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Effects of perioperative interventions for preventing postoperative delirium

A protocol for systematic review and meta-analysis of randomized controlled trials

Xia Li, MMed, Yanting Wang, MMed, Jie Liu, MMed, Yue Xiong, MMed, Shiqiang Chen, MMed, Jingjing Han, MMed, Wanli Xie, MD, PhD, Qingping Wu, MD, PhD*

Abstract

Background: Postoperative delirium (POD) not only increases the medical burden but also adversely affects patient prognosis. Although some cases of delirium can be avoided by early intervention, there is no clear evidence indicating whether any of these measures can effectively prevent POD in specific patient groups.

Objective: The aim of this meta-analysis was to compare the efficacy and safety of the existing preventive measures for managing POD.

Methods: The PubMed, OVID (Embase and MEDLINE), Web of Science, and the Cochrane Library databases were searched for articles published before January 2020. The relevant randomized controlled trials (RCTs) were selected based on the inclusion and exclusion criteria. Data extraction and methodological quality assessment were performed according to a predesigned data extraction form and scoring system, respectively. The interventions were compared on the basis of the primary outcome like incidence of POD, and secondary outcomes like duration of delirium and the length of intensive care unit and hospital stay.

Results: Sixty-three RCTs were included in the study, covering interventions like surgery, anesthesia, analgesics, intraoperative blood glucose control, cholinesterase inhibitors, anticonvulsant drugs, antipsychotic drugs, sleep rhythmic regulation, and multimodal nursing. The occurrence of POD was low in 4 trials that monitored the depth of anesthesia with bispectral index during the operation ($P < .0001$). Two studies showed that supplementary analgesia was useful for delirium prevention ($P = .002$). Seventeen studies showed that perioperative sedation with α_2-adrenergic receptor agonists prevented POD ($P = .0006$). Six studies showed that both typical and atypical antipsychotic drugs can reduce the incidence of POD ($P = .002$). Multimodal nursing during the perioperative period effectively reduced POD in 6 studies ($P < .00001$). Furthermore, these preventive measures can reduce the duration of delirium, as well as the total and postoperative length of hospitalized stay for non-cardiac surgery patients. For patients undergoing cardiac surgery, effective prevention can only reduce the length of intensive care unit stay.

Conclusion: Measures including intraoperative monitoring of bispectral index, supplemental analgesia, α_2-adrenergic receptor agonists, antipsychotic drugs, and multimodal care are helpful to prevent POD effectively. However, larger, high-quality RCTs are needed to verify these findings and develop more interventions and drugs for preventing postoperative delirium.

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Department of Anaesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

** Correspondence: Qingping Wu, Department of Anaesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, China (e-mail: wqp1968@163.com).*

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Abbreviations: BIS = bispectral index, CI = confidence interval, EEG = electroencephalogram, ICU = intensive care unit, MD = mean difference, POD = postoperative delirium, Post- = postoperative hospital day, RCT = randomized controlled trial, Total- = total hospital day.

Keywords: effect, meta-analysis, perioperative, postoperative delirium, prevent, surgery

1. Introduction

Postoperative delirium (POD) is a neurological complication that often occurs following surgery or anesthetization in patients of all age groups.[1] The incidence of POD is as high as 51%,[2] and more common after hip fracture and cardiac surgery.[3] It is characterized by short-term fluctuations in attention, consciousness, and cognition.[4] Advanced age, diabetes, cardiovascular disease, atrial fibrillation, and electrolyte disturbance are identified as independent risk factors of POD.[5] In addition, POD is closely related to a higher risk of mortality and extended hospitalization, which significantly increases the medical expenses.[6,7]

The pathophysiology of POD is not completely understood, although neurotransmitter imbalance, neuroinflammation, infection, abnormal metabolism, and sleep disturbance are the likely contributing factors,[8] and are targeted in the present treatment approaches to enhance recovery. However, approximately 30% to 40% of clinical POD cases are considered preventable.[9] Although several perioperative measures have been reported that can prevent POD, optimal interventions for specific groups of patients are presently unknown. To this end, we conducted a meta-analysis to review and evaluate published randomized controlled trials (RCTs) that compared the efficacy of different interventions for preventing POD in adults, and determine whether these interventions improved the clinical outcomes such as the duration of delirium, intensive care unit (ICU) and hospital length of stay while effectively preventing POD.

2. Methods

The meta-analysis was performed as per the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[10] Our study was registered in the PROSPERO database: CRD42020180787. All the data in present meta-analysis were extracted from the previous published studies and did not involve patients' personal information, so ethical approval or patient consent was not required.

2.1. Literature search

The PubMed, OVID (Embase + MEDLINE), Web of Science, and Cochrane Library databases were screened for papers published in English until January 2020 (Supplemental Digital Content Table S1, http://links.lww.com/MD/G280). The following search terms were used: ("delirium" OR "confusion" OR "acute confusional state" OR "acute confusional syndrome" OR "disorientation" OR "agitation" OR "illusion" OR "hallucination") AND ("postoperative" OR "surgical" OR "operation" OR "surgery") AND ("randomized controlled trial" OR "randomized" OR "randomized") AND ("adult"). The reference list of the selected articles was manually searched for additional articles.

2.2. Study selection criteria

Studies were included in the meta-analysis based on the following criteria: all participants older than 18 years of age, RCT evaluating the effect of different interventions to prevent POD, delirium defined by validated screening tools like Diagnostic and Statistical Manual of Mental Disorders[11] and *International Statistical Classification of Diseases code 10*,[12] and bedside diagnostic tools including Confusion Assessment Method[13] and Confusion Assessment Method-ICU,[14] the outcomes included incidence of delirium. Non-RCTs, trials including patients that did not undergo surgery or were diagnosed with a neurological or psychiatric disorder before surgery, and studies that did not report the effects of preventive measures were excluded.

2.3. Data extraction

Two investigators independently extracted data using a predesigned Excel file according to the inclusion and exclusion criteria. The following data were collected: general information (first author, journal, publication year, country, inclusion and exclusion criteria, and sample size), patient characteristics (sex, age, types of surgery, existing diseases, diagnostic criteria for delirium), intervention and control measures (type, dosage, timing, duration and frequency), outcomes (incidence, duration and severity of delirium, and the length of hospital and ICU stay).

2.4. Quality assessment

The quality of eligible trials was rated by at least 2 authors independently on the basis of the Modified Jadad scores.[15] The latter was calculated using the following items: random sequence generation (0–2), allocation concealment (0–2), double blinding (0–2), and description of dropouts and dropouts (0–1).

Disagreements between the 2 reviewers were resolved through consultation by one of the authors.

2.5. Statistical analysis

RevMan 5.3 software was used for meta-analyzing at least 2 studies with similar interventions. Dichotomous outcomes like the incidence of POD were pooled to estimate the risk ratio (RR) and corresponding 95% confidence intervals (95% CI) using the Mantel-Haenszel method. For continuous outcomes like the duration of delirium and the length of ICU and hospital stay, data were presented as mean difference (MD). The statistical heterogeneity across the included trials was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity.[16] A random-effects model was used in case of significant heterogeneity otherwise, a fixed-effects model was applied.[17] Potential publication bias was determined with funnel plots when there were at least 10 similar interventions. P value <0.05 was considered statistically significant.

3. Results

3.1. Study selection

The literature screening process was outlined in Supplemental Digital Content (Figure S1, http://links.lww.com/MD/G271).

The initial search yielded 3824 articles, of which 2720 were excluded after reviewing the titles and abstracts. The full texts of the remaining 176 articles were examined, and 113 records were further excluded since the inclusion criteria were not fulfilled: 42 studies were not RCTs, 18 included patients with delirium or mental disorders, 4 recruited both surgical and nonsurgical patients, 2 were not published in English, 5 had incomplete data, 10 did not diagnose with validated tools, and 32 did not examine the efficacy of the preventive measures for POD. Finally, 63 RCTs[18–80] that met the inclusion criteria were used for the meta-analysis.

3.2. Study characteristics

The basis characteristics of the included RCTs were summarized in Supplemental Digital Content (Table S2, http://links.lww.com/MD/G281 and S3, http://links.lww.com/MD/G282). The studies were published between 1999 and 2020, and included 21[21] to 1213[22] participants. Furthermore, 22 studies included patients that underwent cardiac surgery,[22–43] 9 focused on abdominal surgery,[44–52] 17 on orthopedic surgery,[21,53–68] 10 on noncardiac surgery,[69–78] 3 on thoracic surgery,[18–20] and 2 on tumor surgery.[79,80] We classified the interventions into 2 major categories: category 1 included perioperative medication and procedures (n = 38, Table S2, http://links.lww.com/MD/G281) such as surgery,[49] anesthesia,[34,35,46,47,57,58,75] intraoperative monitoring,[22,32,33,45,73,74] blood glucose,[42] analgesia,[51,52,67,68] and sedation,[18,23–31,44,53–56,69–72] and category 2 included pharmacological and multicomponent interventions (n = 25, Table S3, http://links.lww.com/MD/G282) like glucocorticoids,[39,40,63] cholinesterase inhibitors,[41,64] anticonvulsants,[21,65] antipsychotics,[19,36,48,59,60,76] sleep restoration by drug or bright light,[20,43,50,66,77,78] and multicomponent interventions.[37,38,61,62,79,80]

3.3. Quality assessment

The quality scores of the studies were listed in Supplemental Digital Content (Table S4, http://links.lww.com/MD/G283). Sixty RCTs were well-designed and of good quality (final score 4–7). The remaining 3 trials were of poor quality (final score 0–3) due to lack of details regarding double blinded analysis.

3.4. Primary outcome: POD incidence

3.4.1. Category 1. Perioperative procedures and drugs

3.4.1.1. Surgical procedure. Jia et al[49] investigated the role of fast-track surgery in preventing POD in 233 elderly patients with colorectal cancer. Optimal perioperative management procedures were adopted in the fast-track group to promote early recovery, which resulted in a lower incidence of POD compared to that in the conventional surgery group (3.4% vs 12.9%, $P = .008$).

3.4.1.2. Anesthesia type. Papaioannou et al[47] tested the effects of general and regional anesthesia on POD in 47 patients undergoing abdominal surgery. Some patients under spinal anesthesia were sedated with propofol during surgery. There was no difference in the incidence of delirium between the 2 groups (21.4% vs 15.8%, $P = .720$).

3.4.1.3. General anesthetics. Nishikawa et al[46] studied POD in 50 elderly patients that underwent laparoscopic surgery, and found that propofol administration resulted in more severe delirium rating scale scores and longer eye opening and extubation times compared to sevoflurane. However, there was no difference in POD incidence (0% vs 16%, $P = .110$). Royse et al[35] compared the effects of desflurane and propofol on the incidence of POD in patients with coronary artery bypass grafting, and did not detect any significant difference (13.2% vs 7.9% respectively, $P = .245$). Leung et al[75] studied the effect of additional N_2O anesthesia (n = 105) relative to that of standard anesthesia (n = 105) in patients undergoing non-cardiac surgery, and found that intraoperative inhalation of N_2O had no effect on the development of POD (41.9% vs 43.8%, $P = .78$). Likewise, Coburn et al[57] found that xenon anesthesia did not reduce the incidence of postoperative delirium compared to sevoflurane in 256 elderly patients undergoing hip fracture surgery (9.7% vs 13.6%, $P = .33$). Hudetz et al[34] found that older patients undergoing cardiac surgery with cardiopulmonary bypass that received ketamine additionally during anesthetization had lower incidence of POD compared to those receiving standard anesthesia (3.4% vs 31%, $P = .01$). Gao et al[58] reported that the incidence of POD in orthopedic patients was lower following transcutaneous electrical acupoint stimulation anesthesia compared to conventional anesthesia (6.3% vs 25%, $P = .039$).

3.4.1.4. Intraoperative monitoring. A total of 6109 patients in 5 studies[22,32,45,73,74] were monitored intraoperatively for POD. Four studies[32,45,73,74] used bispectral index (BIS) to guide anesthesia, and Wildes et al[22] used electroencephalogram (EEG) to monitor the depth of anesthesia. Meta-analysis using the fixed-effects model ($P = .77$, $I^2 = 0\%$) showed that intraoperative monitoring of anesthesia depth with BIS reduced the occurrence of POD (Supplemental Digital Content Figure S2, http://links.lww.com/MD/G272, pooled RR: 0.7, 95% CI: 0.60–0.83, $P < .0001$). However, EEG did not reduce the occurrence of postoperative delirium (26% vs 23%, $P = .22$), and there was no difference in the number of patients with severe delirium in the EEG and control groups (10.1% vs 8.6%, $P = .39$). Lei et al[33] monitored preoperative, intraoperative and postoperative regional cerebral oxygen saturation in patients undergoing cardiac surgery with cardiopulmonary bypass, of which 123 patients received an intervention to promote recovery if the regional cerebral oxygen saturation decreased below 75% of the baseline value for 1 min or longer. POD was observed in 24.4% (30/123) and 24.6% (31/126) patients respectively in the intervention and control groups. Thus, restoring regional cerebral oxygen desaturation did not result in lower POD after cardiac surgery.

3.4.1.5. Sedation depth during spinal anesthesia. Sieber et al conducted 2 studies[55,56] that investigated the effects of deep and light sedation during spinal anesthesia on the incidence of POD in elderly patients with hip fracture. All patients received propofol and intraspinal anesthesia, and were divided into the deep sedation (BIS = 50) and light sedation (BIS ≥80) groups. The former study found that light propofol sedation decreased the prevalence of POD by 50% compared to deep sedation, while the later study showed that limiting the level of sedation provided no significant benefit in reducing delirium incidence. Meta-analysis using the random-effects model ($P = .1$, $I^2 = 63\%$) showed that the degree of sedation during spinal anesthesia had no effect on the incidence of POD (pooled RR: 1.47, 95% CI: 0.82–2.63, $P = .20$).

3.4.1.6. Postoperative analgesia. Two RCTs with 314 patients[51,52] compared the effect of epidural and intravenous analgesia in older patients undergoing major surgeries. Meta-analysis using the fixed-effects model ($P=.77$, $I^2=0\%$) showed that the incidence of POD did not differ between both groups (pooled RR: 0.97, 95% CI: 0.56–1.68, $P=.92$).

3.4.1.7. Additional analgesia. Mouzopoulos et al[67] and Mu et al[68] respectively investigated the effects of fascia iliaca block and parecoxib as complementary analgesia on POD in orthopedic patients. Meta-analysis using the fixed-effects model ($P=.63$, $I^2=0\%$) showed that complementary analgesia in addition to standard analgesia reduced the incidence of POD (pooled RR: 0.51, 95% CI: 0.34–0.78, $P=.002$).

3.4.1.8. Perioperative sedation. We identified 17 RCTs with 4391 patients[18,23–31,44,53,54,69–72] that analyzed the effects of α_2-adrenergic receptor agonists (dexmedetomidine and clonidine) on POD. Except for the study of Rubino et al[31] that used clonidine, other studies compared dexmedetomidine with propofol, midazolam, clonidine, morphine, and placebo. Meta-analysis using the random-effects model showed that perioperative use of α_2-adrenergic receptor agonists helped reduce POD in both cardiac surgery and non-cardiac surgery groups (Supplemental Digital Content Figure S3A, http://links.lww.com/MD/G273, pooled RR: 0.65, 95% CI: 0.5–0.83, $P=.0006$).

3.4.1.9. Intraoperative blood glucose. Saager et al[42] investigated the effect of intraoperative blood sugar control on the incidence of POD in diabetic patients undergoing cardiac surgery. Patients in the intervention group had blood sugar levels between 80 and 110 mg/dL, and those in control group <150 mg/dL. Interestingly, intraoperative control of blood sugar increased the risk of POD (28% vs 14%, $P=.03$).

3.4.2. Category 2. Pharmacological and multicomponent interventions

3.4.2.1. Glucocorticoids. Three studies involving 1356 patients[39,40,63] analyzed the effect of glucocorticoids on POD, with 2[39,63] using methylprednisolone and one[40] dexamethasone. Meta-analysis using the fixed-effects model ($P=0.28$, $I^2=22\%$) revealed that neither methylprednisolone nor dexamethasone prevented POD (pooled RR: 0.82, 95% CI: 0.63–1.07, $P=.15$).

3.4.2.2. Acetylcholinesterase inhibitors. Two RCTs with 193 patients undergoing orthopedic surgery[41,64] assessed the effect of increasing acetylcholine levels in the brain using acetylcholinesterase inhibitors like donepezil and rivastigmine. Meta-analysis using the fixed-effects model ($P=.84$, $I^2=0\%$) showed no difference in the incidence of POD between the 2 studies (pooled RR: 1.11, 95% CI: 0.69–1.79, $P=.66$).

3.4.2.3. Anticonvulsants. Leung et al conducted 2 trials to test the potential therapeutic effects of the anticonvulsant gabapentin in elderly patients undergoing orthopedic surgery.[21,65] All patients received 900 mg gabapentin orally for 4 consecutive days from the day of surgery. Meta-analysis using the random-effects model ($P=.1$, $I^2=62\%$) showed that perioperative administration of gabapentin did not result in a reduction of POD (pooled RR: 0.57, 95% CI: 0.07–4.61, $P=.59$).

3.4.2.4. Antipsychotics. We identified 6 trials with 1626 patients[19,36,48,59,60,76] that tested the role of antipsychotics in preventing POD, of which 4 trials[19,48,59,76] used the typical antipsychotic haloperidol and the remaining 2[36,60] respectively used the atypical antipsychotics risperidone and olanzapine. Meta-analysis using the random-effects model showed that perioperative use of antipsychotics reduced the incidence of POD (Supplemental Digital Content Figure S4, http://links.lww.com/MD/G274, pooled RR: 0.55, 95% CI: 0.38–0.8, $P=.002$). Further subgroup analysis indicated that both typical and atypical antipsychotics had beneficial effects.

3.4.2.5. Sleep restoration. Six studies with 1100 patients[20,43,50,66,77,78] investigated the effects of restoring sleep-wake cycle after surgery on POD. Three RCTs[20,43,66,77] promoted the recovery of sleep-wake cycle by increasing melatonin levels with melatonin, ramelteon, and tryptophan. In the study of Aizawa et al,[50] patients in the experimental group received a combination of diazepam, flunitrazepam, and pethidine for 3 days to restore disturbed sleep. Potharajaroen et al[78] adopted bright light therapy to regulate the sleep cycle for 3 consecutive days after surgery. Meta-analysis showed the occurrence of POD was not reduced by regulating the sleep cycle of patients undergoing surgery (Supplemental Digital Content Figure S5, http://links.lww.com/MD/G275, pooled RR: 0.92, 95% CI: 0.67–1.27, $P=.62$). However, subgroup analysis indicated that while melatonin had no impact on POD, diazepam/flonazepam/pethidine and bright light therapy decreased its incidence.

3.4.2.6. Multicomponent interventions. Multicomponent interventions including comprehensive nursing care, geriatrics consultation, cognitive training, and multimedia education were assessed in 6 RCTs with 895 patients.[37,38,61,62,79,80] Meta-analysis using the fixed-effects model ($P=.21$, $I^2=31\%$) showed that patients receiving perioperative multicomponent intervention had significantly lower incidence of POD (Supplemental Digital Content Figure S6, http://links.lww.com/MD/G276, pooled RR: 0.64, 95% CI: 0.53–0.76, $P<0.00001$).

3.5. Secondary outcomes

Based on the results of individual studies, 29 interventions effectively reduced the incidence of POD. We aggregated the available data on the duration of delirium from 11 studies,[24,25,29,55,60–62,67,68,72,80] the length of ICU stay from 10 studies,[23–25,29,34,36,50,55,69,74] total hospital stay from 11 studies[24,25,29,34,36,49,50,53,61,62,74] and postoperative length of hospital stay from 4 studies.[55,63,69,73]

3.5.1. Duration of POD. We performed a subgroup analysis of 3 studies on 368 patients undergoing cardiac surgery[24,25,29] and 8 studies with 1780 patients undergoing noncardiac surgery.[55,60–62,67,68,72,80] Meta-analysis using a random-effects model ($P<.00001$, $I^2=98\%$) showed a significant difference in the duration of POD among the noncardiac surgery patients between interventions with lower or higher occurrences of POD (MD = −0.80, 95% CI = −0.29 to −0.31, $P=.001$). However, there was no significant difference in duration of POD even when interventions were effective in reducing the incidence of POD after cardiac surgery (Supplemental Digital Content Figure S7, http://links.lww.com/MD/G277, MD=−1.55, 95% CI=−3.08 to −0.02, $P=.05$).

3.5.2. ICU and hospital length of stay. Six studies involving 719 patients that underwent cardiac surgery[23–25,29,34,36] and 4 studies with 1756 patients that underwent noncardiac surgery[50,55,69,74] were included in a subgroup analysis for length of ICU stay. Meta-analysis using a random-effects model ($P<.00001$, $I^2=89\%$) showed no difference in length of ICU stay for noncardiac surgery (Supplemental Digital Content Figure S8A, http://links.lww.com/MD/G278, MD=−0.00, 95% CI=−0.06 to 0.06, $P=1.00$), whereas reduced stay in ICU after cardiac surgery was associated with effective prevention of POD (Supplemental Digital Content Figure S8A, http://links.lww.com/MD/G278, MD=−0.45, 95% CI=−0.86 to −0.04, $P=.03$). Data of total hospitalized duration were presented in 5 cardiac surgical studies with 631 participants,[24,25,29,34,36] and 6 noncardiac surgical studies with 1953 patients.[49,50,53,61,62,74] Meta-analysis using the random-effects model ($P<.00001$, $I^2=95\%$) showed that effective interventions reduced the total length of hospital stay in patients undergoing non-cardiac surgery (Supplemental Digital Content Figure S8B, http://links.lww.com/MD/G278, MD=−2.15, 95% CI=−4.17 to −0.13, $P=.04$) but not in the cardiac surgery group (Supplemental Digital Content Figure S8B, http://links.lww.com/MD/G278, MD=−1.24, 95% CI=−2.82 to 0.34, $P=.12$). Four noncardiac surgery studies[55,63,69,73] showed a significant difference in postoperative hospital length of stay (Supplemental Digital Content Figure S8C, http://links.lww.com/MD/G278, MD=−0.96, 95% CI=−1.13 to 0.79, $P<.00001$).

3.6. Publication bias

The funnel plots were used to evaluate the potential publication bias of α_2-adrenergic receptor agonis on POD incidence and effective intervention on the other 3 outcome indicators (duration of POD, length of ICU stay, and total hospital stay). The funnel plot of α_2-adrenergic receptor agonists on POD incidence depicted in Supplemental Digital Content (Figure S3B, http://links.lww.com/MD/G273) was generally symmetric, which indicated the low risk of publication bias. Although the funnel plots of the other 3 outcome indicators in Supplemental Digital Content (Figure S9, http://links.lww.com/MD/G279) were asymmetric, it can be seen that the points of the clinical trials were mainly concentrated at the top, indicating a higher accuracy and a larger sample size.

4. Discussion

Our meta-analysis comprehensively revealed that intraoperative monitoring of BIS, supplemental analgesia, α_2-adrenergic agonists, antipsychotic drugs, and multimodal care can prevent POD. There was a certain degree of heterogeneity between these studies and there was limited data for most interventions. The incidence of POD also varied according to the risks associated with the surgical procedure, and was more prevalent after abdominal and cardiac surgeries compared to otolaryngological and general surgeries.[81] Considering that these factors might affect the accuracy and reliability of the outcomes, the results should be interpreted carefully.

Based on individual studies, fast-track surgery, transcutaneous electrical acupoint stimulation, light sedation during spinal anesthesia, ketamine administration during anesthesia induction, single preoperative dose of methylprednisolone, sleep restoration using diazepam/flunitrazepam/pethidine, and bright light therapy can prevent POD. In contrast, the type of anesthesia and analgesic methods had no effect on POD. Tight intraoperative glucose control between 80 and 110 mg/dL in patients with diabetes during cardiac surgery on the other hand increased the risk of POD. Furthermore, effective interventions that reduced the duration of POD after cardiac surgery also reduced postoperative hospital stay and total hospital stay but had no effect on the length of ICU stay. For cardiac surgery patients, effective preventive measures only shortened the length of ICU stay, which can be attributed to the complexity of the surgical process that requires massive blood transfusion and cardiopulmonary bypass. Furthermore, since most patients undergoing cardiac surgery are elderly and have underlying cardiovascular and cerebrovascular diseases,[82] their recovery depends on their cognitive status and requires longer hospital stays. It is critical to address these differences as prolonged hospital stay increases the burden on the health care system and should be regarded as a clinical end point of delirium prevention.

Compared to general anesthesia, spinal anesthesia needs fewer types of anesthetics, and a previous meta-analysis demonstrated that general anesthesia may increase the risk of postoperative cognitive dysfunction without affecting POD.[83] Hudetz et al[34] found that an additional injection of ketamine during anesthetic induction reduced the incidence of POD, which may be related to its neuroprotective effects. Ketamine is known to prevent excitotoxic injury after cerebral ischemia and inhibit inflammatory response in the central nervous system after injury.[84,85] We found that BIS monitoring of the depth of anesthesia prevented POD, whereas EEG monitoring was not effective. BIS quantifies the depth of anesthesia based on EEGs, which enables a more accurate control of anesthetic concentration and increases patient safely. Only 1 RCT on EEG monitoring was included in this meta-analysis, and further research is needed to explore the effect of EEG monitoring on POD. Opioids are administered to manage the intense postoperative pain that significantly affects the prognosis and mental state of patients, which is a potential underlying factor of POD.[86] One study[87] showed that the method of postoperative analgesia was not a contributing factor to the increased risk of delirium. However, better control of postoperative pain can effectively reduce the incidence of delirium, which was similar to our findings regarding the effect of supplementary analgesia on POD.

Dexmedetomidine, a highly selective α_2-adrenergic receptor agonist, is widely used for anxiolysis, sedation, and modest analgesia with minimal respiratory depression.[88,89] It can also reduce the release of inflammatory mediators and neurotransmitters caused by ischemic hypoxic damage, and maintain intracranial homoeostasis and alleviate ischemic brain injury.[90] Consistent with our results, another meta-analysis by Duan et al[91] on 7 studies included in this present meta-analysis[24,25,27,28,54,69,70] found that perioperative administration of dexmedetomidine decreased the occurrence of POD in adult patients. However, since we did not further analyze the effect of dosage and timing of dexmedetomidine administration, the optimal dose and duration will have to be determined. Five previous meta-analyses[92–96] reported the beneficial effects of typical and atypical antipsychotics for POD, which are consistent with our findings. However, Neufeld et al[97] later found that the therapeutic effect of antipsychotics against delirium is not supported by present evidence. These discrepancies could be the result of heterogeneity among studies in terms of the dosage and duration.

Melatonin is produced by the pineal gland acts and has sedative, hypnotic and anti-anxiety effects.[98] Patients with POD frequently have low concentrations of tryptophan, which impedes melatonin production.[99] A meta-analysis of 8 RCTs showed that exogenous melatonin supplementation greatly reduced the prevalence of delirium in ICU patients.[100] However, we did not observe a beneficial effect of increasing melatonin level postoperatively, which was consistent with the findings of another systematic review.[101] Thus, large randomized clinical trials are needed to conclusively determine the preventive effect of melatonin on POD.

Several potential limitations should be considered when interpreting the results in this meta-analysis. First, it should be noted that significant heterogeneity was observed among these studies. Multiple types of surgery were included in the same intervention study, and the incidence of POD itself varies depending on the type of surgery and surgical experience, which may be the main source of heterogeneity. Second, the doses and frequency of drug interventions varied from study to study. The included clinical trials may have some subtle differences in the diagnosis and severity assessment methods of delirium and the time point and frequency of postoperative visits may also be different, which may influence the final incidence of POD. Third, 11 of the studies we included had a sample size of <110, so there may be a small study bias effect in this study. Strict study screening and data extraction were carried out to enhance the stability and accuracy of this meta-analysis.

Despite the advancements in surgery and postoperative care, POD is still a common complication that calls for effective treatment and prevention. Successful prevention strategies include multifactor methods to reduce risk factors, with nonpharmacological interventions as the mainstay. Before surgery, patients are routinely evaluated for early cognitive function. For high-risk patients, relevant education and multimodal care should be conducted to reduce preoperative fear and anxiety and optimize vision and hearing. According to the depth of anesthesia monitored by BIS, the dose of anesthetic drugs can be adjusted reasonably during the operation, which can effectively reduce the occurrence of POD. In addition, dexmedetomidine, as a highly selective alpha-2 adrenergic agonist, has a significant effect on POD when used for postoperative sedation. Sufficient analgesia and effective follow-up are also the keys to prevent POD in the postoperative setting.

5. Conclusion

Our research results indicated that measures such as intraoperative monitoring of BIS, auxiliary analgesia, antipsychotics, and perioperative multimodal care can help prevent POD. The sedation depth during spinal anesthesia and postoperative analgesia had no effect on POD. Glucocorticoids and acetylcholinesterase inhibitors and melatonin were also largely ineffective. The interventions that reduce the risk of POD can also shorten the duration of delirium and hospital stay in noncardiac surgical patients, and the length of stay in ICU for cardiac surgery.

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Author contributions

LX and WYT participated in the study concept and design, statistical analyses and manuscript preparation and drafting. XY and LJ collected the data, performed the quality. CSQ and HJJ helped to perform statistical analyses and search strategy. XWL and WQP participated in the manuscript revision, editing, and approval. All authors read and approved the final manuscript.
Data curation: Yue Xiong.
Investigation: Shiqiang Chen, Jingjing Han.
Methodology: Jie Liu.
Software: Yanting Wang.
Supervision: Qingping Wu.
Writing – original draft: Xia Li.
Writing – review & editing: Wanli Xie.

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