebrovascular disease or wound infections. We excluded animal studies, studies involving patients under 18 years of age, and insufficient data to be extracted such as abstracts, reviews, pharmacological presentations, and other literature. Literature that does not agree with the content of this study will also be excluded. If we need relevant research data, we contact the authors. Chizophrenia, epilepsy, parkinsonism, or coma were excluded from the study population. Non-intravenous administration, inappropriate control group settings, and inaccurate data extraction were also excluded.

Data extraction

Three authors undertook the data extraction independently, using the established standard data collection table. The extracted data are as follows: the first author's name, the year of publication, the basic characteristics of the participants, the type of surgery, the method of assessment of POD, the strategy of dexmedetomidine infusion, outcomes mentioned above, method of anesthesia and exclusion criteria.

Bias & quality assessment

Two researchers independently selected and reviewed the literature data using a uniform and standardized method and included them in the literature in strict compliance with the eligibility and exclusion criteria. They then collected information. The quality of the selected articles was assessed according to the standards of the Cochrane Reviewer Handbook, version 5.1.0 [10], using the RoB 2.0 tool. We used the funnel plot to assess the publication bias of the studies, and to ensure the accuracy of the results, we considered excluding studies with significant publication bias.

Data synthesis and analysis

The meta-analysis was conducted using RevMan 5.4. Data that met the criteria for homogeneity ($P > 0.10$ and $I^2 \leq 50\%$) as determined by the heterogeneity test were subjected to meta-analysis using the fixed-effect model (M-H). In cases where the above homogeneity criteria were not met ($P \leq 0.10$ or $I2 > 50\%$) and the presence of heterogeneity could not be excluded, the random effects model was used to consolidate the effects [11]. A prespecified subgroup analysis was performed according to the control group (saline or propofol) administration strategy. Estimates are expressed as relative risk (RR) or mean difference (MD) with a 95% confidence interval (CI). A p value less than 0.05 was considered statistically significant.

Certainty assessment

This study assessed research certainty according to the criteria of theGRADE (Grading of Recommendations Assessment, Development, and Evaluation) Guidelines Working Group [12]. According to the corresponding evaluation criteria, the evidence level was classified (divided into 4 categories: high, moderate, low and very low) [13].

Results

The flowchart provides a summary of the process for identifying and selecting studies for review (Fig. 1). A total of 219 related literatures were retrieved, of which 91 were excluded due to duplicates. In addition, 109 studies were excluded after a preliminary assessment of titles and abstracts. The remaining 19 studies underwent a more comprehensive assessment through a thorough reading of the full texts. Data from nine studies [14–22] evaluating the efficacy and safety of dexmedetomidine for the prevention of delirium in elderly patients undergoing orthopedic surgery were included in the final analysis.

The trials included in this review were published between 2016 and 2024 and included a total of 3159 patients (1580 in the dexmedetomidine group and 1579 in the control group). The detailed characteristics of the included trials were presented in Table 1.

A total of nine studies with a total of 3159 patients showed that dexmedetomidine significantly reduced the incidence of POD in elderly patients after orthopedic surgery compared to the control group (Fig. 2, RR: 0.55; 95% CI: 0.45–0.66, $P < 0.01$, I^2=0%). Subgroup analysis suggested that dexmedetomidine was significantly different from saline(RR: 0.56; 95% CI: 0.44–0.73, P<0.01, I = 31%) and propofol(RR: 0.52; 95% CI: 0.39–0.70, P<0.01, I^2=0%) in reducing postoperative delirium in elderly fracture patients. Regarding the length of hospital stay (after surgery), we removed studies with significant publication bias that showed no statistically significant difference between dexmedetomidine and control groups (Fig. 3, MD: 0.00; 95% CI: -0.08–0.08, $P = 1.00$, I^2=0%). Furthermore, it had no effect on the visual analogue scale (VAS) (Fig. 4, RR: -1.10; 95% CI: -2.87–0.66, $P = 0.22$, I^2=99%). Three studies reported postoperative complications within 30 days after surgery, which was not a statistically significant difference (Fig. 5, RR: 0.87; 95% CI: 0.61–1.23, $P = 0.23$, I^2=33%).

RevMan software is used to see how an individual study affects the overall outcome for each endpoint. The RoB 2.0 tool was used to assess the quality of the research. The quality of included studies was affected by missing outcome data and selection of the reported result, which caused some concerns. GRADE is used to assess the certainty of evidence affected by the risk of bias, inconsistency and imprecision, as described in the **supplementary file**. Certainty of evidence for postoperative delirium was moderate.

Discussion

Previous research has shown that delirium is a significant health problem [23] that is strongly associated with prolonged hospital stays, mortality, and other complications in patients. Several risk factors have been identified, including a history of cognitive impairment,

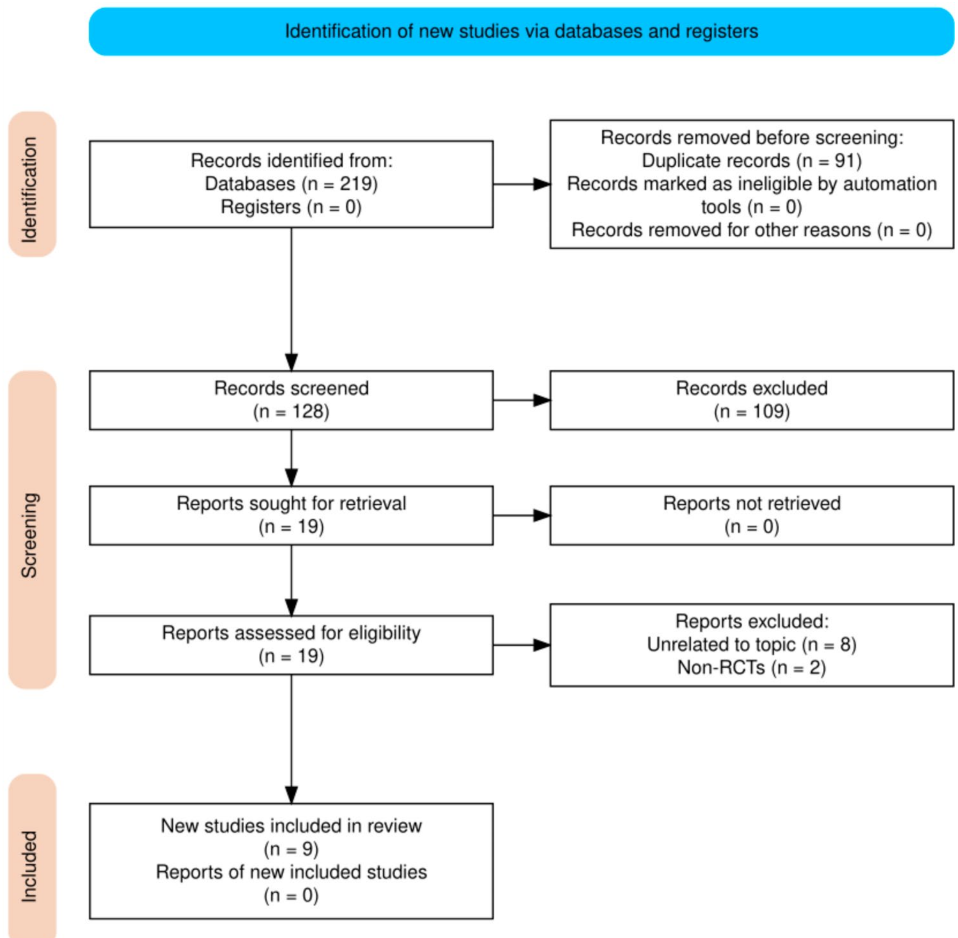

Fig. 1 The flow chart of the search and study selection process

postoperative pain, use of opioids and sedatives, and postoperative inflammation. These factors have been shown to be associated with delirium [24–26]. Consequently, proactive prevention of delirium through non-pharmacological and pharmacological means is a crucial aspect of perioperative management [26].

Dexmedetomidine is a potent α2-adrenergic receptor agonist. Dexmedetomidine inhibits norepinephrine release by activating the α2-adrenergic receptor postsynaptic G proteins, thereby reducing the sympathetic response without significant respiratory depression [6, 7]. Therefore, dexmedetomidine is widely used in orthopedic surgery and postoperative analgesia. The results of this study suggest that perioperative administration of dexmedetomidine may potentially reduce the incidence of POD in elderly patients undergoing orthopedic surgery. The exact etiology of POD remains unclear. The following hypotheses have been proposed: The first hypothesis is the neuroinflammatory process. Surgical trauma promotes the release of cytokines and inflammatory mediators [27], destroys the blood-brain barrier, and increases the inflammatory response of the nervous system, leading to cerebral ischemia and nerve cell apoptosis. Among the studies included in this meta-analysis [14, 18, 20], postoperative serum inflammatory factor levels were measured in included patients, but they could not be combined because the original data could not be extracted. Two studies [14, 20] showed that postoperative serum IL-6 and TNF-a levels were significantly lower in the dexmedetomidine group than in the control group. Secondly, considering the stress response theory [28], patients with bone trauma often suffer from severe pain and long-term abnormal excitation of the sympathetic nerve, resulting in strong stimulation during tracheal intubation and extubation under general anesthesia. This can lead to fluctuations in hemodynamic status and cognitive impairment, with elderly patients being particularly at risk of cognitive impairment due to stress reactions. Third, postoperative sleep arrhythmias [29], postoperative fatigue and metabolic disorders are important risk factors for the occurrence of POD. Studies have shown that sleep deprivation can directly increase astrocyte phagocytosis and promote microglial activation, which has been shown to be a promoting factor for POD

Table 1 Design and outcomes of the studies included in the meta-analysis

Auther/year	Group(*N*)	Age(year)	Gender(M/F)	Grade of ASA	Timing of administering DEX	Type of surgery	Strategy of DEX	Control Group	Delirium assessment	Primary outcome	Mode of anesthesia	Exclusion
Hong/2021	Dex(356)Control(354)	DEX(71 ± 5) Control(71 ± 5)	DEX(116/240) Control(113/241)	I–IV	Post	Joint arthroplasty; Spinal surgery; Hip fracture repair	DEX: 200 μg DEX + 200 μg sufentanil, diluted with 0.9% saline to 160 ml. The patient-controlled pump was programmed to deliver 2-ml boluses with a lockout interval of 8 min and a background infusion of 1 ml.h − 1	Saline	CAM; CAM-ICU	Delirium incidence	NR	Chizophrenia, epilepsy, parkinsonism, or myasthenia gravis; coma, profound dementia
Li/2024	Dex(120)Control(120)	DEX(69.48 ± 6.36) Control(69.38 ± 5.86)	DEX(45/75) Control(37/83)	II-IV	Intra	Total hip arthroplasty; Total knee arthroplasty	DEX: 0.4 mL/kg within 15 min, then 0.3 mL·kg-1·h-1	Saling	CAM	Delirium incidence	General anesthesia combined with nerve block anesthesia	Psychiatric disease; Preoperative cognitive impairment
Liu/2016	Dex(60)Control(58)	DEX(71.23 ± 8.08) Control(72.81 ± 9.22)	DEX(26/34) Control(29/29)	II-III	Intra	Total hip joint or knee joint or shoulder joint replacement surgery	DEX 0.2–0.4 μg/kg/h and stopped 20 min before the end of surgery	Saling	CAM	Delirium incidence	General anesthesia	Neurological diseases that may affect cognitive function
Lv/2022	Dex(152)Control(157)	DEX(67.9 ± 5.9) Control(68.4 ± 6.6)	DEX(73/79) Control(74/83)	NR	Post	Total hip joint replacement	DEX: 0.1 μg/kg/h intravenously within 72 h following surgery	Saling	CAM	Delirium incidence	General anesthetization	Any history of brain injury, neurosurgery, mental illness, epilepsy
Mei/2018	Dex(148)propofol(148)	DEX(76 ± 7 Control(74 ± 6)	DEX(64/84) Control(71/77)	I–IV	Intra	hip arthroplasty	DEX: 0.8–1.0 μg/kg over 15–20 min, then 0.1–0.5 μg·kg-1·h-1	Propofol	CAM; MMSE	Delirium incidence	NR	Patients exhibiting cognitive impairment and/or preoperative delirium
Mei/2019	Dex(183)propofol(183)	DEX(72 ± 9) Control(73 ± 11)	DEX(78/105) Control(69/114)	I–IV	Intra	total knee hip arthroplasty	DEX: 0.8–1.0 μg/kg in 15–20 min and then at 0.1–0.5 μg·kg-1·h-1	Propofol	CAM; MMSE	Delirium incidence	NR	Patients exhibiting cognitive impairment and/or preoperative delirium
Shin/2023	Dex(342)propofol(341)	DEX(68–76) Control(67–75)	DEX(77/289) Control(78/288)	I-II	Intra	Orthopedic Lower Limb Surgery: Hip and femur Knee and tibia/fibula Ankle and foot	DEX: 1 μg/kg for more than 10 min, then 0.1 to 0.5 μg/kg/h	Propofol	CAM	delirium incidence	Spinal anesthesia	Neuropsychiatric diseases
Ye/2024	Dex(110)Control(108)	Dex(78.5 ± 6.4) Control(79.1 ± 6.8)	DEX(34/76) Control(34/74)	NR	Intra	Thoracolumbar compression fractures utilizing percutaneous kyphoplasty (PKP).	DEX: 1 μg/kg/h in 10 min, then adjusted to 0.2 to 0.4 μg/kg/h,	Saline	CAM	Delirium incidence	NR	Psychiatric disorders
Zhu/2023	DEX(109)Propofol(110)	Dex(80/71–84) Control(75/72–82)	DEX(42/66) Control(54/56)	I-III	Intra	Total hip arthroplasty with/without cement, hemiarthroplasty with/without cement and Intramedullary nail	DEX: 0.3 μg/kg for more than 10 min, then 0.2–0.7 μg/kg per hour	Propofol	CAM	Delirium incidence 3days postoperatively	Spinal anesthesia	Severe dementia, intraoperative delirium

ASA = American Society of Anesthesiologists; CAM = Confusion Assessment Method; DEX: dexmedetomidine; ICU Intensive Care Unit; Intra = in operation; MMSE Mini-mental State Examination; NR = no report; Post = post-operation

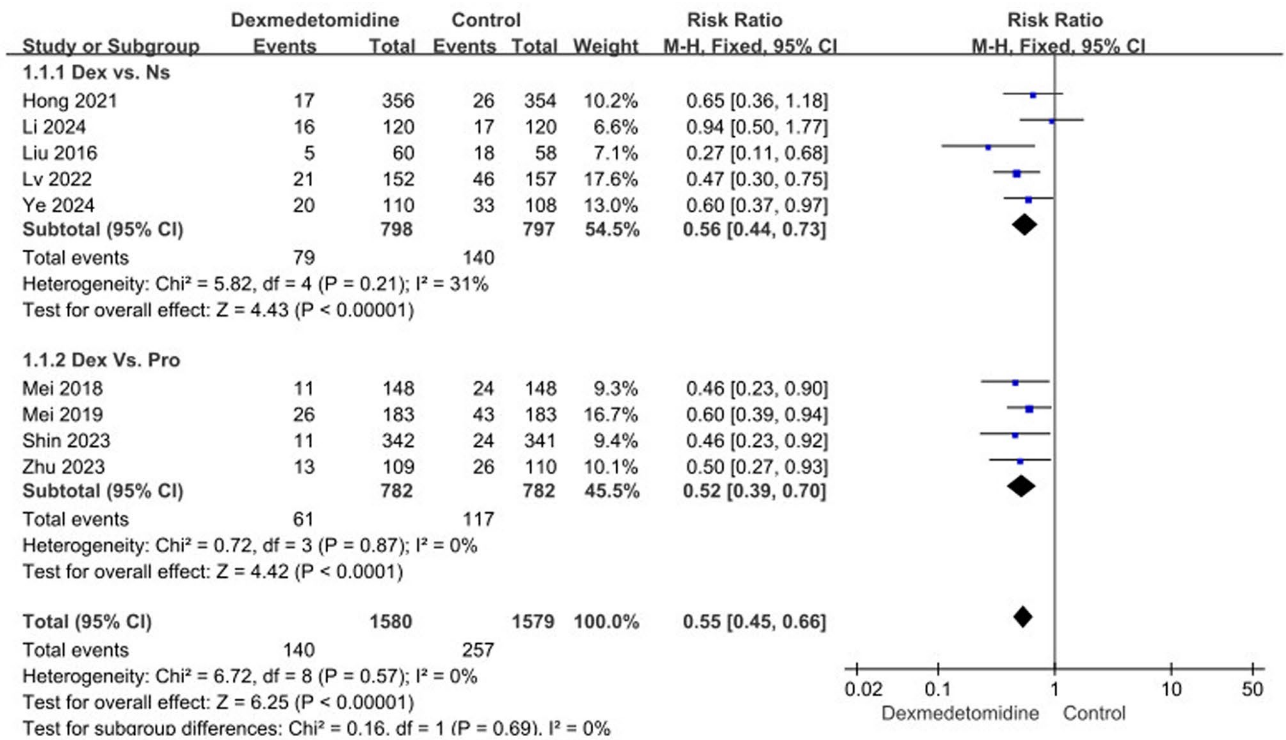

Fig. 2 Forest plot of postoperative delirium (Ns: saline, Pro: propofol)

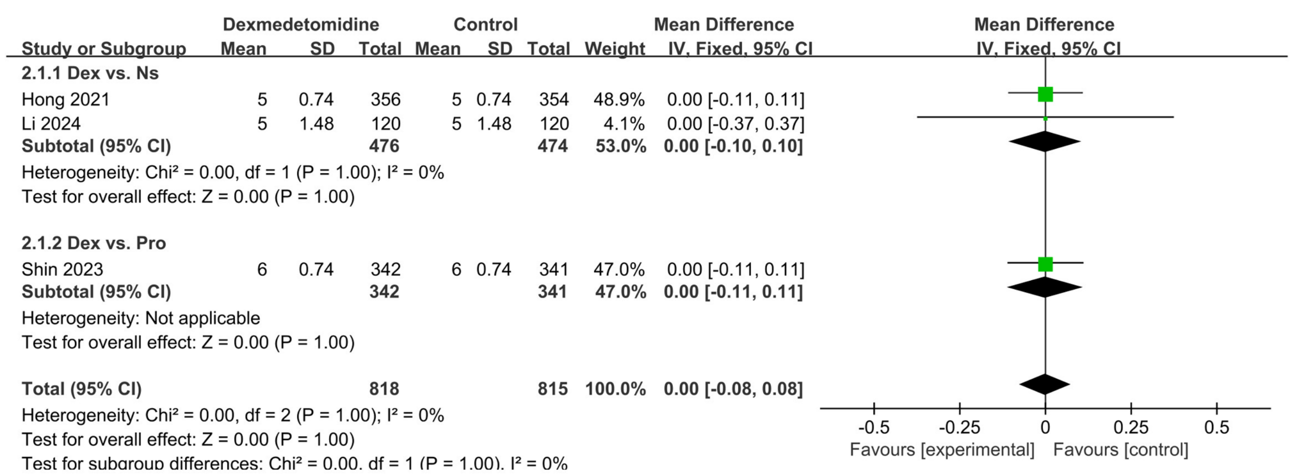

Fig. 3 Forest plot of length of stay (Ns: saline, Pro: propofol)

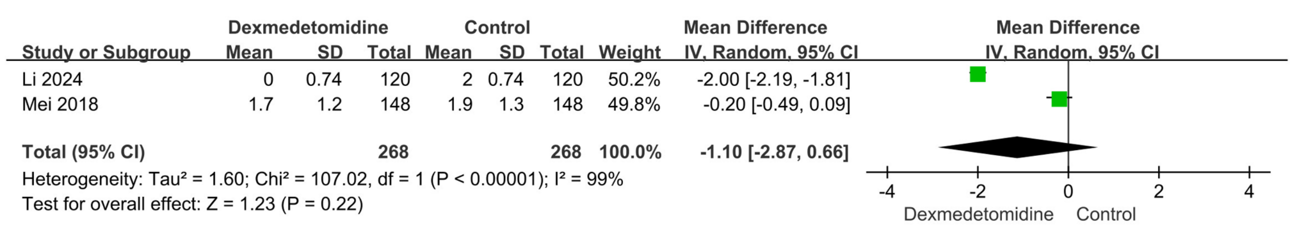

Fig. 4 Forest plot of visual analogue scale

Study or Subgroup	Dexmedetomidine Events	Dexmedetomidine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hong 2021	11	356	18	354	30.3%	0.61 [0.29, 1.27]
Mei 2018	22	140	18	148	29.4%	1.29 [0.72, 2.30]
Mei 2019	18	183	24	183	40.3%	0.75 [0.42, 1.33]
Total (95% CI)		**679**		**685**	**100.0%**	**0.87 [0.61, 1.23]**
Total events	51		60			
Heterogeneity: Chi² = 2.97, df = 2 (P = 0.23); I² = 33%						
Test for overall effect: Z = 0.80 (P = 0.42)						

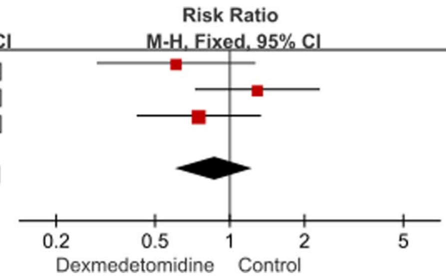

Fig. 5 Forest plot of postoperative complications within 30 days of surgery

development [30]. A study in this meta-analysis showed [14] that intraoperative administration of dexmedetomidine significantly reduced the likelihood of sudden awakening after fast-wave anesthesia compared to controls, a progression comparable to that observed in rapid eye movement sleep, which is often associated with sleep disorders [31]. Finally, opioids are often used for intraoperative analgesia, and the incidence of POD is directly related to the use of opioids, the acute effect of which is to increase the release of serotonin in a wide area ofthe forebrain, which can affect various neurotransmitters [32–33]. The pain assessment in this study was limited to the number and heterogeneity of studies and other factors, and the results showed no statistical differences, which requires further research verification in the future. Regarding the length of stay, this study was also limited by factors such as the number of studies and the small number of participants, and no statistical differences in the results were found, which still need to be verified by further research in the future.

The limitations of this study are as follows. First, in this study, different surgical types, anesthesia methods, and dexmedetomidine application strategies may increase the heterogeneity of outcome measurements. Second, this meta-analysis mainly focuses on studies in China and South Korea, and there are certain differences in the exclusion criteria of different studies, which also increases the calculation of outcome indicators to a certain extent. Third, due to the limited sample size of the study, we did not include 30-day all-cause mortality as an end event, which is a significant limitation, and the sensitivity analysis may also affect the accuracy of the results due to the small number of included studies. In conclusion, multicenter, large-scale, randomized, controlled trials on postoperative delirium in orthopedic patients are still the future research direction. Of course, research into the clinical effects of different strategies for dexmedetomidine administration, including in combination with other medications or care measures, on older orthopedic patients is also a future direction. It is also worth examining the influence of different surgical anesthesia methods on postoperative delirium in orthopedic patients.

Conclusion

This meta-analysis suggests that perioperative administration of dexmedetomidine significantly reduces the incidence of POD in elderly orthopedic postoperative patients.

Abbreviations

ASA	American Society of Anesthesiologists
CAM	Confusion assessment method
CI	Confidence interval
ICU	Intensive care unit
MD	Mean difference
MMSE	Mini-mental State Examination
POD	Postoperative delirium
RCT	Randomized controlled trials
RR	Relative risk

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-025-00841-2.

Supplementary Material 1

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None.

Author contributions

JS, DW and YZ conducted a comprehensive review of the scientific literature and drafted the manuscript. YB provided assistance in the compilation of data. S-FW assisted in the processing of the data and the creation of visual representations. CM, G-BM and PL were instrumental in the conceptualization, design, interpretation of data, revision of the manuscript for critical intellectual content, and supervision of the study. The authors have read and approved the final manuscript.

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Data availability

Data sets are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors approved the final manuscript and the submission to this journal.

Competing interests

The authors declare no competing interests.

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