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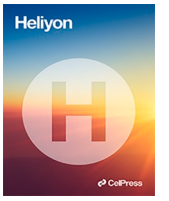

Research article

Impact of the addition of dexmedetomidine to patient-controlled intravenous analgesia on postoperative pain-sleep interaction cycle and delirium: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: The reciprocal nexus between sleep and pain is well-documented, with the deleterious impact of operative trauma potentially playing a pivotal role in the dysregulation of this interplay, which could significantly contribute to the manifestation of postoperative delirium (POD). Studies have investigated the effect of adding dexmedetomidine (DEX) to patient-controlled intravenous analgesia (PCIA) pumps on postoperative pain-sleep interaction cycle and POD, but conclusions remained uncertain. The objective of this investigation is to perform a meta-analysis that thoroughly assesses the impact of integrating DEX into PCIA, focusing on analgesic effectiveness, sleep quality, and the incidence of delirium in postoperative patients.

Methods: PubMed, Embase, Cochrane Library, SinoMed, and Wanfang Data Knowledge Service Platform were searched, for publications in any language, from database inception to September 2023. Our analysis encompassed randomized controlled trials (RCTs) that examine the therapeutic efficacy and risk profile of adding DEX to the PCIA on the postoperative pain-sleep interaction cycle, by focusing on changes in postoperative analgesia (Visual analog scale (VAS) score), sleep efficiency, sleep structure, subjective sleep score (Assen insomnia scale and numerical rating scale) and adverse event rate.

Results: 34 RCTs (4324 patients) were analyzed. This study shows DEX improved analgesia and reduced VAS scores at 6, 12, and 24 h after surgery. Sleep efficiency was enhanced on the 1st and 2nd postoperative night. DEX improved sleep structure at the 1st postoperative night by reducing non-rapid eye movement stage 1 (N1) sleep and increasing non-rapid eye movement stage 2 (N2) and non-rapid eye movement stage 3 (N3) sleep. At the 2nd night, DEX reduced N1 sleep and increased N2 sleep, but not N3 sleep. Data from AIS and NRS showed improvement in subjective sleep scores on the 1st postoperative night and 2nd night. Additionally, DEX decreased the occurrence of POD on the 24 h and first-three days.

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Conclusion: This study shows that the typical DEX doses added to PCIA with sufentanil were 2–5 μg/kg or approximately 200–250 μg, and the addition of DEX to PCIA can improve pain-sleep interaction cycle from multiple perspectives, and further decrease the occurrence of POD.

1. Introduction

Sleep serves a restorative function, and its significance in the recovery and survival of critically ill patients cannot be overstated [1]. Sleep constitutes a crucial element of maintaining good health, following a circadian rhythm lasting approximately 24 h. This rhythm encompasses 90-min cycles consisting of non-rapid eye movement (NREM) and rapid eye movement (REM) phases. NREM sleep is classified to 3 phases: non-rapid eye movement stage 1 (N1), non-rapid eye movement stage 2 (N2), and non-rapid eye movement stage 3 (N3). N2 occupies roughly 50% of the NREM sleep duration, while REM sleep constitutes 15%–20% of the overall sleep time [2]. Sleep deprivation frequently occurs in patients after surgery, characterized by disruptions in sleep architecture, diminished duration of both slow-wave and REM period under polysomnography (PSG) [3]. Postoperative sleep often becomes fragmented due to frequent awakenings, which can result in a shortened sleep duration, heightened arousal, diminished sleep quality, and an elevated occurrence of nightmares. These effects are discernible on PSG as an elevated N1 percentage and a reduction in N2 and N3 percentages [4].

Pain induced by surgical trauma significantly contributes to sleep deprivation among postoperative patients, operating through various potential mechanisms, including endocrine, autonomic, and inflammatory stress responses [4,5]. Surgical trauma, a primary pain inducer, triggers immediate responses at the injury locus via macrophages and monocytes, resulting in the exudation of pro-inflammatory cytokines such as TNF-α and IL-1β. These cytokines have the potential to alter sleep patterns, notably by augmenting slow-wave sleep and diminishing REM sleep phases [6,7]. Overactivity of the sympathetic nerves and release of high stress hormones caused by extensive surgical trauma and pain could also disrupt sleep [8]. Moreover, sleep deprivation could amplify individuals' sensitivity to pain, leading to a vicious cycle of pain-sleep interaction [9]. During the perioperative period, surgical trauma is a significant factor in disturbing sleep patterns and modifying the experience of pain. This creates a complex interplay between pain and sleep, affecting both simultaneously.

Perioperative neurocognitive disturbances, including postoperative delirium (POD), are linked to the cycle of perioperative pain and sleep deprivation [10]. Sleep deprivation is particularly prevalent among older adults, and it becomes more pronounced in cases of critical illness and neurodegenerative conditions like Alzheimer's disease. This demographic is also highly susceptible to negative perioperative outcomes. Possible overlapping mechanisms linking sleep deprivation and delirium encompass disruptions in melatonin synthesis, dysregulation of neurotransmitters, and diminished neuroprotective effects due to critical nutrient shortfalls [5,11,12]. At the same time, research indicates that disruptions in sleep and circadian rhythms can extend the duration of postoperative recovery, elevate the risk of cardiovascular diseases, and compromise immune system functionality [13,14]. Therefore, reducing the negative impact of surgery on the perioperative pain-sleep deprivation interaction cycle and promoting sleep quality may be helpful for the recovery of post-operative patients.

Patient-controlled intravenous analgesia (PCIA) is a widely favored method for managing pain, where healthcare professionals configure the analgesic dosage based on the patient's reported pain intensity and physiological status. When pain is recognized, analgesics are administered under the control of the patient with the guidance of the physician. Dexmedetomidine (DEX) is the selective α2 adrenergic receptor activators recognized with its combined sedative and analgesic attributes. Distinguished from other sedative medications, DEX operates via innate sleep-inducing pathways, inducing a state similar to N2 sleep [15]. Research has demonstrated that low-dose DEX at night could enhance sleep pattern, characterized by an extension of entire sleep duration, increment with N2 stage duration, and an enhancement of subjective sleep quality assessments [16,17]. Meanwhile, DEX can modulate pain pathways through α2 receptors in the dorsal horn of the spinal cord and enhance opioid effects. DEX can also reduce postoperative inflammatory factors through PI3K-Akt signal and the occurrence of POD [18,19]. Due to these advantages, much research revolved around the effects of DEX for postoperative pain, sleep, and delirium, but sample size of related research was insufficient, the results inconclusive, and systematic reviews of methodological quality were lacking. Hence, the propose of the meta-analysis is to comprehensively examine the therapeutic efficacy and risk profile of adding DEX to PCIA on postoperative pain-sleep deprivation interaction cycle and occurrence of POD through meta-analysis.

2. Materials & methods

This meta-analysis of RCTs was registered in the International Prospective Register of Systematic Reviews (PROSPERO) trial registry (CRD42023471592). This meta-analysis conformed to the protocols specified in the Cochrane Handbook and disseminated findings in alignment with the PRISMA 2020 framework. And Reporting checklist based on the PRISMA guidelines was in Supplementary Fig. S1.

2.1. Literature search

Two researchers, Xu W and Zheng Y, meticulously conducted a literature review, employing comprehensive searches across several databases including PubMed, Embase, the Cochrane Library, SinoMed, and Wanfang Data Knowledge Service Platform. The search spanned from the inception of each database to September 1, 2023, focusing on studies that examined the impacts of integrating DEX

into PCIA postoperatively, specifically investigating its effects on sleep and delirium. Terms selected for querying were as follows: (1) "Dexmedetomidine" OR "MPV-1440" OR "Precedex" OR "Dexmedetomidine hydrochloride", (2) "Sleep" OR "Sleep apnea" OR "OSA" OR "Insomnia" OR "Hypersomnia" OR "Narcolepsy" OR "Sleep quality" OR "Sleep quantity" OR "Sleep duration" OR "Sleep Wake Disorders", (3) "Surgery" OR "Operative" OR "Surgical" OR "Postsurgical" OR "Postoperative" OR "Post-surgical" OR "Post-operative" OR "Surgical Procedures, Operative", (4) "Patient-controlled analgesia" OR "Postoperative analgesic pump" OR "PCIA". The previously mentioned four sets of search terms use "and" to form a combination to refine the search process. Details on the exhaustive search strategies are available in Supplementary Table S1. No linguistic limitations were imposed during the process of literature exploration.

2.2. Inclusion and exclusion criteria

Randomized trials evaluating the incorporation of DEX versus a placebo in post-surgical patients utilizing PCA were all included for analysis. Eligible research must document a minimum of one designated result, including VAS (Visual analogue scale/score), subjective sleep quality, sleep structure, sleep efficiency, POD. Criteria for exclusion including: (1) reviews, letters, editorials, or observational (prospective or retrospective cohort) study; (2) comparisons between DEX with other sedative agents; (3) no intravenous administration; (4) no target outcomes; (5) data was unable to obtain or insufficient. (6) DEX used for anesthesia intraoperative rather than for PCIA after surgery. In cases where there was data overlap across two or more studies, the one with most extensive sample size would be chosen.

2.3. Analysis selection and information summary

Two assessors (Xu W and Zheng Y) independently reviewed the titles and abstracts from electronic databases. Following this, eligible studies were selected through detailed text evaluations based on pre-established criteria. Any differences in opinions were settled through discussions among the assessors or by consulting a third adjudicator (Ni C). Data extracted included: study specifics (first author, publication year, study design), participant demographics, baseline attributes (age, sample size, interventions, anesthesia technique), and outcomes (subjective sleep quality, sleep architecture, sleep duration/efficiency, POD, VAS), along with the statistical data (sample size and event counts across groups).

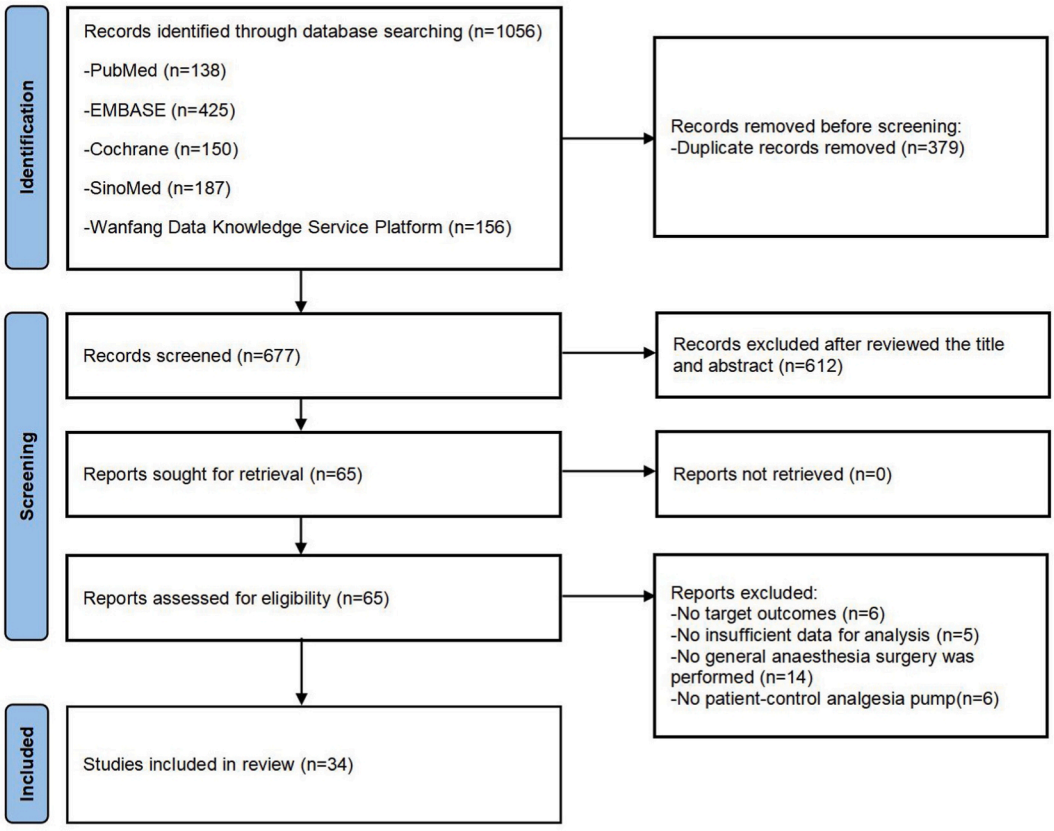

Fig. 1. The flow chart of literature retrieval of this meta-analysis.

Table 1
Attributes of involved trials.

Author, year	Trial type	Sample size		Mean Age		Intervention study	Comparators	Neoplasm's type
		Control	DEX	Control	DEX			
Shao XC, 2019 [21]	RCT	30	30	49.2 ± 7.3	50.3 ± 7.5	2 μg/kg sufentanil + 200 μg DEX in 100 ml saline	2 μg/kg sufentanil in 100 ml saline	Gynecological laparoscopic surgery
Hong H, 2021 [29]	RCT	354	356	71.0 ± 5.0	71.0 ± 5.0	200 μg sufentanil + 200 μg DEX in 100 ml saline	200 μg sufentanil in 100 ml saline	Major orthopedic surgery
Jiang ZM, 2018 (2.4 μg/kg) [38]	RCT	32	32	65.0 ± 6.0	64.0 ± 7.0	0.6 mg/kg oxycodone + 2.4 μg/kg DEX in 100 ml saline	0.6 mg/kg oxycodone in 100 ml saline	Laparoscopic resection of gastrointestinal tumors
Jiang ZM, 2018 (4.8 μg/kg)	RCT	32	33	65.0 ± 6.0	64.0 ± 5.0	0.6 mg/kg oxycodone + 4.8 μg/kg DEX in 100 ml saline	0.6 mg/kg oxycodone in 100 ml saline	Laparoscopic resection of gastrointestinal tumors
Sun Y 2020 [74]	RCT	276	281	69.0	68.0	2 μg/kg sufentanil + 6 mg tropisetron + 4.8 μg/kg DEX in 100 ml saline	2 μg/kg sufentanil + 6 mg tropisetron in 100 ml saline	Non-cardiac surgery
Xiao F, 2021 (0.5 μg/kg) [22]	RCT	31	32	47.5 ± 11.6	49.1 ± 11.2	1 μg/kg sufentanil + 0.5 μg/kg DEX in 100 ml saline	1 μg/kg sufentanil in 100 ml saline	Laparoscopic operation
Xiao F, 2021 (1 μg/kg)	RCT	31	32	47.5 ± 11.6	46.1 ± 11.9	1 μg/kg sufentanil + 1 μg/kg DEX in 100 ml saline	1 μg/kg sufentanil in 100 ml saline	Laparoscopic operation
Li Q, 2019 (2 μg/kg) [75]	RCT	20	20	53.8 ± 10.0	53.6 ± 10.7	3 μg/kg sufentanil + 2 μg/kg DEX in 100 ml saline	3 μg/kg sufentanil in 100 ml saline	Pulmonary lobectomy surgery
Li Q, 2019 (3 μg/kg)	RCT	20	20	53.8 ± 10.0	50.3 ± 12.3	3 μg/kg sufentanil + 3 μg/kg DEX in 100 ml saline	3 μg/kg sufentanil in 100 ml saline	Pulmonary lobectomy surgery
Li Q, 2019 (4 μg/kg)	RCT	20	20	53.8 ± 10.0	49.7 ± 12.2	3 μg/kg sufentanil + 4 μg/kg DEX in 100 ml saline	3 μg/kg sufentanil in 100 ml saline	Pulmonary lobectomy surgery
Yan Q, 2020 [23]	RCT	47	48	49.5 ± 9.5	50.2 ± 10.1	3 μg/kg sufentanil + 5 mg tropisetron + 200 μg DEX in 100 ml saline	3 μg/kg sufentanil + 5 mg tropisetron in 100 ml saline	Radiation surgery of ovarian cancer
Liu J, 2019 [39]	RCT	40	40	50.2 ± 3.3	53 ± 4.2	1.2 mg/kg nalbuphine + 1 μg/kg DEX in 100 ml saline	1.2 mg/kg nalbuphine in 100 ml saline	Laparoscopic surgery for gastrointestinal tumors
Wei H, 2018 [31]	RCT	30	30	73.0 ± 7.0	73.0 ± 8.0	2 μg/kg sufentanil + 5 mg tropisetron + 2 μg/kg DEX in 100 ml saline	2 μg/kg sufentanil + 5 mg tropisetron and in 100 ml saline	Tumorectomy
Tan X, 2019 [35]	RCT	36	36	48.5 ± 5.9	47.8 ± 6.3	100 μg sufentanil + 250 μg DEX in 100 ml saline	100 μg sufentanil in 100 ml saline	Laparohysterectomy
Cao G, 2018 [24]	RCT	60	60	69.0 ± 11.2	68.6 ± 12.0	1.5–2.5 μg/kg sufentanil + 5 mg tropisetron + 2 μg/kg DEX in 100 ml saline	1.5–2.5 μg/kg sufentanil + 5 mg tropisetron in 100 ml saline	Unilateral artificial hip replacement
Hu X, 2019 [43]	RCT	60	60	53.4 ± 7.6	52.8 ± 6.8	1 mg/kg dezocine + 8 mg ondansetron + 3 μg/kg DEX+ in 100 ml saline	1 mg/kg dezocine + 8 mg ondansetron in 100 ml saline	Thoracoscopic lobectomy
Wu XL, 2019 [76]	RCT	20	20	67.0 ± 3.0	68.0 ± 4.0	15 μg/kg fentanyl + 5 mg tropisetron + 1 μg/kg DEX in 100 ml saline	15 μg/kg fentanyl+ 5 mg tropisetron in 100 ml saline	Thoracic surgery
Cao J, 2020 [34]	RCT	45	45	47.6 ± 19.6	47.4 ± 19.7	15 μg/kg fentanyl + 4 μg/kg DEX in 100 ml saline	15 μg/kg fentanyl in 100 ml saline	Laparoscopic cholecystectomy
Jin N, 2022 [77]	RCT	31	30	56.9 ± 12.1	55.0 ± 10.9	0.02μg/(kg·h) sufentanil + 0.01μg/(kg·h) dezocine + 0.02–0.04μg/(kg·h) DEX	0.02μg/(kg·h) Sufentanil + 0.01μg/(kg·h) dezocine	Open gynecological surgery
Tang R, 2017 [36]	RCT	29	30	54.7 ± 4.3	52.5 ± 5.0	100 μg sufentanil + 250 μg DEX in 100 ml saline	100 μg sufentanil in 100 ml saline	Complete hysterectomy
Wang M, 2020 [30]	RCT	35	35	44.9 ± 5.1	49.0 ± 4.0	100 μg sufentanil + 250 μg DEX in 100 ml saline	100 μg sufentanil in 100 ml saline	Laparohysterectomy
Gao W, 2021 [42]	RCT	30	30	57.9 ± 7.1	58.4 ± 6.8	1.5 μg/kg sufentanil + 5 μg/kg DEX in 100 ml saline	1.5 μg/kg sufentanil in 100 ml saline	Partial laryngectomy

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Table 1 (*continued*)

Author, year	Trial type	Sample size		Mean Age		Intervention study	Comparators	Neoplasm's type
		Control	DEX	Control	DEX			
Zhang X, 2020 [28]	RCT	30	30	38.9 ± 9.9	40.7 ± 10.2	1μg/(kg·d) sufentanil + 5 mg tropisetron + 1μg/(kg·d) DEX in 100 ml saline	1μg/(kg·d) sufentanil + 5 mg tropisetron in 100 ml saline	Free skin flap transplantation
Yang D, 2022 [37]	RCT	30	30	50.2 ± 5.6	51.0 ± 4.9	1.5 μg/kg sufentanil + 5 μg/kg DEX in 100 ml saline in 100 ml saline	1.5 μg/kg sufentanil in 100 ml saline	Radical resection of esophageal cancer
Liu Q, 2020 [45]	RCT	75	75	50.4 ± 15.0	51.7 ± 10.5	20 mg dezocine + 50 μg sufentanil + 200 μg DEX in 100 ml saline	20 mg dezocine + 50 μg sufentanil in 100 ml saline	Cervical cancer radical surgery
Qiu Z, 2019 [20]	RCT	72	72	51.3 ± 3.6	52.1 ± 3.9	100 μg sufentanil + 250 μg DEX in 100 ml saline	100 μg sufentanil in 100 ml saline	Laparohysterectomy
Yuan F, 2014 [49]	RCT	30	30	70.0 ± 5.0	71.0 ± 6.0	2 μg/kg sufentanil + 6 mg ramosetron + 0.02 μg/kg/h DEX in 100 ml saline	2 μg/kg sufentanil + 6 mg ramosetron in 100 ml saline	Radical operation for carcinoma of colon
Yu L, 2018 (1 μg/kg) [27]	RCT	25	25	/	/	1.5 μg/kg sufentanil + 1 μg/kg DEX in 100 ml saline	1.5 μg/kg sufentanil in 100 ml saline	Radical excision of gastric malignancy
Yu L, 2018 (1.5 μg/kg)	RCT	25	25	/	/	1.5 μg/kg sufentanil + 1.5 μg/kg DEX in 100 ml saline	1.5 μg/kg sufentanil in 100 ml saline	Radical excision of gastric malignancy
Yu L, 2018 (2 μg/kg)	RCT	25	25	/	/	1.5 μg/kg sufentanil + 2 μg/kg DEX in 100 ml saline	1.5 μg/kg sufentanil in 100 ml saline	Radical excision of gastric malignancy
Su Z, 2015 [26]	RCT	85	86	/	/	2 μg/kg sufentanil + 2.5 μg/kg DEX in 100 ml saline	2 μg/kg sufentanil in 100 ml saline	Laparoscopic cholecystectomy.
Chen J, 2018 [25]	RCT	40	40	67.2 ± 6.3	66.8 ± 6.1	2 μg/kg sufentanil + 100 μg/kg tropisetron+2.5 μg/kg DEX in 100 ml saline	2 μg/kg sufentanil + 100 μg/kg tropisetron in 100 ml saline	Total hip joint replacement surgery
Cai X, 2020 (1 μg/kg) [46]	RCT	20	20	66.8 ± 5.6	68.3 ± 6.3	2 μg/kg sufentanil + 1 μg/kg DEX in 100 ml saline	2 μg/kg sufentanil in 100 ml saline	Upper abdominal operation
Cai X, 2020 (1.5 μg/kg)	RCT	20	20	66.8 ± 5.6	67.1 ± 6.3	2 μg/kg sufentanil + 1.5 μg/kg DEX in 100 ml saline	2 μg/kg sufentanil in 100 ml saline	Upper abdominal operation
Cai X, 2020 (2 μg/kg)	RCT	20	20	66.8 ± 5.6	67.0 ± 6.5	2 μg/kg sufentanil + 2 μg/kg DEX in 100 ml saline	2 μg/kg sufentanil in 100 ml saline	Upper abdominal operation
Chen S, 2021 [47]	RCT	80	80	68.9 ± 6.4	70.9 ± 8.1	2 μg/kg sufentanil + 5 mg totoxestron + 3 μg/kg DEX in 100 ml saline	2 μg/kg sufentanil + 5 mg totoxestron in 100 ml saline	Total hip joint replacement surgery
Han C, 2021 [48]	RCT	70	70	71.9 ± 3.0	70.3 ± 2.8	0.15 mg/kg butorphanol + 100 mg DEX in 100 ml saline	0.2 mg/kg butorphanol in 100 ml saline	Lumbar surgery
Dai Q, 2022 [33]	RCT	40	40	46.3 ± 5.2	47.4 ± 4.9	0.3 mg/kg dezocine + 1.5 μg/kg sufentanil + 3 mg granisetron + 5 μg/kg DEX in 100 ml saline	0.3 mg/kg dezocine + 1.5 μg/kg sufentanil + 3 mg granisetron in 100 ml saline	Laparoscopic Total Hysterectomy
Xie Q, 2022 [32]	RCT	40	40	52.1 ± 12.2	52.1 ± 11.3	100 μg sufentanil + 200 μg DEX in 150 ml saline	100 μg sufentanil in 150 ml saline	Radicaltomy for gastric/colorectal cancer

2.4. Study quality assessment

Two reviewers (Xu W and Zheng Y) evaluated the potential bias risks in RCTs using the Revised Cochrane risk-of-bias tool for randomized trials (RoB2), renowned for its enhanced depth and comprehensiveness compared to RoB 1. RoB2 encompasses five key domains: randomization process, deviations from intended interventions, handling of missing outcome data, outcome measurement, and selection of reported results. Bias risk within every region, as well as the overall bias risk, were categorized into three levels: 'low risk,' 'some concerns,' or 'high risk'.

2.5. Statistical analysis

Statistical evaluations for the meta-analysis were executed employing Review Manager (version 5.4). Aggregate outcomes were determined and depicted through the standard mean difference (SMD) with a 95% Confidence Interval (CI) and risk ratio with a 95% CI. Significant heterogeneity in this analysis was identified with a P-value of <0.01 in the Cochrane Q test or $I^2 > 50\%$, prompting the adoption of random-effects models and investigation into heterogeneity sources. In the absence of significant heterogeneity, fixed-effects models were applied.

3. Results

3.1. Study selection outcome

The schematic representation of the literature search process is illustrated in Fig. 1. The initial investigation uncovered 1056 papers, with 379 duplicates subsequently eliminated. Screening narrowed the selection to 677 pertinent articles. A review of titles and abstracts further distilled the pool to 65 likely candidates, which underwent detailed full-text evaluation. Adhering to strict inclusion and exclusion criteria, 35 studies were later excluded for specific reasons: (1) no target outcomes (n = 6); (2) insufficient data for analysis (n = 5); (3) no general anesthesia and surgery was performed (n = 14); (4) no patient-control analgesia pump (n = 6), culminating in 34 studies being incorporated into this article.

3.2. Baseline characteristics

In our analysis, we ultimately selected 34 RCTs that encompassed 4324 participants (DEX group: 2088; comparator group: 2076), all undergoing surgeries under general anesthesia and utilizing PCIA. The age of participants across these studies spanned from 40.7 to 73.4 years, with study sizes ranging from 40 to 557 individuals. These 34 RCTs specifically explored the efficacy of combining DEX

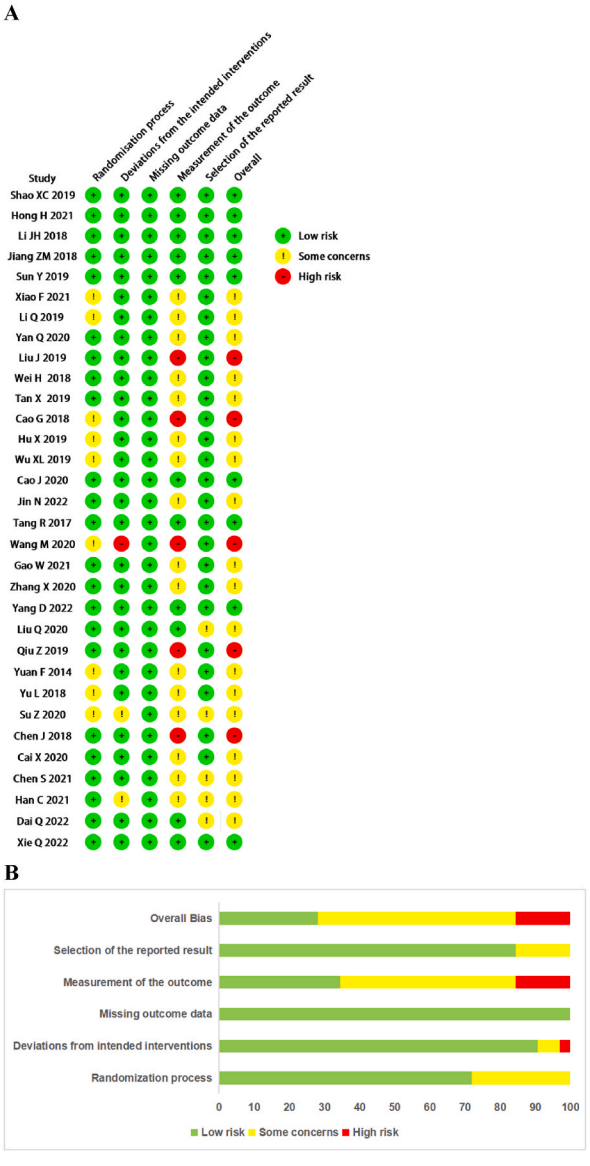

Fig. 2. (A) Methodological quality graph and summary of the included studies: Risk of bias summary, (B) Risk of bias graph.

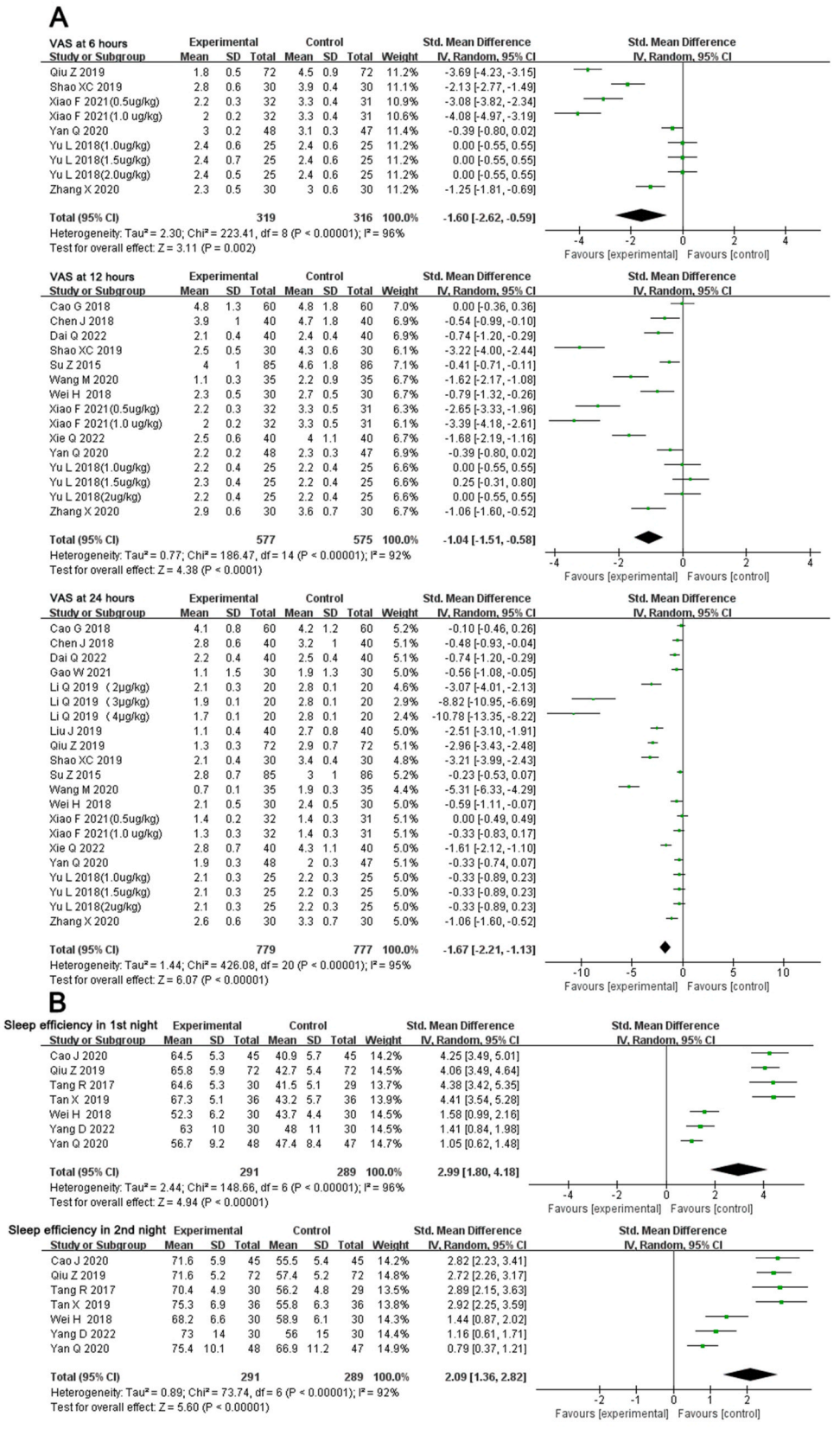

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Fig. 3. Effects of DEX on VAS and sleep efficacy. (A) Effects of DEX on VAS. Forest plot of Std. Mean Difference analyzed by Mantel-Haenszel statistics in the random-effect model. Meta-analysis of the DEX effect on 6 h, 12 h, 24 h respectively. (B) Effects of DEX on sleep efficacy. Forest plot of Std. Mean Difference analyzed by Mantel-Haenszel statistics in the random-effect model. Meta-analysis of the DEX effect on sleep efficacy of the 1st and 2nd nights after surgery respectively.

with a comparator versus using the comparator alone in the context of postoperative PCIA. These RCTs exclusively used DEX in postoperative PCIA pumps, without intraoperative or other postoperative applications. Of the 26 studies, the chosen comparators were sufentanil, 2 studies were fentanyl, 1 study was oxycodone, 1 study was butorphanol, 1 study was dezocine, 1 study was nalbuphine. Analgesic dosages across the studies varied, and key details of the included studies are outlined in Table 1.

3.3. Bias risk evaluation

The evaluation of bias risk in each study is depicted in Fig. 2A and Fig. B. Among the studies reviewed, nine lacked a detailed process for random allocation, leading to classification under "some concerns." A single study strayed from the prescribed intervention, while five were deemed high risk regarding outcome metrics due to clinicians' awareness of patient assignment, potentially influencing the results. Conversely, eight studies were determined to have a minimal risk of bias.

3.4. Synthesis of results

Results from 34 studies were integrated, revealing a significant connection between sleep deprivation and pain. Therefore, we first focused on the changes in postoperative analgesia (based on VAS scores), then we observed the effects of DEX on sleep efficiency, sleep structure, and subjective sleep scores (Assen Insomnia Scale (AIS) and Numerical Rating Scale (NRS)). Disruptions in sleep and circadian rhythms post-surgery pose significant challenges, potentially precipitating cognitive impairments and associated complications in patients, so we further investigated the effects of DEX on the occurrence of POD. To sum up, this study thoroughly evaluated the impact of DEX on analgesia, sleeping quality, pain-sleep deprivation interaction cycle and POD.

3.5. Effects of DEX on postoperative pain

14 RCTs reporting the postoperative VAS scores at postoperative hour 6, 12 and 24 in 1396 patients with PCIA were included [20–33]. As demonstrated in Fig. 3A, the findings indicated the discomfort ratings in individuals undergoing PCIA with the DEX-equivalent combination were notably inferior compared to those in individuals undergoing only the comparator. The aggregated outcomes derived from the random-effects model illustrated a notable correlation between the utilization of DEX and diminished VAS scores after 6 h (SMD = −1.60, 95%CI: −2.62, −0.59), 12 h (SMD = −1.04, 95%CI: −1.51, −0.58), and 24 h (SMD = −1.67, 95%CI: −2.21, −1.13) after surgery. Thus, DEX could alleviate postoperative pain, which is an important factor for the occurrence of sleep deprivation.

3.6. Effects of DEX on postoperative sleep efficiency

7 investigations, involving 580 individuals, examined the impacts of DEX on sleep effectiveness of the 1st and 2nd postoperative night (Sleep efficiency = sleep time/bed time × 100%) [20,23,31,34–37]. All experiments were conducted with PSG to measure the patient's postoperative sleep efficiency, and the higher it means the better the quality of sleep. Separately, there was an obvious difference in the sleep effectiveness on the 1st (SMD = 2.99, 95%CI: 1.80, 4.18) and the 2nd postoperative night (SMD = 2.09, 95%CI: 1.36, 2.82) between patients with and without DEX in PCIA (Fig. 3B).

3.7. Effects of DEX on postoperative sleep structure

To further determine the effect of DEX on postoperative sleep quality, random-effects model was used to synthesize the sleep structure at the 1st and 2nd postoperative night in 6 RCTs, including 542 patients, which assessed sleep structure with PSG [20,34–36,38,39]. In the lightest sleep state, an increased percentage of N1 sleep indicates sleep fragmentation [40], and higher N2 sleep is associated with improved sleep satisfaction associated with lower arousals [41]. As shown in Fig. 4, incorporating DEX into PCIA reduced the percentage of N1 sleep (SMD = −5.31, 95%CI: −7.02, −3.60), and increased the percentage of N2 (SMD = 3.71, 95%CI: 2.08, 5.33) and N3 sleep (SMD = 0.43, 95%CI: 0.23, 0.64) on the 1st postoperative night. DEX also reduced the percentage of N1 sleep (SMD = −6.68, 95%CI: −10.25, −3.12) and augmented the proportion of N2 sleep (SMD = 4.14, 95%CI: 1.82, 6.46), but had no effects on N3 sleep (SMD = 0.35, 95%CI: −0.22, 0.92) on the 2nd postoperative night.

3.8. Effects of DEX on postoperative subjective sleep scores

To determine the impact of DEX on postoperative sleep from the subjective level, we comprehensively analyzed 10 RCTs, including 969 patients, by AIS and NRS [20,21,23,31,32,39,42–45]. For AIS, as an internationally recognized sleep quality self-measurement scale, the greater the rating, the poorer the sleep quality. In this analysis, the incorporating of DEX to PCIA reduced patients' AIS

scores on the 1st (SMD = −2.48, 95%CI: −3.41, −1.56) and 2nd (SMD = −2.06, 95%CI: −3.02, −1.11) postoperative night. For NRS, patients subjectively evaluate the sleep quality, where 0 signifies very poor sleep and 10 indicates quality sleep. The addition of DEX to PCIA improved NRS on the 1st (SMD = 2.43, 95%CI: 1.23, 3.62) and 2nd (SMD = 1.16, 95%CI: 0.83, 1.49) postoperative night (Fig. 5A). These results suggest that postoperative pumping of DEX via PCIA could improve postoperative sleep quality of patients.

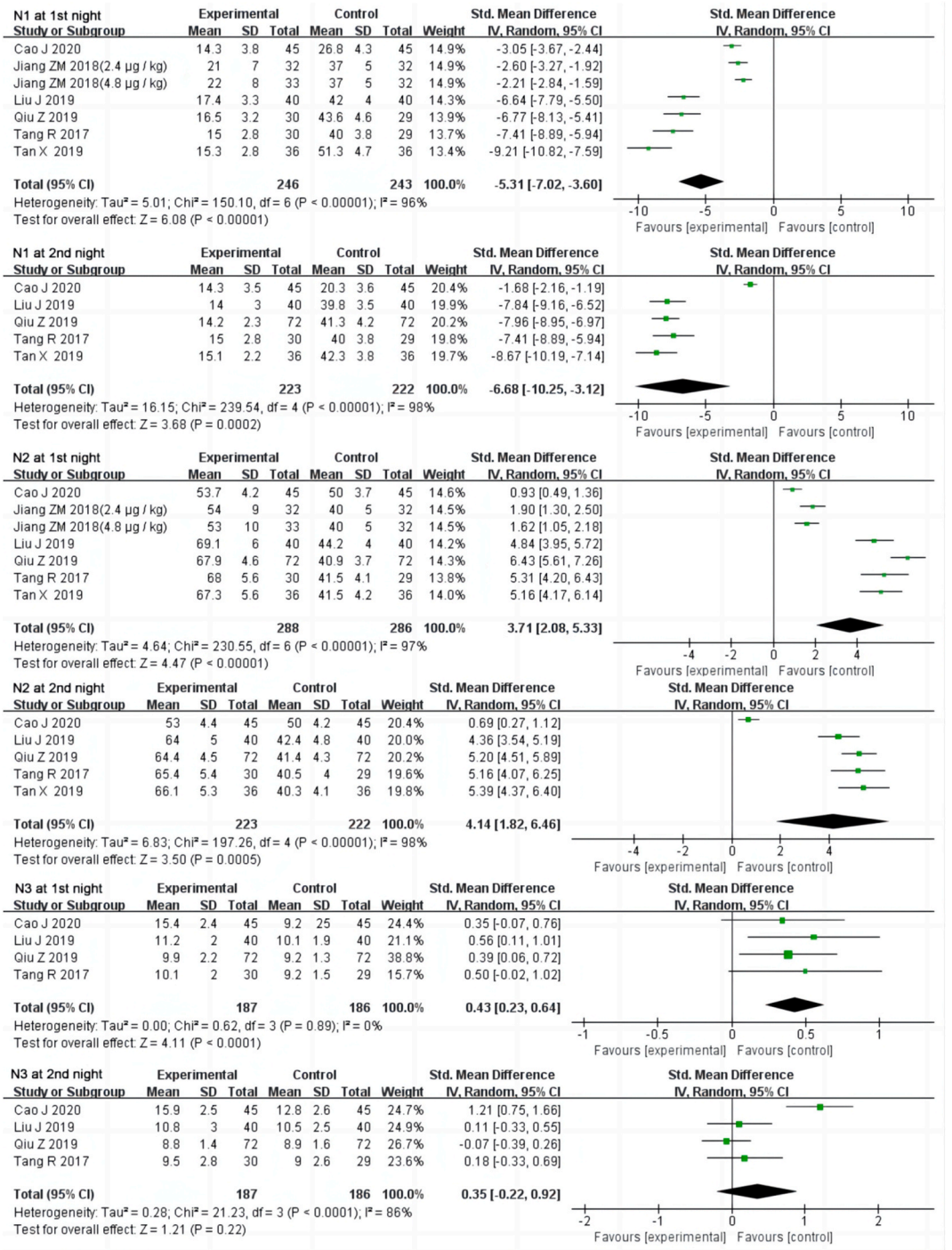

Fig. 4. Effects of DEX on postoperative sleep structure. Forest plot of Std. Mean Difference analyzed by Mantel-Haenszel statistics in the random-effect model. Meta-analysis of the percentage of N1, N2, N3 in the 1st and 2nd nights after surgery respectively.

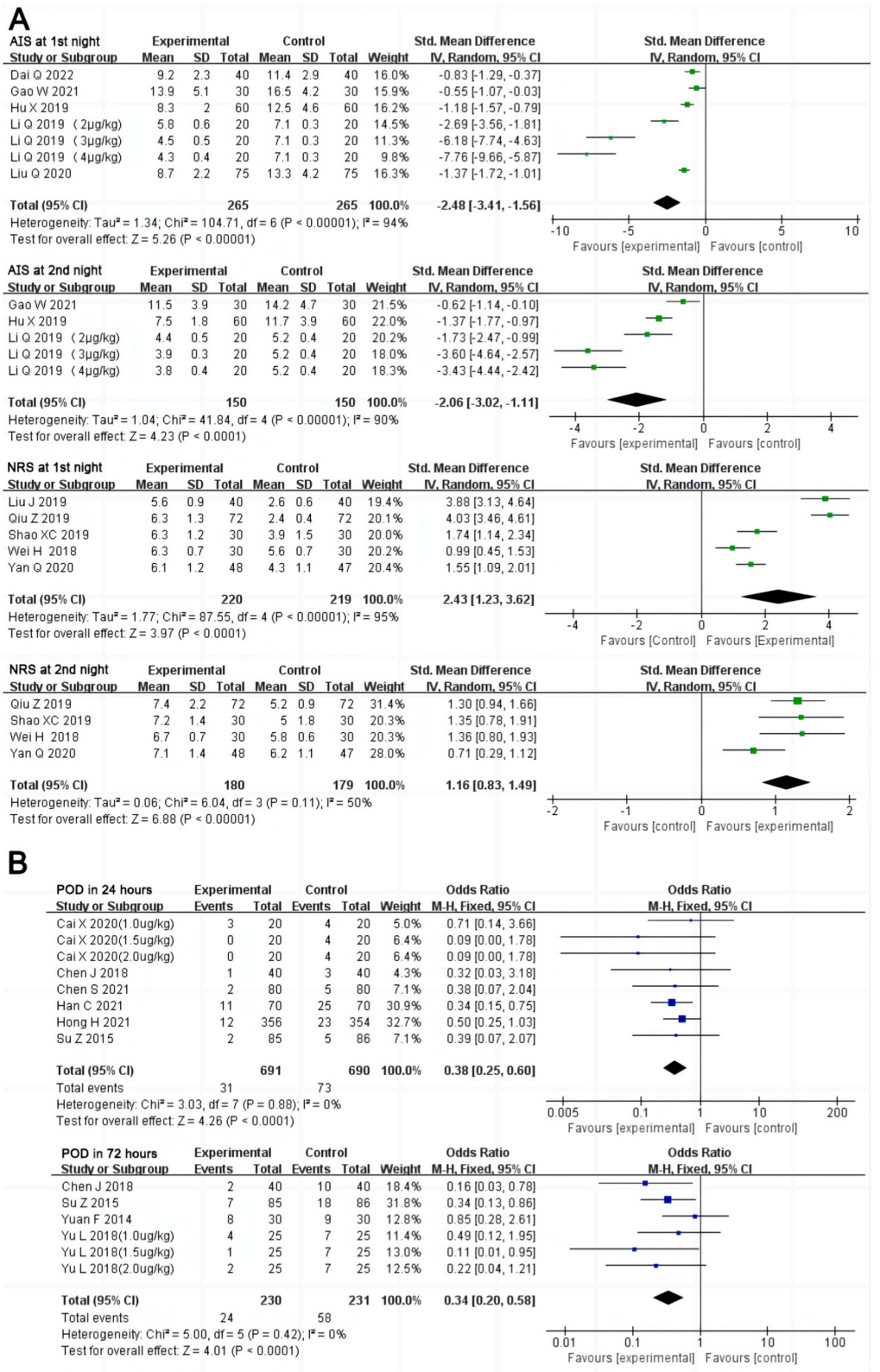

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Fig. 5. Effects of DEX on subjective sleep quality and the occurrence of POD. (A) Effects of DEX on subjective sleep quality. Forest plot of Std. Mean Difference analyzed by Mantel-Haenszel statistics in the random-effect model. NRS and AIS were analyzed synthetically in the 1st and 2nd nights after surgery respectively. (B) Effects of DEX on the occurrence of POD. Forest plot of Odds Ratio analyzed by Mantel-Haenszel statistics in the fixed model. The effects of DEX on the occurrence of POD were analyzed at 24 h and 72 h after surgery respectively.

3.9. Effects of DEX on POD

The interaction between pain and sleep deprivation forms a vicious circle, which jointly leads to a series of postoperative complications, especially in the progression of POD [25,26,29,46–49]. Therefore, the incidence of POD among 1842 patients was synthesized using a fixed-effects model from 10 RCTs, of which 9 articles utilized Confusion Assessment Method (CAM), and one article utilized Delirium Rating Scale (DRS) to assess POD. As shown in Fig. 5B, incorporating DEX into PCIA decreased the occurrence of POD on the 1st (OR = 0.38, 95%CI: 0.25, 0.60) and first-three (OR = 0.34, 95%CI: 0.20, 0.58) postoperative days.

3.10. Safety of incorporating DEX into PCIA

As incorporating DEX into PCIA to PCIA improved postoperative pain-sleep interaction cycle and cognitive function, we further evaluated its safety. We selected and collected the adverse events (including postoperative hypotension, respiratory depression, nausea and vomiting, and bradycardia) from 10 RCTs, including 1620 patients [20,22,28,29,37,39,42,43,46,48]. As shown in Fig. 6, the findings indicate that incorporating DEX into PCIA was not associated with significant increase of postoperative hypotension (SD = 0.04, 95%CI: −0.03, 0.10), respiratory depression (SD = 0.00, 95%CI: −0.01, 0.02), nausea and vomiting (SD = 0.03, 95%CI: −0.02, 0.08), and bradycardia (SD = 0.02, 95%CI: −0.01, 0.05). Thus, incorporating DEX into PCIA is an effective and safe way to prevent and treat pain-sleep interaction cycle and POD.

4. Discussion

This meta-analysis investigated the impacts of adding DEX to PCIA on postoperative pain, sleep quality and delirium. This analysis suggested that in terms of analgesia, incorporating DEX into PCIA reduced postoperative VAS score. In terms of sleep, incorporating DEX into PCIA improved postoperative sleep efficiency, sleep structure, and patients' subjective sleep scores. Considering the relationship between pain-sleep interaction cycle and delirium, we explored the effect of DEX on POD, and this analysis suggested incorporating DEX into PCIA reduced the occurrence of POD. In terms of safety, the results indicated incorporating DEX into PCIA did not increase the incidence of adverse events including postoperative hypotension, respiratory depression, nausea and vomiting, and bradycardia. Therefore, incorporating DEX into PCIA could be a safe and effective treatment that can improve postoperative pain-sleep interaction cycle and prevent the occurrence of POD.

There is already evidence that sleep and pain have a bidirectional relationship [50]. On one hand, pain plays a key role and affects postoperative sleep, influences sleep from the following aspects: 1) Increased postoperative sympathetic activity due to pain related norepinephric activity, could keep patients maintaining wakefulness [51]. 2) A variety of inflammatory mediators caused by surgical trauma, such as IL-1, TNF-α, etc., could lead to heightened non-REM period and reduced REM period [52,53]. 3) Cortisol is key mediator related to pain. Its administration could reduce REM period and heighten non-REM period, just as the sleep variation after surgery [54]. On the other hand, previous studies showed that the decrease in quality and amount of sleep led to 2–3 times increase of painful conditions in patients, however, the mechanism was not drastically clarify [9]. It's hypothesized that short-term sleep deprivation during the perioperative period may enhance the expression and activity of L-type calcium channels in the lumbar dorsal root ganglion, potentially prolonging rehabilitation time [44,55]. The interaction between sleep deprivation and pain is complex during postoperative period, and sleep deprivation has become an important predictor for postoperative pain [56].

Postoperative patients experienced sleep fragmentation due to frequent arousal and changes in sleep structure, which was manifested by an increase in the percentage of N1 sleep and a decrease in N2 and N3 sleep [57]. DEX could increase biomimetic N3 sleep in a dose-dependent manner and improve synaptic plasticity and cognition [58]. Our previous meta-analysis has shown that intraoperative use of DEX can reduce postoperative immune dysfunction and reduce underlying neuroinflammation, which may indicate the role of DEX in improving postoperative sleep disorders [59]. The present results in this meta-analysis suggest that through postoperative PCIA, DEX reduces N1 sleep and increases N2 and N3 sleep, indicating the reduction of sleep fragmentation. Previous animal studies showed, DEX could stimulate the sleep nucleus and inhibit the awakening nucleus through c-Fos, the marker of neuronal activity, which could display changes in different brain regions during spontaneous sleep-wake episodes, increase in ventrolateral preoptic nucleus neurons and the sleep-promoting system, and decrease in cerebral cortex and subcortical arousal system, then promote NREM sleep in mice. The present results also indicated that DEX reduced postoperative pain. Previous studies showed that DEX enhanced pain control through α-2 receptor and substance P related pain pathways in spinal dorsal horn, thereby improved sleep quality through pain-sleep interaction cycle [44].

Previous articles indicated that the incidence of POD ranges from 7% to 56% [60]. This meta-analysis showed that the POD incidence within three days post-surgery was approximately 25%, which was associated with cognitive decline, prolonged hospital stay, increased morbidity and mortality [61]. Evans et al. found that reduced sleep duration and increased sleep latency on the 1st postoperative day were associated with increased occurrence and severity of POD, loss of sleep on 1st postoperative night is an early predictor of subsequent delirium [62]. The current finding showed DEX reduced the incidence of POD, which was associated with

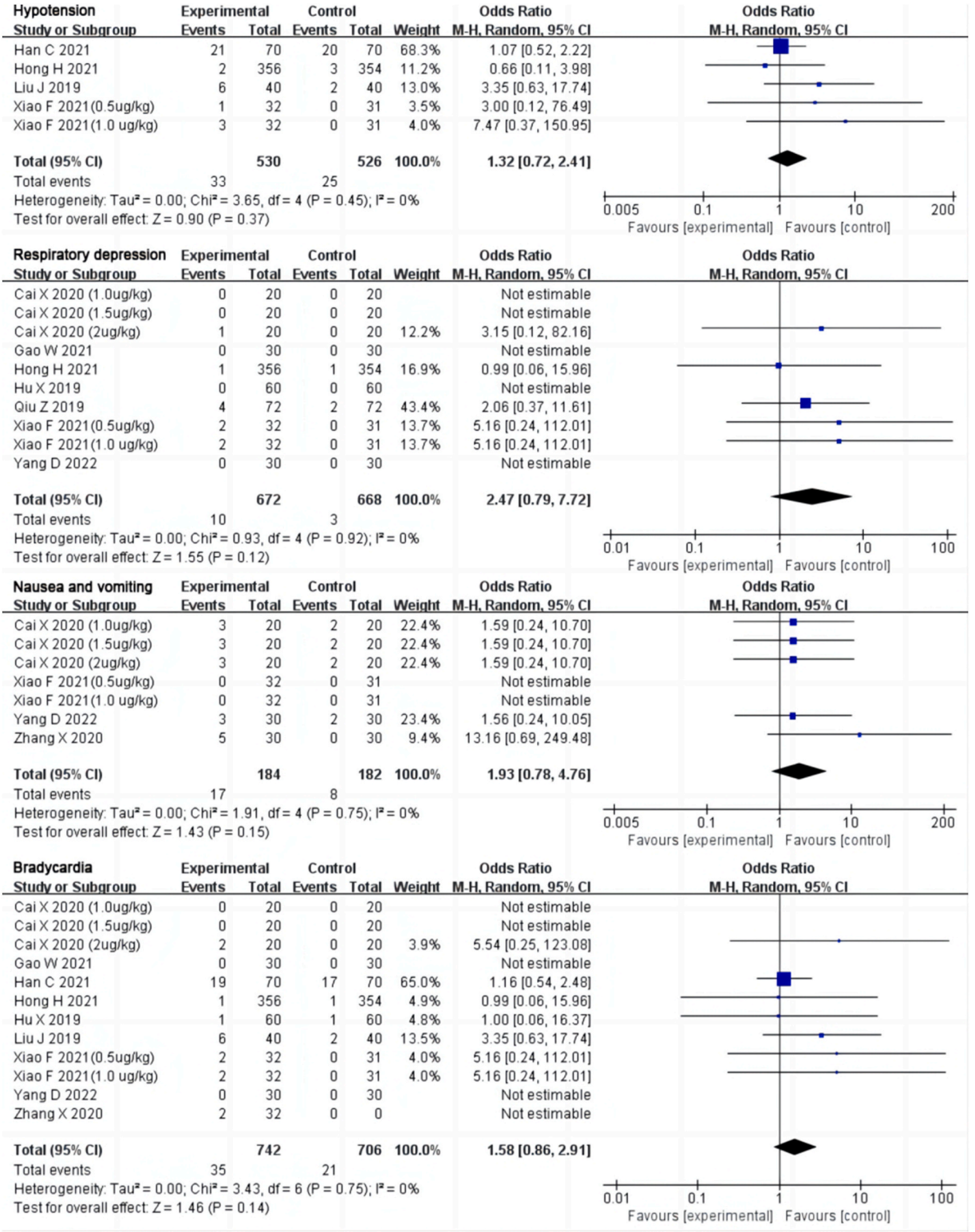

Fig. 6. Safety of the addition of DEX to PCIA. Forest plot of risk difference, analyzed by Mantel-Haenszel statistics in the random model. Meta-analysis of the DEX effect on the occurrence of adverse events included postoperative hypotension, respiratory depression, nausea and vomiting, and bradycardia.

improved postoperative pain-sleep interaction cycle. The sleep-wake cycles induced by DEX were similar to natural sleep, which was associated with DEX's inhibitory effects on postoperative central nervous inflammation [59], and multiple factors contributed the process [63]. DEX inhibited glial cell activation and TLR4 expression, which involved its effects on inflammation and neuronal apoptosis, and cognitive dysfunction [64,65]. The addition of DEX also reduced the amount of anesthetics and opioids, stabilized hemodynamics, which contributed to the reduction of POD [66,67].

In this meta-analysis, we adhered to the internationally recognized PRISMA guidelines and utilized predefined inclusion and exclusion criteria to minimize the risk of selection bias. Based on the inclusion criteria including postoperative administration of drugs via PCIA, and consistent doses of medications other than DEX between control and experimental groups, as well as the exclusion criteria, the studies included were predominantly from China. In the studies from USA and Turkey, the DEX application was initiated during the intraoperative period [68–70]. In the study from India, a reduced dose of other analgesics was used in the experimental group compared to the control group [71]. In the study from Egypt, the administration method other than PCIA was used [72]. Nevertheless, results of these studies also suggested that perioperative application of DEX improved postoperative sleep and pain.

This study has several limitations. First, in this meta-analysis, the drugs selected for compatibility with DEX in PCIA differed among the 34 studies. In 28 of the 34 studies, the combination agent was sufentanil, two fentanil, one oxycodone, one butorphanol, one dizocine, and one nalbuphine, which may lead to heterogeneity. There were also variations in the dose of DEX in the studies, some are based on body weight, others are fixed doses. However, the funnel plots showed no significant asymmetry (Supplementary Fig. S2, Supplementary Fig. S3). Second, the effect of intraoperative DEX infusion on postoperative sleep, which is a commonly used drug administration mode, was not discussed in this meta-analysis. Therefore, further data collection is necessary to explore this aspect. Finally, Studies have shown that by improving sleep quality, patients can increase their recovery and range of motion after surgery and improve long-term prognosis [73]. Data regarding the long-term effects of DEX remains scarce in treatment of postoperative sleep deprivation in this meta-analysis. Hence, conducting additional extensive and rigorous RCTs to compile and scrutinize some data will be essential to validate the finding.

5. Conclusion

This study revealed that the typical DEX doses added to PCIA with sufentanil were 2–5 μg/kg or approximately 200–250 μg. And the addition of DEX to PCIA could reduce postoperative pain level, improve postoperative sleep quality from the aspects including sleep efficiency, sleep structure, and subjective sleep quality. Through dual promotion of analgesia and sleep, a benign effect on the pain-sleep interaction cycle was achieved, which reduced the occurrence of POD. And the addition of DEX didn't increase the incidence of adverse events. These results provide potential mechanisms and therapeutic strategy for postoperative central nervous system function and recovery in patients.

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Data availability statement

The datasets analyzed during the current study are derived from publicly available sources. Details regarding the sources of the data used in this meta-analysis are provided in the References section. All data sources referenced in this study are publicly accessible through their respective repositories or publications.

CRediT authorship contribution statement

Wenjie Xu: Writing – original draft, Investigation, Data curation, Conceptualization. **Yuxiang Zheng:** Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **Qing Wang:** Writing – original draft, Visualization, Validation. **Zizheng Suo:** Writing – review & editing, Conceptualization. **Lingling Fang:** Writing – review & editing, Project administration, Conceptualization. **Jing Yang:** Writing – original draft, Visualization. **Shuai Li:** Writing – review & editing, Writing – original draft, Conceptualization. **Peng Li:** Writing – review & editing, Conceptualization. **Xixi Jia:** Formal analysis, Data curation, Conceptualization. **Xiaoyan Liu:** Writing – review & editing. **Hui Zheng:** Writing – review & editing, Supervision, Project administration, Formal analysis, Conceptualization. **Cheng Ni:** Writing – review & editing, Validation, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27623.

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