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Review Article

Preventive effects of perioperative drug injection on postoperative delirium after hip fracture surgery: a systematic review and meta-analysis

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Abstract: Objective: To systematically evaluate the efficacy of perioperative drug injection in preventing postoperative delirium (POD) following hip fracture (HF) surgeries. Methods: This research scheme was published on the PROSPERO platform (registration number: CRD42024602190). Databases searched included PubMed, Web of Science, Embase, and Cochrane. The search deadline was July 2024. Statistical analyses were conducted using StataSE15.0 software. Paired analysis and network meta-analysis were performed in R Studio, with included drugs ranked using the cumulative ranking probability plot area (SUCRA) for each outcome measure. The incidence, severity, and duration of delirium were analyzed using risk ratios (RR), weighted mean differences (WMD), and their corresponding 95% confidence intervals (CI). Results: This meta-analysis included 13 studies: 9 RCTs and 4 cohort studies involving 2,291 patients with HF. The results indicated a significant reduction in the incidence of POD among patients who received perioperative drug injections, with a combined RR of 0.56 [95% CI (0.47, 0.67), P < 0.001]. There was also a significant reduction in the severity of delirium, with a combined WMD of -2.78 [95% CI (-4.38, -1.19), P = 0.01]. However, there were no significant differences in the duration of delirium or the incidence of adverse events, with combined values of [WMD = -1.81, 95% CI (-3.89, 0.27), P = 0.088] and [RR = 1.34, 95% CI (0.78, 2.32), P = 0.294], respectively. Network meta-analysis identified morphine as the most effective drug for preventing delirium, with a SUCRA value of 19.1%. Conclusion: In patients undergoing surgery for HF, perioperative drug injections significantly reduce the incidence and severity of postoperative delirium, with intrathecal morphine being the most effective option for prevention. These findings provide valuable insights for managing postoperative delirium prevention in HF patients. Further high-quality randomized controlled studies are needed to validate these results.

Keywords: Hip fracture, perioperative period, injection of medication, delirium, meta-analysis

Introduction

Hip fracture (HF) is the most debilitating brittle fracture in the elderly, ranking among the top 10 causes of disability in this population [1]. Nearly all HF patients require surgical reduction. Reports indicate that the incidence of postoperative delirium (POD) in elderly HF patients ranges from 20% to 50%, leading to impaired postoperative function and cognitive decline, longer hospital stays, and increased medical costs. Delayed recovery from delirium may progress to dementia, which is an independent risk factor for mortality at both 30 days and 1 year post-surgery [2, 3]. POD is characterized by changes in consciousness, attention, cognition, and perception within 7 days postoperation, typically occurring 24-72 hours after surgery. Since most patients with POD exhibit hypoactive symptoms such as lethargy and silence, the condition is often overlooked clinically [4, 5]. The pathogenesis of POD has not been fully elucidated, but it is associated with factors such as postoperative pain, adverse psychological states, and sleep disorders [6]. A widely accepted hypothesis suggests that neu-

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roinflammation and oxidative stress resulting from the initial trauma of HF and subsequent surgery are key mechanisms of delirium [7, 8]. Studies have indicated that the dosage of anesthetics, such as propofol, may be a significant risk factor for the development of POD [9]. Consequently, it is recommended to minimize surgical invasiveness, avoid excessive anesthesia, and reduce the dosage of anesthetic drugs both before and during surgery to lower the incidence of POD [10].

Additionally, studies have confirmed that postoperative drug injections can help reduce anxiety, provide analgesia, induce sedation, and inhibit the sympathetic stress response triggered by surgical traction and stress, thereby decreasing the incidence of POD. Drugs investigated in clinical and experimental studies include donepezil, nimodipine, parecoxib, dexmedetomidine (DEX), bupivacaine, lidocaine, dexamethasone, statins, lipid mediator agonists, methylprednisolone, and others [11, 12]. However, no systematic analysis has yet been conducted on the effectiveness of perioperative drug injections in preventing POD. This meta-analysis aims to provide robust evidence and an objective basis for clinical application.

Methods

Literature search strategy

Databases searched included PubMed, Web of Science, Embase, and Cochrane. Search terms were: "hip fracture", "intertrochanteric fractures", "subtrochanteric fractures", "trochanteric fractures", "femur trochlear fracture", "femoral trochlear fracture", "delirium", "mixed origin delirium", "subacute delirium", "subacute deliriums", "perioperative period", "injection of medication", "bupivacaine", "lidocaine", "dexamethasone", "bupivacaine", and "dexmedetomidine". The last retrieval date was July 1, 2024. The study followed the PRISMA guidelines for systematic reviews and meta-analyses [13].

Inclusion and exclusion criteria

Inclusion criteria: (1) Studies evaluating the impact of perioperative drug injections on the incidence and severity of POD in patients. (2) Literature published in Chinese or English. (3) Outcome indicators included delirium incidence, severity, duration, and the incidence of adverse events. (4) Study designs restricted to randomized controlled trials (RCTs).

Exclusion criteria: (1) Studies where drug interventions did not align with the objectives. (2) Studies with missing data or incomplete results. (3) Publications not meeting or uncertainty in fitting the required study type, such as reviews, systematic evaluations, or animal studies.

Data extraction

Duplicate literature was eliminated using EndNote X9. Two researchers (LJ and WX) independently screened the literature based on the predetermined inclusion and exclusion criteria. Data extraction was performed independently using a standardized extraction form, and the results were cross-checked by both researchers. Disagreements were resolved through discussion. Studies lacking relevant data were excluded. For each study, the following information was collected: (1) Basic details: First author, country, year of publication, study type, and type of drug injected. (2) Patient baseline information: Number of participants, age, gender, and body mass index (BMI). (3) Study results: Incidence, severity, duration, and adverse events of POD.

Literature quality assessment

The Cochrane Collaboration software Review Manager 5.4.1 was used to assess the methodological quality of the included studies using the risk of bias assessment method [14]. This method evaluates six indicators across seven categories: random allocation method, allocation concealment, blinding, completeness of outcome data, selective reporting of study results, and other sources of bias. Each indicator was classified as high risk, low risk, or unclear, with independent assessments conducted by two researchers.

The quality of the included cohort studies was assessed independently using the Newcastle-Ottawa Scale (NOS) [15], which evaluates three criteria: cohort selection, comparability between radical resection and localized resection groups, and outcome assessment. The modified NOS uses a 9-star scale, assigning 1-3 stars for low-quality studies, 4-6 stars for mod-

erate quality, and 7-9 stars for high quality. Scoring was carried out independently by two investigators, and third-party experts were consulted to resolve any significant discrepancies that could affect the study's inclusion in the final analysis.

Statistical analysis

Statistical analysis was conducted using StataSE15.0 software to calculate pooled risk ratios (RR), weighted mean differences (WMD), and 95% confidence intervals (95% CI). The I^2 test was used to assess heterogeneity among the included studies, with significant statistical heterogeneity indicated by $I^2 > 50\%$ and $P \leq 0.1$. For studies with $I^2 < 50\%$, a fixed-effect model was used, while a random-effects model was applied when $I^2 \geq 50\%$. Network meta-analysis was performed in R Studio using the gemtc software package, where a Bayesian model was established, a probability graph was drawn, and probability rankings were calculated. In the presence of a closed loop among interventions, an inconsistency test was performed to assess the consistency between direct and indirect comparisons. The node analysis method was used for the inconsistency test, and if $P > 0.05$, no significant difference was indicated. The SUCRA value of each intervention was calculated to determine the overall ranking, with the interventions ranked according to the size of their SUCRA values. In cases of substantial heterogeneity among studies, the following steps were taken: first, verification of the accuracy of data collection and entry; second, investigation of potential sources of heterogeneity through methods such as transformation of statistical models, subgroup analysis, meta-regression, and sensitivity analysis. Publication bias was assessed using Begg's funnel plot and Egger's test [16]. If $P > 0.05$, no publication bias was indicated. A *P*-value of less than 0.05 was considered statistically significant.

Results

Literature search results

In this meta-analysis, 4,164 studies were screened, of which 1,340 duplicates were removed, and 2,776 studies were excluded based on the inclusion and exclusion criteria. After reviewing the full text, 35 additional studies were excluded, leaving 13 studies included in the final analysis (**Figure 1**).

Literature baseline data

A total of 2,291 patients with HF were evaluated across the 13 included studies, of which 9 were RCTs and 4 were cohort studies (**Table 1**).

Quality assessment of literature

The Cochrane risk of bias tool was used to evaluate the quality of the 9 RCTs, with RevMan 5.4 software used for visualization. Each of the 9 RCTs described a specific randomization method, so they were assessed as having a low risk of bias. Four studies [18, 20, 25, 29] did not report the blinding method, and were therefore considered high risk. Additionally, none of the 9 RCTs mentioned allocation concealment, so the evaluation was deemed unclear (**Figure 2**). The Newcastle-Ottawa Scale (NOS) was used to assess the included cohort studies, with the results presented in **Table 2**.

Certainty of evidence

GRADEpro was used to assess the certainty of the evidence in this study. **Table 3** shows that the incidence of delirium is based on high-quality evidence, while the other results are based on medium-quality evidence. High heterogeneity, low methodological quality, and the high risk of bias in some outcomes may have contributed to the lower quality of evidence for these results.

Meta-analysis results

Incidence of POD: Thirteen studies were reviewed [17-29]. There was minimal heterogeneity among the studies ($P = 0.394$, $I^2 = 5.2\%$). Therefore, a fixed-effect model was used for the meta-analysis, and the combined RR was 0.56 [95% CI (0.47, 0.67), $P < 0.01$]. The analysis showed that drug injection significantly reduced the incidence of POD in HF patients during the perioperative period (**Figure 3**).

Delirium severity score: Four studies were reviewed [18, 20, 23, 29]. There was considerable heterogeneity among the studies ($P < 0.001$, $I^2 = 95.6\%$). Therefore, a random-effects model was used for the meta-analysis, and the

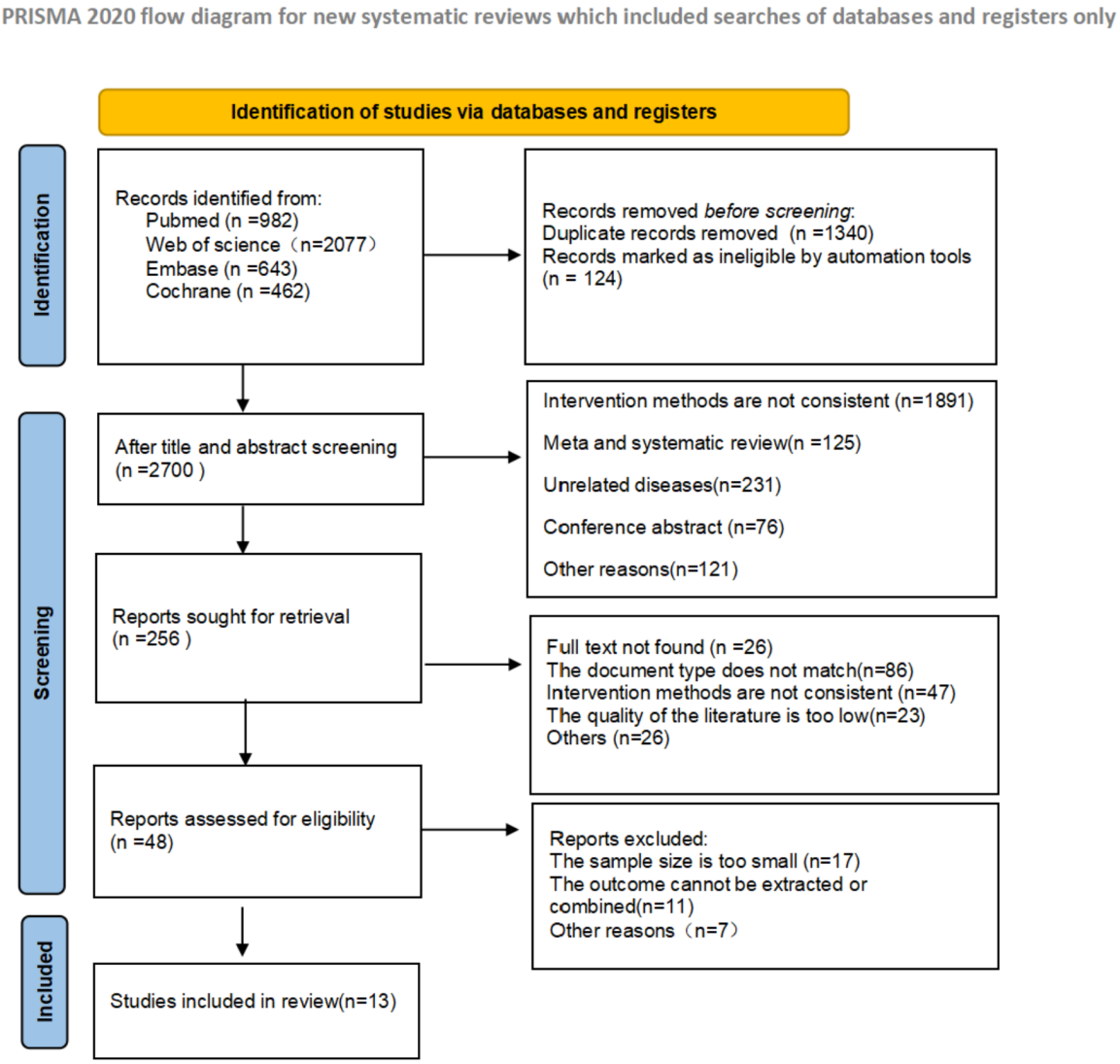


Figure 1. Flow chart of screening.

combined WMD was -2.78 [95% CI (-4.38, 1.19), P = 0.01]. The analysis showed that drug injection significantly reduced the severity of delirium in HF patients during the perioperative period (**Figure 4**).

Duration of POD: Three studies were reviewed [18, 25, 29]. There was considerable heterogeneity among the studies (P < 0.001, I^2 = 95.8%). Therefore, a random-effects model was used for the meta-analysis, and the combined WMD was -1.81 [95% CI (-3.89, 0.27), P = 0.088]. The analysis indicated that there was no significant difference in the duration of POD after drug injection in HF patients during the perioperative period (**Figure 5**).

Adverse events: Four studies were reviewed [22, 23, 25, 26]. There was substantial heterogeneity among the studies (P = 0.02, I^2 = 69.4%). Therefore, a random-effects model was used for the meta-analysis, and the combined RR was 1.34 [95% CI (0.78, 2.32), P = 0.294]. The analysis indicated that there was no significant difference in the occurrence of adverse events after drug injection in HF patients during the perioperative period (**Figure 6**).

Sensitive analysis: Sensitivity analysis was performed by excluding studies of low quality and those using different evaluation criteria for efficacy or exclusion criteria. A combined analysis

Table 1. Baseline data

First author	Publishing year	Research type	Country	Intervention approach		Cases		Gender (Male/Female)		Age		BMI		Injection drug	Outcome indicators
				T	C	T	C	T	C	T	C	T	C		
Jung Wook Huh [17]	2024	Retrospective cohort	Republic of Korea	SINBs	Normal saline	42	41	17/25	14/25	76.24	77.49	22.08	22.05	Bupivacaine	(1)
Xiaofen Li [18]	2023	RCT	China	Lidocaine	Normal saline	50	50	24/26	22/28	75.3±6.8	76.8±5.5	NA	NA	Lidocaine	(1) (2) (3)
Jinhuo Wang [19]	2023	Retrospective cohort	China	Parecoxib	Normal saline	40	40	12/28	15/25	74.86±5.38	73.43±6.44	21.65±3.76	22.15±4.68	Ramosetron palonosetron	(1)
Jianwen Huang [20]	2023	RCT	China	Dexamethasone	Normal saline	80	80	30/50	32/48	84.5 (79.0, 89.0)	85.0 (79.8, 90.2)	20.1 (19.3, 20.8)	20.3 (19.2, 21.5)	Dexamethasone	(1) (2)
Nirpeksh Jain [21]	2022	Retrospective cohort	US	FICB	Opioid	81	85	54/27	58/27	79.0 (13.2)	79.5 (15.5)	NA	NA	Bupivacaine epinephrine	(1)
Rafael Bielza [22]	2021	RCT	Spain	Intravenous iron	Normal saline	126	127	95/31	89/38	87.0 (82.4-91.6)	87.0 (82.5-91.5)	NA	NA	Iron	(1) (4)
M. T. Kluger [23]	2021	RCT	New Zealand	Dexamethasone	Normal saline	40	39	18/22	15/24	81.4 (7.2)	81.4 (8.9)	25.9 (6.6)	25.6 (5.1)	Dexamethasone	(1) (2) (4)
Mark Vincent Koning [24]	2020	Retrospective cohort	Netherlands	Morphine	Normal saline	34	451	12/22	138/313	84 (75-89)	83 (75-90)	24.0 (21.3-27.6)	23.3 (21.2-25.5)	Morphine	(1)
Anna Unneby [25]	2020	RCT	Sweden	FNB	Opioid	116	120	37/79	43/77	83.7 (7.1)	84.4 (6.4)	NA	NA	Levobubivacaine	(1) (3) (4)
Wenchao Zhang [26]	2020	RCT	China	Dexmedetomidine	Normal saline	120	120	37/83	38/82	78.1±6.4	79.0±6.8	23.8±2.5	24.2±3.0	Dexmedetomidine	(1) (4)
Jianhong Hao [27]	2019	RCT	China	FICB	Normal saline	43	42	23/20	23/19	72.30±3.78	72.52±4.26	NA	NA	Ropivacaine	(1)
C. G. Clemmesen [28]	2018	RCT	Denmark	Methylprednisolone	Normal saline	59	58	22/37	20/38	79 (8)	81 (9)	23.5 (4.4)	22.8 (3.6)	Methylpredniso-lone	(1)
George Mouzopoulos [29]	2009	RCT	Greece	FICB	Normal saline	102	105	78/24	76/29	72.3±4.1	73.1±3.8	NA	NA	Bupivacaine	(1) (2) (3)

Notes: (1): Incidence of delirium; (2): Severity of delirium; (3): Duration; (4): Adverse event. Abbreviations: T: Test group; C: Control group; SINBs: Serial-injection nerve blocks; MDAS: Memorial Delirium Assessment Scale; FICB: Fascia iliaca compartment block; FNB: Femoral Nerve Block; NA: Not applicable.

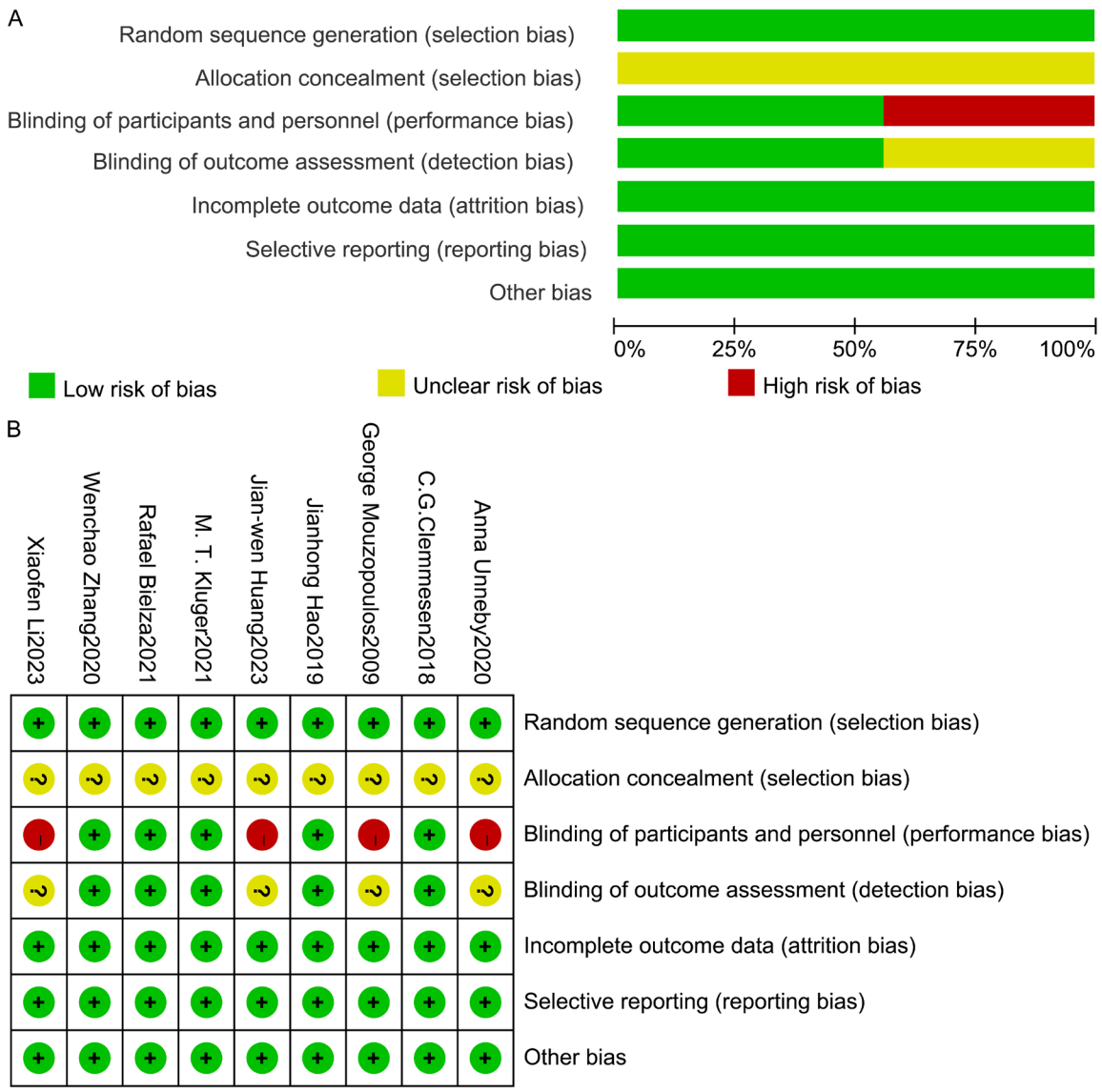


Figure 2. Risk of bias graph.

Table 2. Evaluation using Newcastle-Ottawa Scale

Study	Selection	Comparability	Outcomes	Total
Jung Wook Huh	3	1	3	7
Jin-Huo Wang	3	1	3	7
Nirpeksh Jain	3	2	3	8
Mark Vincent Koning	3	1	3	7

was then conducted to compare the effect size before and after these exclusions. The results showed that excluding certain studies (specifically low-quality studies and those with differing exclusion criteria) did not significantly alter the combined effect size, indicating a robust meta-analysis. However, if significant differences or contradictory conclusions emerged, it would suggest that the stability of the meta-analysis results is compromised. **Figure 7** shows the sensitivity analysis for POD incidence. After sequentially removing each study, the effect size remained consistent within the original range, indicating that the study model was robust and reliable.

Publication bias: The funnel plot was used to evaluate publication bias for POD incidence. The results showed that (**Figure 8**) Egger's P = 0.29 and Begg's P = 0.36 for POD incidence; Egger's P = 0.054 and Begg's P = 0.734 for

Table 3. Certainty of evidence

			Quality assessment				No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delirium severity score	Control	Relative (95% CI)	Absolute	Quality	Importance
Incidence of Delirium (assessed with: RR)												
9	Randomised trials	No serious risk of bias	No serious inconsistency	Serious	No serious imprecision	Strong association dose response gradient	129/736 (17.5%)	219/741 (29.6%) 30%	RR 0.6 (0.49 to 0.72)	118 fewer per 1000 (from 83 fewer to 151 fewer) 120 fewer per 1000 (from 84 fewer to 153 fewer)	ÅÅÅÅ HIGH	CRITICAL
Delirium severity score (Better indicated by lower values)												
4	Randomised trials	Serious	No serious inconsistency	Serious	No serious imprecision	Dose response gradient	272	274	-	MD 2.78 lower (4.38 to 1.19 lower)	ÅÅÅO MODERATE	IMPORTANT
Duration of POD (Better indicated by lower values)												
3	Randomised trials	Serious	no serious inconsistency	Serious	No serious imprecision	Strong association	268	275	-	MD 1.81 lower (3.89 lower to 0.27 higher)	ÅÅÅO MODERATE	IMPORTANT
Adverse Event												
4	Randomised trials	Serious	No serious inconsistency	Serious	No serious imprecision	Strong association	110/402 (27.4%)	87/406 (21.4%) 22.7%	RR 1.34 (0.78 to 2.32)	73 more per 1000 (from 47 fewer to 283 more) 77 more per 1000 (from 50 fewer to 300 more)	ÅÅÅO MODERATE	IMPORTANT

Abbreviations: CI: confidence interval; MD: mean difference; RR: risk ratio.

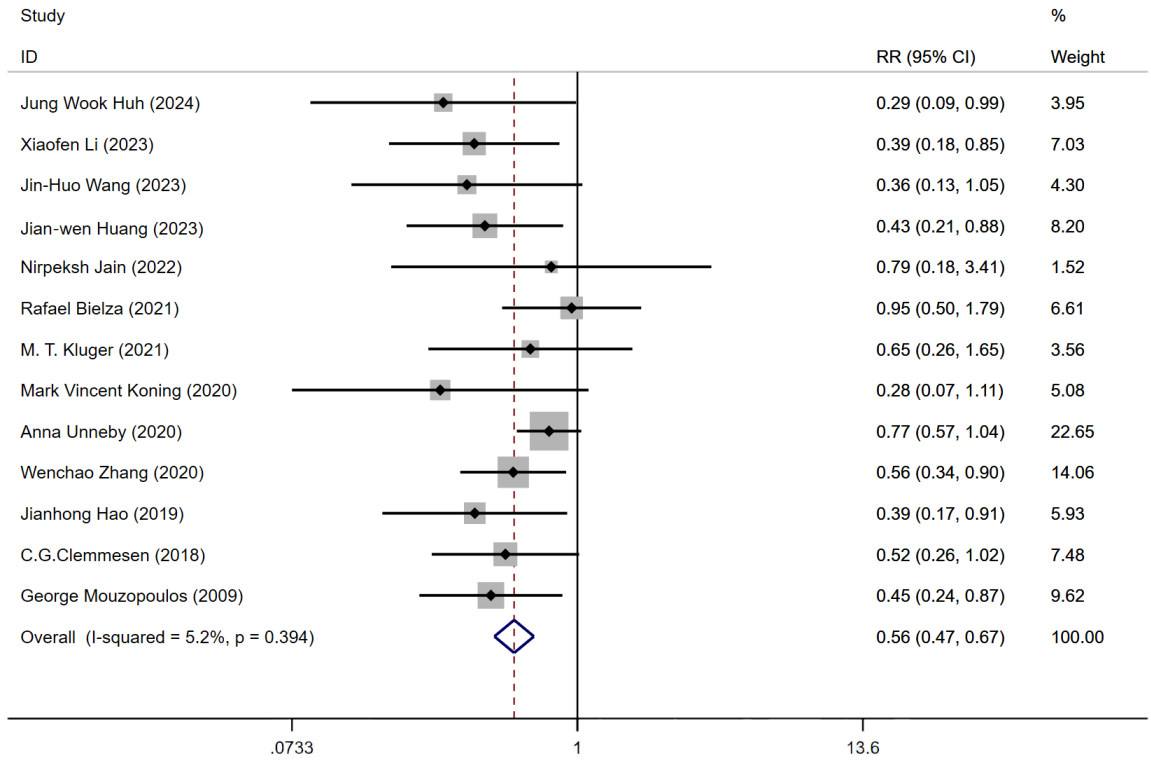


Figure 3. Forest plot for incidence of postoperative delirium.

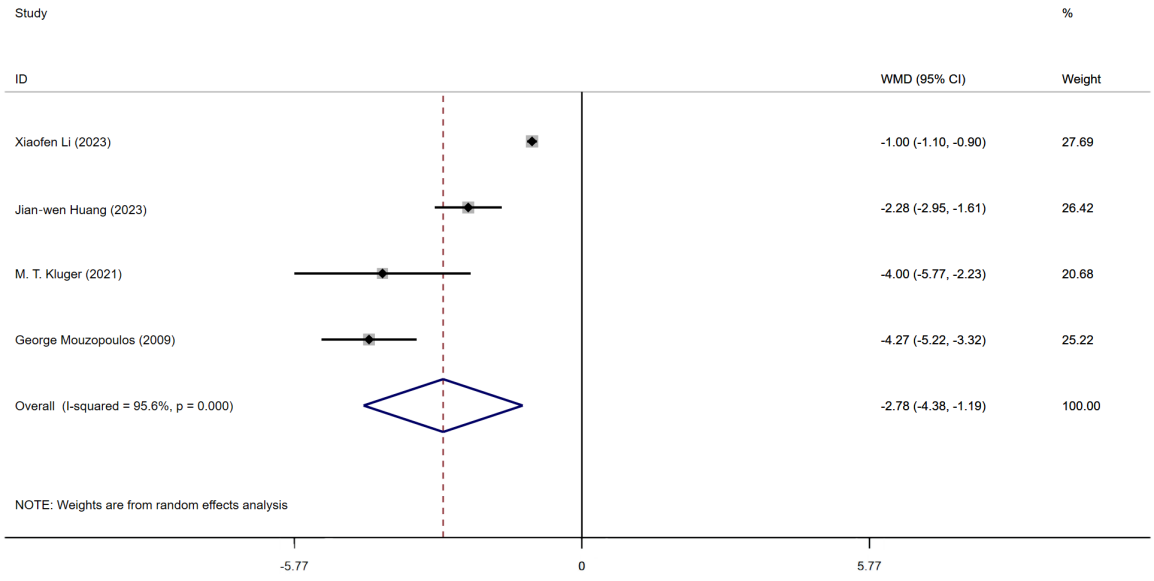


Figure 4. Forest plot of delirium severity.

delirium severity; Egger's P = 0.335 and Begg's P = 0.296 for delirium duration; and Egger's P = 0.161 and Begg's P = 0.308 for adverse events, indicating no significant publication bias. The funnel plot shape was not significantly asymmetric.

Network meta-analysis

Network evidence graph

Delirium incidence was reported in 12 studies, including 11 interventions: A) Normal saline, B)

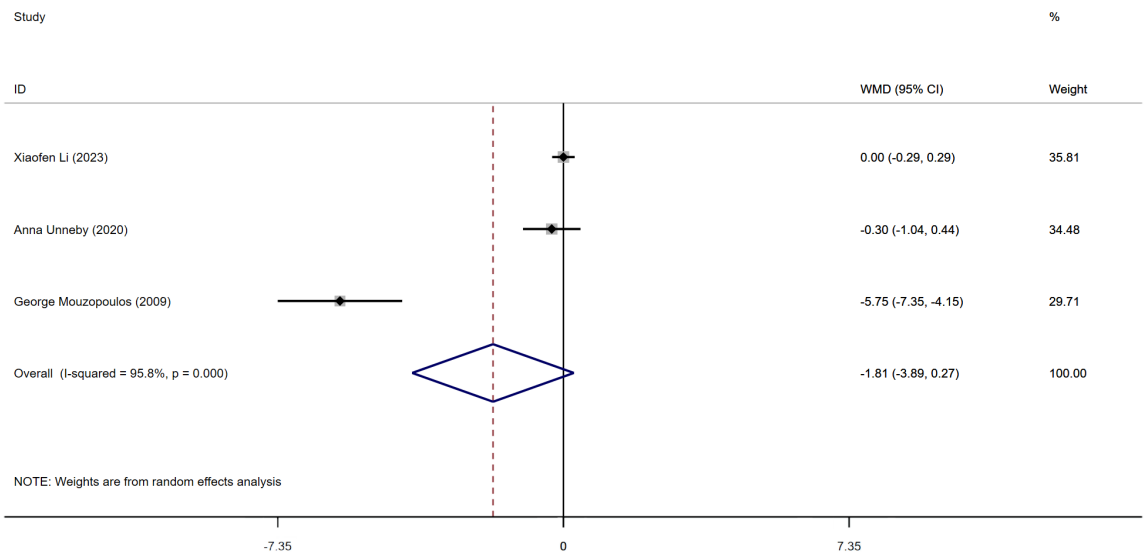


Figure 5. Forest plot for duration of postoperative delirium.

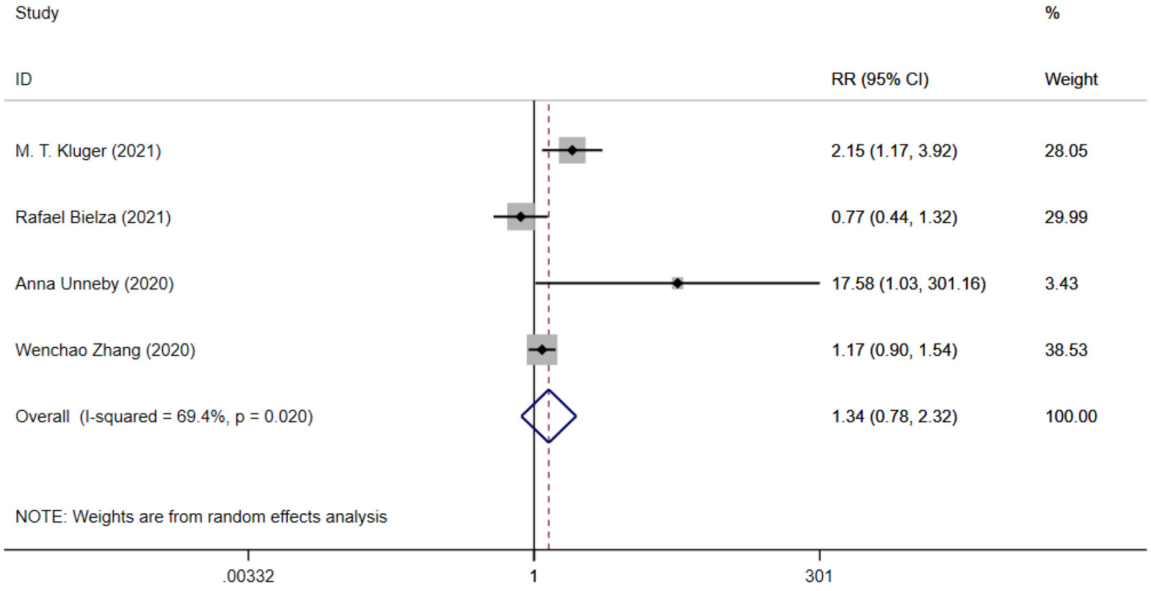


Figure 6. Forest plot for incidence of adverse events.

SINBs, C) Lidocaine, D) Parecoxib, E) Dexamethasone, F) FICB, G) Opioid, H) Intravenous iron, I) Morphine, J) DEX, and K) Methylprednisolone. The network relationship is generally centered on normal saline treatment. The dots represent the interventions, while the lines connecting two dots represent direct comparisons, with the thickness of the line reflecting the number of studies included. No closed loops were identified in the network, and therefore, no node analysis was required. The results of the network meta-analysis are shown in **Figure 9A**, **9C**.

Efficacy ranking

The SUCRA probability ranking showed the following order: Morphine (19.1%) < SINBs (23.2%) < Parecoxib (32.2%) < Lidocaine (35.0%) < FICB(40.7%)<Dexamethasone(51.7%)<Methylprednisolone (52.9%) < Opioid (56.6%) < DEX (58.3%) < Intravenous iron (87.2%) < Normal saline (92.5%). This indicates that the lower the probability, the better the clinical effect for preventing delirium. The SUCRA diagram is shown in **Figure 9B**.

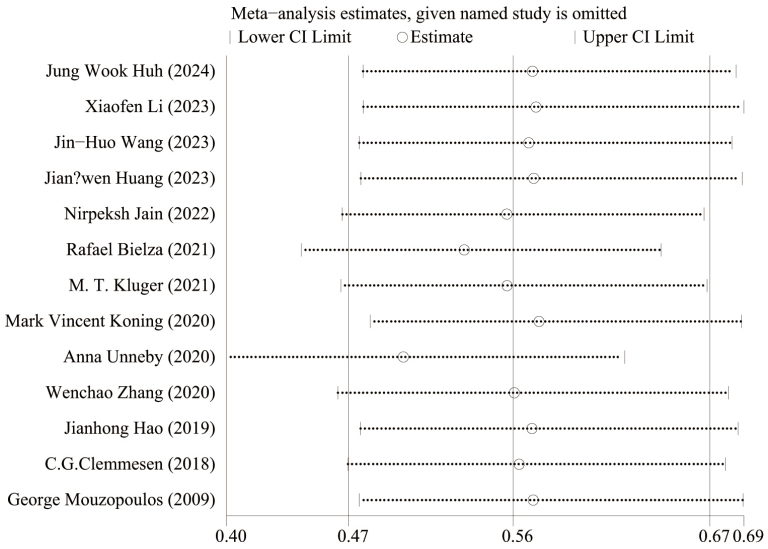


Figure 7. Sensitivity analysis of incidence of postoperative delirium.

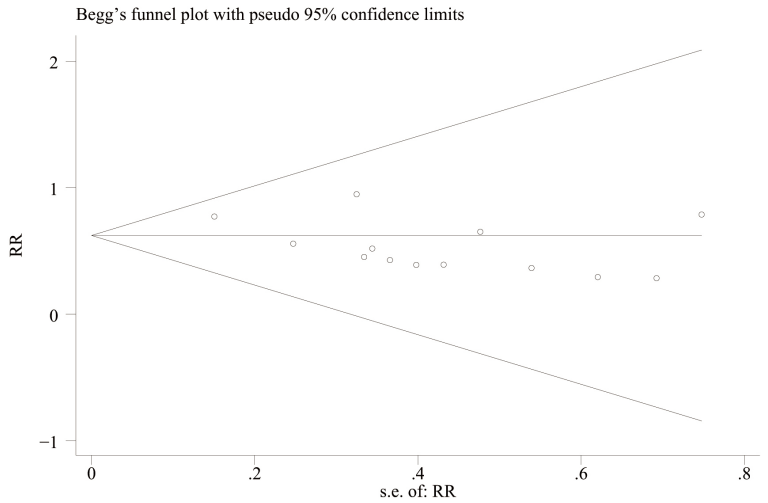
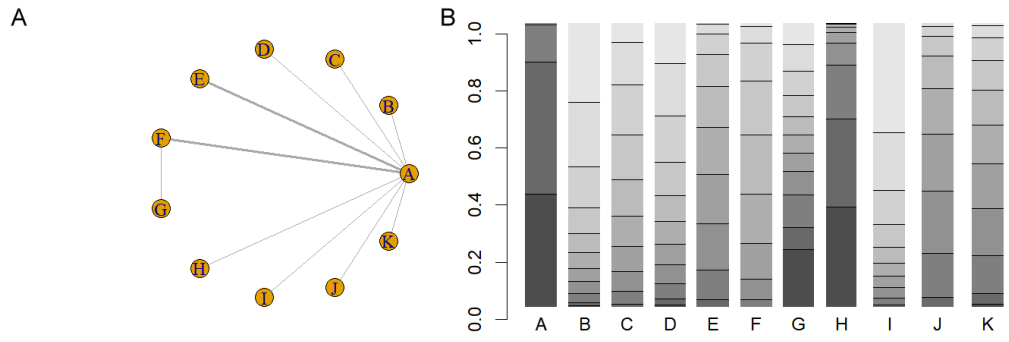


Figure 8. Funnel plot for evaluating publication bias in the incidence of postoperative delirium.

Discussion

Hip joint replacement is a common surgical procedure for elderly patients with HFs, and the causes of POD are multifactorial, including age, preoperative cognitive function, use of narcotic drugs, anesthesia depth, operation time, intraoperative complications, and pain [30]. Elderly patients undergoing hip surgery often have multiple degenerative diseases and organ dysfunctions, placing the brain in a vulnerable state. Severe postoperative pain can disrupt the immune system of elderly patients and impair sleep quality. Chronic sleep deprivation leads to an abnormal increase in inflammatory cells, damaging central hippocampal neurons, which results in memory impairment, affects spatial perception, and disrupts neurotransmitter transmission, ultimately leading to postoperative cognitive decline or delirium. This is a critical risk factor for increased mortality in elderly patients following surgery [31, 32]. Postoperative acute pain activates multiple neurotransmitter pathways, leading to a synergistic effect of oxidative stress and inflammation, as well as disruption of neuronal signaling, which contributes to the development of POD [33]. Animal studies have shown that neurodegenerative diseases can activate microglia and astrocytes, alter central cholinergic and noradrenergic neurons, and trigger the body's immune cascade, leading to the excessive production of inflammatory mediators. This exacerbates neuroinflammation and induces POD [34]. Additionally, anesthetics and anesthesia methods are also associated with the occurrence of POD. Excessive anesthesia during surgery can result in residual anesthetics fluctuating patients' blood pressure, causing cerebral hypoperfusion, reducing brain tissue oxygenation, increasing nerve-specific inflammatory responses, and elevating dopaminergic neurotransmitters while decreasing cholinergic neurotransmitters in the central nervous system, ultimately contributing to POD [35]. Studies have demonstrated that shallower anesthesia (BIS = 50) is associated with a reduced incidence of POD compared to deeper anesthesia (BIS = 35) [36]. Moreover, previous research indicated that more than 50% of elderly patients with HF failed to receive adequate postoperative analgesia due to the side effects of opioids, leading to varying degrees of chronic pain and further increasing the risk of



C

Intervening measure	Normal saline	SINBs	Lidocaine	Parecoxib	Dexamethasone	FICB	Opioid	Intravenous iron	Morphine	Dexmedetomidine
SINBs	1.30(0.16, 2.80)									
Lidocaine	0.96 (0.23, 1.85)	-0.32(-1.999, 1.09)								
Parecoxib	1.05(0.05, 2.30)	-0.24 (-2.03, 1.44)	0.09(-1.25, 1.54)							
Dexamethasone	0.69(0.14, 1.28)	-0.60(-2.19, 0.68)	-0.27(-1.30, 0.67)	-0.36(-1.73, 0.79)						
FICB	0.85(0.35, 1.40)	-0.44(-2.02, 0.81)	-0.11(-1.13, 0.80)	-0.20(-1.548, 0.93)	0.16(-0.61, 0.94)					
Opioid	0.58(-1.12, 2.21)	-0.74(-2.94, 1.28)	-0.39(-2.29, 1.41)	-0.50(-2.59, 1.45)	-0.10(-1.92, 1.62)	-0.26(-1.91, 1.27)				
Intravenous iron	0.05(-0.58, 0.70)	-1.25(-2.86, 0.06)	-0.92 (-1.99, 0.07)	-1.01(-2.41, 0.20)	-0.64(-1.51, 0.21)	-0.80(-1.64, 0.02)	-0.53(-2.28, 1.31)			
Morphine	1.430(0.27, 3.34)	0.14(-1.76, 2.31)	0.46(-1.01, 2.49)	0.38(-1.33, 2.51)	0.75(-0.57, 2.71)	0.58(-0.71, 2.54)	0.89(-1.17, 3.387)	1.39(0.04, 3.39)		
Dexmedetomidine	0.59(0.12, 1.10)	-0.70(-2.26, 0.54)	-0.37(-1.37, 0.51)	-0.46(-1.79, 0.66)	-0.09 (-0.85, 0.65)	-0.25(-0.97, 0.45)	0.01(-1.68, 1.78)	0.54(-0.26, 1.35)	-0.84(-2.79, 0.43)	
Methylprednisolone	0.66(0.01, 1.40)	-0.63(-2.24, 0.72)	-0.30(-1.39, 0.73)	-0.39(-1.79, 0.85)	-0.02(-0.90, 0.88)	-0.18(-1.02, 0.69)	0.08(-1.65, 1.94)	0.61(-0.30, 1.59)	-0.77(-2.77, 0.61)	0.07(-0.75, 0.94)

Figure 9. Mesh structure plot for evaluating the incidence of postoperative delirium. A: Network evidence map; B: Cumulative ranking SUCRA chart; C: League table.

POD [37]. Therefore, optimizing perioperative anesthesia management and improving postoperative pain control are essential for enhancing the prognosis of elderly patients and preventing or reducing postoperative complications. Currently, perioperative drug injections have been shown to inhibit the release of peripheral inflammatory factors, thereby lowering the concentration of central inflammatory mediators and protecting brain function. Analgesic strategies include intravenous analgesics, epidural analgesia, and peripheral nerve blocks [38, 39].

According to the results of this meta-analysis, perioperative drug injection effectively reduced the incidence of POD in patients with HF [RR = 0.56, 95% CI (0.47, 0.67), P < 0.001], and alleviated the severity of POD [WMD = -2.78, 95% CI (-4.38, 1.19), P = 0.01]. However, no significant differences were found in delirium duration or the incidence of adverse events, with combined values of [WMD = -1.81, 95% CI (-3.89, 0.27), P = 0.088] and [RR = 1.34, 95% CI (0.78, 2.32), P = 0.294], respectively. This study did not analyze the effect of individual drugs but rather included various drugs and injection methods, which may have introduced some risk of bias for certain outcome indicators, leading to high heterogeneity. Nevertheless, the main outcome, the incidence of POD, demonstrated a low risk of bias and a stable model. Therefore, we consider the results of this study to be reliable, and they support the potential preventive effect of drug injections on POD.

Specifically, this study included drugs including bupivacaine, lidocaine, palonosetron, dexamethasone, epinephrine, DEX, morphine, levobupivacaine, and methylprednisolone, as well as injection methods including intravenous administration and nerve blocks. Network meta-analysis indicated that intrathecal morphine was the most effective drug for preventing POD. The mechanism through which intrathecal morphine reduces POD may be related to its ability to alleviate postoperative pain, thus reducing

the need for systemic opioid administration. Due to its hydrophilic nature, morphine, when administered intrathecally, may produce selective spinal effects while minimizing systemic effects.

Network meta-analysis indicated that intrathecal morphine was the most effective drug for preventing POD, with its SUCRA rank being Morphine (19.1%) < SINBs (23.2%) < Parecoxib (32.2%) < Lidocaine (35.0%) < FICB (40.7%) < Dexamethasone (51.7%) < Methylprednisolone (52.9%) < Opioid (56.6%) < DEX (58.3%) < Intravenous Iron (87.2%) < Normal Saline (92.5%). The mechanism through which intrathecal morphine reduces POD may be associated with its ability to alleviate postoperative pain and reduce the need for systemic opioid administration. Due to morphine's hydrophilic nature, intrathecal administration can produce selective spinal effects while minimizing systemic side effects [40]. The European Society for Regional Anesthesia and Regional Therapy has recommended peripheral nerve blocks and intrathecal morphine injections as effective postoperative analgesic methods for total hip arthroplasty [41]. Furthermore, morphine was the first opioid approved for intrathecal injection in the United States. Since its initial use in subarachnoid morphine injection for cancer pain management in 1979, intrathecal analgesia has become widely recognized for pain management across various clinical contexts [42]. Additionally, a study by Yao et al. [43] reported that in the observation group, two cases of POD occurred during the first 48 hours after surgery, compared to nine cases in the control group ($P < 0.05$), suggesting that the use of intrathecal morphine may be beneficial in reducing the incidence of delirium in postoperative patients.

Lidocaine has been shown to provide brain protection by crossing the blood-brain barrier to regulate inflammatory mediators, protect cerebral blood flow, reduce brain metabolism, and slow ischemic ion flow [44]. By blocking inflammatory signaling pathways, lidocaine reduces the release of pro-inflammatory factors such as IL-6 by glial cells in the central nervous system. It also decreases the open frequency of sodium ion channels during cell membrane depolarization, which reduces energy consumption in nerve cells and helps prevent delirium. Additionally, intravenous lidocaine can lower the demand for opioids post-surgery [45]. A study by Lai et al. [46] demonstrated that intravenous lidocaine infusion effectively reduced surgical stress and inflammatory responses, leading to a lower incidence of POD two days after surgery (13.3% vs. 30.0%) compared to general anesthesia alone.

Fascia iliaca compartment block (FICB) is a regional nerve block technique where local anesthetics are injected into the plane containing the obturator nerve, lateral femoral cutaneous nerve, and femoral nerve, located between the iliac muscle and iliac fascia. This block effectively interrupts nociceptive stimulation, inhibits sympathetic nerve excitability, improves blood flow to the surgical area, and enhances tissue oxygenation, all of which help to reduce pain and inflammation [47]. Studies have found that patients receiving continuous FICB experience less pain pre-surgery, and the preemptive analgesia provided by FICB reduces opioid requirements. Compared to traditional analgesia methods, continuous FICB has been found to be a more efficient and cost-effective preoperative analgesic option for elderly patients with hip fractures [48, 49].

Dexamethasone is commonly used to treat various inflammatory diseases. It achieves effective analgesic and anti-inflammatory effects by reducing the expression of inflammatory factors in tissues and inhibiting the aggregation of neutrophils and macrophages, which in turn reduces the risk of POD [50]. In an animal model of systemic inflammation induced by MENES, the use of dexamethasone resulted in a significant reduction in the recruitment of brain cells, such as microglia, along with a decrease in the release of inflammatory mediators [51]. Orena et al. [52] conducted a systematic review and found that dexamethasone could effectively reduce the risk of POD. Additionally, the glucocorticoid methylprednisolone also exhibits strong anti-inflammatory and immunosuppressive effects. High-dose methylprednisolone pulse therapy has been shown to reduce the expression levels of IL-18 and other inflammatory factors, thereby inhibiting nonspecific inflammatory responses [53]. Studies have demonstrated that methylprednisolone can reduce the number of activated microglia and the expression of ED-1 protein, effectively suppressing inflammation and promoting the release of neurotrophic factors and other cytokines, thus offering neuronal protection [54].

DEX, a highly selective α2-adrenergic receptor agonist, has sedative, analgesic, and anxiolytic effects, making it an effective option for reducing postoperative pain and anxiety, which may also help prevent the onset of POD [55, 56]. In addition, DEX has been shown to prevent and treat POD by improving patients' sleep, regulating inflammatory factors, and reducing postoperative stress. The possible mechanisms behind this effect are as follows: (1) Central sympathetic nervous system inhibition: DEX inhibits the central sympathetic nervous system, reducing the systemic inflammatory response and helping regulate the immune system. (2) Analgesic effects: By acting on α2-adrenergic receptors located on the presynaptic membrane, DEX inhibits the release of norepinephrine, thus achieving its analgesic effects. (3) Neuroprotection: DEX increases the expression of brain-derived neurotrophic factors in astrocytes, which is important for brain health. (4) Activation of focal adhesion kinase (FAK): DEX activates FAK to regulate extracellular signal-regulated kinase 1/2 (ERK1/2), which plays a role in neuroprotection [57, 58]. In summary, perioperative anti-inflammatory and analgesic drug injections, such as DEX, for patients with HF can effectively reduce the inflammatory response and minimize intraoperative anesthetic consumption. This approach holds significant promise in the prevention of POD.

This meta-analysis is the first to explore the prevention of POD through drug injections in patients with HF during the perioperative period. The literature retrieval process was comprehensive, and the findings provide valuable insights for clinical guidance on drug use in this context. However, this study has certain limitations. First, diverse drug injections: The included studies did not focus on a single drug injection, which introduces some degree of publication bias. The heterogeneity observed may also be attributed to the variations in the types of drugs used. Second, limited data on some outcome indicators: Key outcome indicators, such as the duration and intensity of delirium, were less frequently reported in the literature, leading to greater heterogeneity and affecting the consistency of the analysis.

Conclusion

Perioperative drug injections can effectively reduce the incidence and severity of POD in patients undergoing surgery for HF, providing valuable insights for postoperative management strategies aimed at preventing delirium in this patient group. Among the various drugs evaluated, intrathecal morphine injection was identified as the most effective in preventing POD. We anticipate that future high-quality RCTs will provide further evidence to strengthen the findings of this analysis.

Disclosure of conflict of interest

None.

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