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The effect of neuromuscular blocking reversal agents on perioperative neurocognitive function after general anaesthesia: a systematic review and meta-analysis

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Abstract

Background Perioperative neurocognitive dysfunction (PND) is influenced by various perioperative factors. Recent studies suggest that neuromuscular blocking reversal agents (NMBRs) may impact on PND. However, the results have been inconsistent. Therefore, we aimed to compare the effects of perioperative NMBRs on PND through this systematic review and meta-analysis.

Methods We searched PubMed, CENTRAL, Embase, Web of Science, Scopus, and China Biology Medicine from their inception until May 2024. Two reviewers independently identified randomized controlled trials (RCTs) that compared the perioperative use of NMBRs with either a placebo or other NMBRs in patients undergoing general anaesthesia. We assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The primary outcome was the incidence of PND within 7 days following surgery, while the secondary outcomes included the time required to achieve a Train-of-Four ratio (TOF) ≥ 0.9 after administration of NMBRs, length of stay (LOS) in both the post-anaesthesia care unit (PACU) and the hospital, as well as the risk of adverse events (i.e. postoperative nausea and vomiting (PONV) and mortality).

Results A total of 10 randomized controlled trials involving 1705 patients compared the effects of NMBRs on PND. Neostigmine and sugammadex are the most commonly used NMBRs in clinical anaesthesia practice. In the primary analyses of all regimens, sugammadex significantly reduced the incidence of PND compared to neostigmine (risk ratio [RR] 0.67; 95% confidence interval [CI]:0.48–0.94; $I^2 = 0\%$; $P = 0.02$; moderate quality). However, the results indicated that there is no significant association between neostigmine and PND when compared to placebo (RR 0.76; 95% CI: 0.55–1.05; $I^2 = 35\%$; $P = 0.09$; moderate quality). The secondary outcomes revealed that sugammadex could significantly shorten the time of TOF ≥ 0.9 compared to neostigmine (mean difference [MD] -4.52; 95%CI: -5.04 to -3.99; $I^2 = 80\%$; $P < 0.01$; Moderate quality). Furthermore, no significant differences were observed in the incidence of adverse events or hospital LOS.

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Conclusions This meta-analysis demonstrated that the use of sugammadex was associated with improved early perioperative neurocognitive function compared to neostigmine when used to reverse neuromuscular blockade, without an increase in the incidence of adverse events.

Systematic review protocol PROSPERO CRD42024520287.

Keywords Meta-analysis, Neuromuscular blocking reversed agents, Postoperative neurocognitive disorders, Neostigmine, Sugammadex, Systematic review

Introduction

Perioperative neurocognitive disorders (PND) are a prevalent central nervous system complication in patients undergoing anaesthesia and surgery, characterized by changes in cognitive function, including memory impairment, attention shortfall, and deterioration of executive functions, which may persist for months or even years after surgery [1]. Based on the timing of symptom onset, PND can be categorized into preoperative neurocognitive disorders (NCD), postoperative delirium (POD), and postoperative neurocognitive disorders (POND) [2]. The occurrence of PND following major surgery varies significantly, with reported rates ranging from 17 to 28% at one month postoperatively [3]. PND is independently linked to prolonged hospitalization, increased 30-day mortality, elevated medical expenses, and a greater economic burden on families and society [4]. While the underlying causes of PND remain unclear, factors such as age, psychological stress, neuroinflammation, genetic predisposition, and neurotransmitter abnormalities may play significant roles [5].

Given the limited current treatment options for PND, it is increasingly important to focus on prevention strategies that target modifiable risk factors. One of the important measures in this regard is to preserve the functionality of the cholinergic system while minimizing the perioperative anticholinergic load to safeguard cognitive function [6]. Numerous perioperative anaesthesia and surgical factors have been shown to adversely impact the cholinergic system, further exacerbating cognitive impairment [7, 8]. Neostigmine, an acetylcholinesterase inhibitor (ACEI), is commonly used as an NMBRs for the reversal of postoperative residual neuromuscular blockade through increasing the level of acetylcholine at the neuromuscular junction. Although neostigmine does not interfere with normal brain function due to its inability to cross the blood-brain barrier (BBB), the elevated acetylcholines can also agonize muscarinic receptors in the precordial membrane of the autonomic junction, leading to adverse parasympathetic effects [9]. To mitigate these side effects, ACEIs are often administered alongside anticholinergic agents, such as atropine and glycopyrrolate. However, these anticholinergic agents can penetrate the BBB and have been associated with mild postoperative memory deficits [10]. Therefore, the administration of ACEIs in combination with anticholinergic drugs may disrupt the normal function of the cholinergic system and increase the risk of PND.

Sugammadex or adamgammadex, a kind of innovative non-ACEI muscle relaxant antagonist designed to efficiently encapsulate neuromuscular blocking agents through a mechanism distinct from that of neostigmine [11]. Sugammadex is unable to cross the blood-brain barrier (BBB) due to its large molecular weight [12]. Several studies have indicated that sugammadex is more effective than neostigmine in reversing neuromuscular blocks, resulting in a faster recovery of consciousness and earlier extubation [13, 14]. While sugammadex objectively enhances the reversal of neuromuscular block, it remains unclear whether it positively impacts important postoperative clinical outcomes, such as cognitive function. Recent clinical trials focusing on NMBRs for PND have been completed; however, no consensus appears to exist to date. Evidence from preclinical and clinical studies suggests that sugammadex can potentially protect cerebral function and improve postoperative cognition [15–18]. Nonetheless, a recent large retrospective study involving 49,468 patients found that sugammadex was significantly associated with an increased incidence of early postoperative delirium compared to neostigmine [19].

Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials to summarize the current evidence and compare the incidence of PND for different NMBRs. To achieve a more comprehensive understanding of the impact of NMBRs on PND, we also included studies that utilized saline as a placebo, although acknowledging that reversing the residual muscle blockade has been one of the routine measures to facilitate patient rapid recovery following surgery. Our study primarily focuses on PND outcomes and includes secondary outcomes such as the duration until TOF ≥ 0.9, extubation time, the incidence of PONV, and LOS in the PACU and hospital.

Methods

This study was pre-registered in PROSPERO (CRD42024520287). The meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search strategy and data sources

To comprehensively gather relevant studies, we employed an extensive search strategy across various electronic databases to explore the impact of NMBRs on PND. The databases searched included PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Web of Science, Scopus, and China Biology Medicine (CBM) from their inception to May 31, 2024. A combination of MeSH terms and free-text keywords related to 'neostigmine', 'cholinesterase inhibitors', 'sugammadex', 'adamgammadex', 'surgery', 'perioperative neurocognitive disorders', 'postoperative cognitive dysfunction', 'postoperative delirium', and 'randomized controlled trial (RCT)' was utilized. Additionally, a manual examination of reference lists from included articles and reviews was conducted to ensure no relevant articles were overlooked. There were no language limitations. The keywords used for one of the databases are outlined in Supplementary Table S1.

Selection process for studies

Two independent reviewers (LW[1] and FLM) screened the titles and abstracts of the records retrieved from the database searches. Articles that met the preliminary criteria or were uncertain based on the title and abstract were retrieved for full-text assessment. Any discrepancies between the reviewers were resolved through discussion or, if necessary, consultation with a third senior reviewer. (YLL)

Inclusion and exclusion criteria

Based on the Population/Intervention/Comparator/Outcome/Study design (PICOS) framework, the inclusion criteria for screening eligible studies were as follows: (1) Population - adult patients who underwent elective surgery under general anaesthesia and received neuromuscular blocking agents; (2) Intervention- intravenous administration of NMBRs (neostigmine, sugammadex, or adamgammadex) at the end of surgery to reverse residual neuromuscular blockade; (3) Comparator - placebo or other drugs used in the intervention; (4) Outcome - the incidence of PND (POD, POCD, dNCR, and PNCD) as defined and measured by the study authors; (5) Study Design: The peer-reviewed RCTs serve as the primary source of evidence for our analysis.

The exclusion criteria for this study included: (1) case reports, conference abstracts, and reviews; (2) patients under 18 years of age; (3) administration of drugs via routes other than intravenous; (4) studies for which full texts were not available.

Data collection

A standardized data extraction form was designed to ensure consistent information collection across all studies. This form included key details such as the first author's name, publication year, country of origin, study design, sample size, type of surgery, patient characteristics (e.g., age, gender, and ASA classification), characteristics of NMBRs usage (e.g., type, dosage, timing), and the specific metrics or scales utilized to evaluate PND. In cases where data were incomplete or missing, the primary authors were contacted for further details.

Outcome and subgroup analysis

This study focused on the incidence of PND within 7 days after surgery as the primary outcome of interest. The diagnoses of PND for each study were based on the authors' own questionnaires and reported outcomes, which included POD, POCD, dNCR, and PNCD. In cases where these events were reported at multiple time points, the final assessment was used for analysis. Secondary outcomes comprised PONV, extubation time, time to TOF ≥ 0.9, LOS in the PACU and hospital, and other adverse events. Subgroup analyses of primary outcomes were mainly restricted to the comparison of sugammadex versus neostigmine, and performed by the timing of PND evaluation (day 1, day 3, and day 7 after surgery) and patients' age range (younger patients [< 65 years] vs. older patients [≥ 65 years]).

Quality assessment for the included studies

Two independent examiners (LW[1] and FLM) evaluated the methodological quality and potential biases of the included studies using the Cochrane Risk of Bias Tool [20]. The overall risk of bias for each study was categorized as 'low risk of bias,' 'some concerns,' or 'high risk of bias.' Studies were classified as having an overall 'high risk of bias' if they were rated as having a high risk of bias in a single domain or unclear risk of bias in two or more domains. We assessed the quality of pooled effect estimates for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Statistical analyses

Cochrane Review Manager (RevMan 5.4; The Cochrane Collaboration, 2020) was utilized for data synthesis. Mean difference (MD) with corresponding 95% confidence intervals (CIs) was used to express effect size for continuous variables, while dichotomous outcomes were analyzed using pooled risk ratios (RRs) and their corresponding 95% CIs. If the mean and standard deviation are not available in the included studies, these values were estimated using a method previously reported in the literature for converting the median (interquartile range) to the mean (standard deviation) [21, 22]. Heterogeneity was judged using the I^2 statistic, which was categorized as low ($I^2 = 0 \sim 25\%$), moderate($I^2 = 26 \sim 50\%$),

or high($I^2 > 50\%$). Considering the anticipated heterogeneity among the studies, a random-effects model was employed for outcome evaluation irrespective of the observed statistical heterogeneity. Sensitivity analyses were conducted using a leave-one-out approach to examine the influence of individual studies on the overall meta-analysis results. To assess potential publication bias or small-study effects, funnel plots were constructed for outcomes where more than 10 studies contributed data. A two-sided of P-value < 0.05 was considered statistically significant throughout the analyses.

To avoid redundant sample size calculations in multi-arm studies, participant counts were equally distributed [23]. In cases with two intervention groups and one control group, the patient count in the control group was proportionally allocated for comparison with each intervention group. No adjustments were necessary for the mean and standard deviation in continuous outcomes, while the number of participants experiencing events was proportionally distributed for dichotomous outcomes.

Results

Selection process and study characteristics

PubMed, CENTRAL, Embase, Web of Science, Scopus, and China Biology Medicine were systematically searched, resulting in an initial identification of 401 records (Fig. 1). After removing duplicates (n=89), 312 articles were screened based on their titles and abstracts, leading to the exclusion of 283 records. Subsequently, the full texts of the remaining 29 articles were reviewed and evaluated for eligibility. Ultimately, 10 RCT studies were deemed eligible and included in the meta-analysis [24–33].

The characteristics of the 10 included studies are summarized in Table 1. These studies encompassed 1,705 patients, with sample sizes ranging from 84 to 401 individuals and publication dates spanning from 2016 to

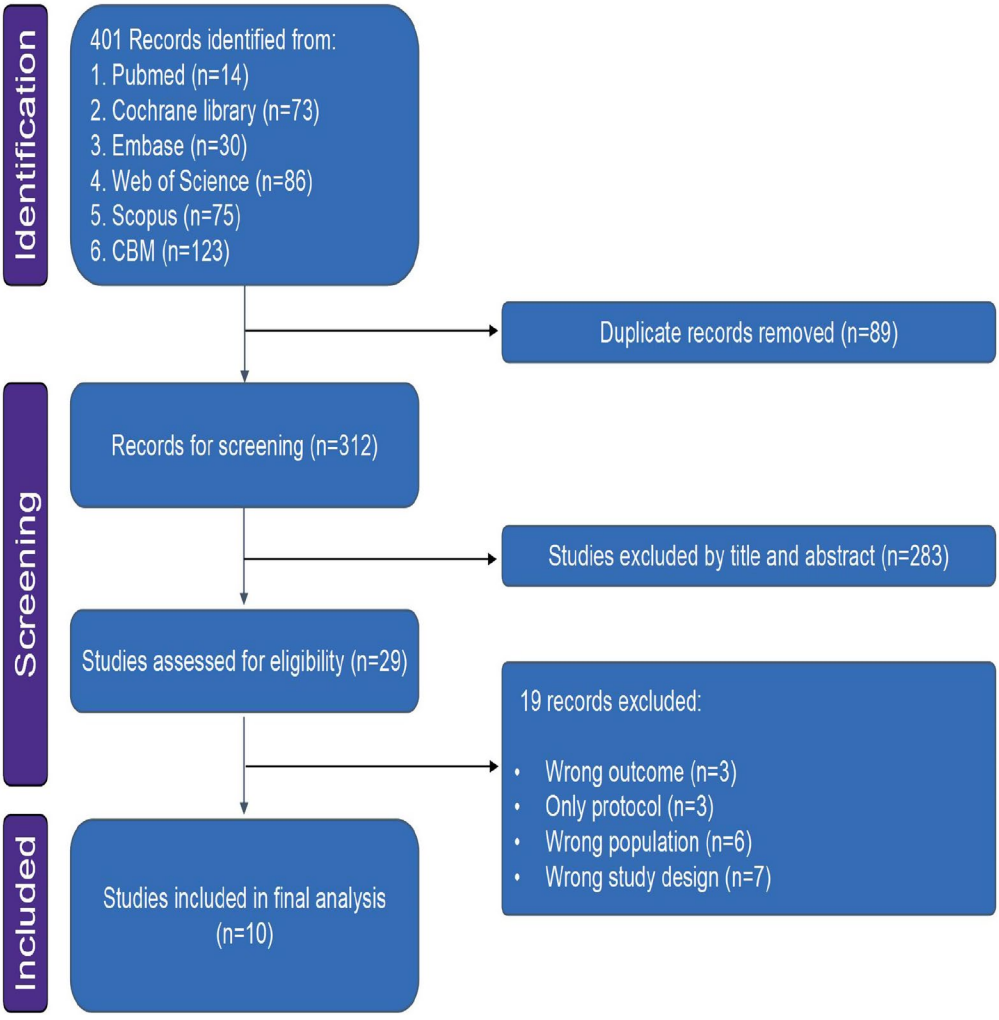

Fig. 1 The flow chart of study selection

Table 1 Characteristics of studies

Studies	Country	*n*	Design	Type of surgery	ASA	NMBRs (Intervention/comparator)	Age (years)*	Male (%)*	Outcome(s) assessed	Tool(s) used
Piskin [26]	Turkey	87	Double-blinded RCT	Noncardiac Surgery	I-II	Neostigmine/Sugammadex	37/32	51/71	POCD	MMSEMoCA
Batistaki [25]	Greece	160	Double-blinded RCT	Noncardiac Surgery	I-III	Neostigmine/Sugammadex	61/62	46/36	POCD	MMSE
Claroni [26]	Italy	109	Double-blinded RCT	Robotic-Assisted Radical Cystectomy	I-III	Neostigmine/Sugammadex	60/63	73/78	POCD	MMSE
Kim [27]	Korea	84	Double-blinded RCT	Pars PlanaVitrectomy	I-III	Neostigmine/Sugammadex	63/64	41/35	POCD	PQRS
Boggett [28]	Australia	350	Single-blinded RCT	laparoscopic surgery	I-III	Neostigmine/Sugammadex	55/55	42/55	POCD	PQRS
Zhu [29]	China	61	Double-blinded RCT	Radical section of gastrointestinal tumors	I-III	Neostigmine/Placebo	73/73	53/52	POCD	MMSE
Zhu [29]	China	59	Double-blinded RCT	Radical section of gastrointestinal tumors	I-III	Neostigmine/Placebo	74/73	53/52	POCD	MMSE
Liu [30]	China	401	Double-blinded RCT	colon carcinoma surgery	I-III	Neostigmine/Placebo	64/63	54/55	POD	CAM
Sabuncu [32]	Turkey	84	Open-label RCT	Bariatric surgery	I-III	Neostigmine/Sugammadex	> 18	NR	POCD	MMSE
Cao [31]	China	64	Double-blinded RCT	Noncardiac Surgery	I-III	Neostigmine/Placebo	68/67	47/43	POCD	MMSE
Cao [31]	China	66	Double-blinded RCT	Noncardiac Surgery	I-III	Neostigmine/Placebo	68/67	44/43	POCD	MMSE
Cao [31]	China	66	Double-blinded RCT	Noncardiac Surgery	I-III	Neostigmine/Placebo	68/67	30/43	POCD	MMSE
Deng [33]	China	114	Double-blinded RCT	Noncardiac Surgery	I-III	Neostigmine/Placebo	71/71	64/47	POCD	MMSEMoCA

RCT, Randomized Controlled Trials; ASA, American Society of Anesthesiologists; NMBRs, Neuromuscular Blocking Reversed Agents; POCD, Postoperative Cognitive Dysfunction; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; CAM, Confusion Assessment Scale; PQRS, Post-operative Quality Recovery Scale; NR, not reported; *Presented as Neostigmine/Placebo groups or Neostigmine/Sugammadex groups

2024. The ages of patients across these studies varied from 32 to 74 years, with male representation ranging from 30 to 78%. The majority of the studies (9 RCTs) enrolled patients classified as ASA I-III, while only one study was limited to ASA I-II [24]. Various surgical procedures were performed; however, no cardiac procedures were included in these studies. Among the included RCTs, neostigmine and sugammadex were the most extensively researched NMBRs. Sugammadex was compared to neostigmine in six studies [24–28, 32], while no studies compared placebo with sugammadex. The remaining four studies focused on the comparison of neostigmine versus a saline placebo [29–31, 33]. The dose of sugammadex administered was 2 mg kg^{-1}, whereas the dosing regimens for neostigmine ranged from 0.01 to 0.05 mg kg^{-1}, with most studies (6 studies) employing a dose of 0.04 mg kg^{-1}.

Figure 2 illustrates the methodological quality of the included studies. The majority of the studies(60%) showed a low overall risk of bias, implying reliable methodologies and results [26–30, 33]. In contrast, 30% of the studies presented an overall unclear risk of bias. The domains contributing most significantly to these unclear risk determinations were allocation concealment and the blinding of participants and personnel, which complicates the assessment of the reliability of their findings [25, 31, 32]. Notably, one study exhibited a high overall risk of bias, as it did not employ blinding for participants and personnel during performance and outcome evaluation [24].

Primary outcome

A total of ten RCTs [24–33] assessed the impact of NMBRs on PND within 7 days postoperative. Cognitive function during the postoperative period was evaluated using four different assessment tools: the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Confusion Assessment Scale (CAM), and the Post-operative Quality Recovery Scale (PQRS), as detailed in Table 1.

The quantitative synthesis of four studies involving 612 participants indicated that sugammadex potentially decreases the incidence of PND within 7 days post-surgery when compared to neostigmine [25, 27, 28, 32], with a relative risk (RR) of 0.67 (95% CI: 0.48–0.94; $I^2 = 0\%$; $P = 0.02$; moderate quality) (Fig. 3). However, the quantitative synthesis from three studies involving 635 participants revealed no significant association between neostigmine and PND within 7 days post-surgery when compared to placebo [29, 30, 33], with a relative risk (RR) of 0.76 (95% CI: 0.55–1.05; $I^2 = 35\%$; $P = 0.09$; moderate quality) (Supplementary Fig S1).

We conducted two pre-specified subgroup analyses for the outcome of PND in sugammadex vs. neostigmine

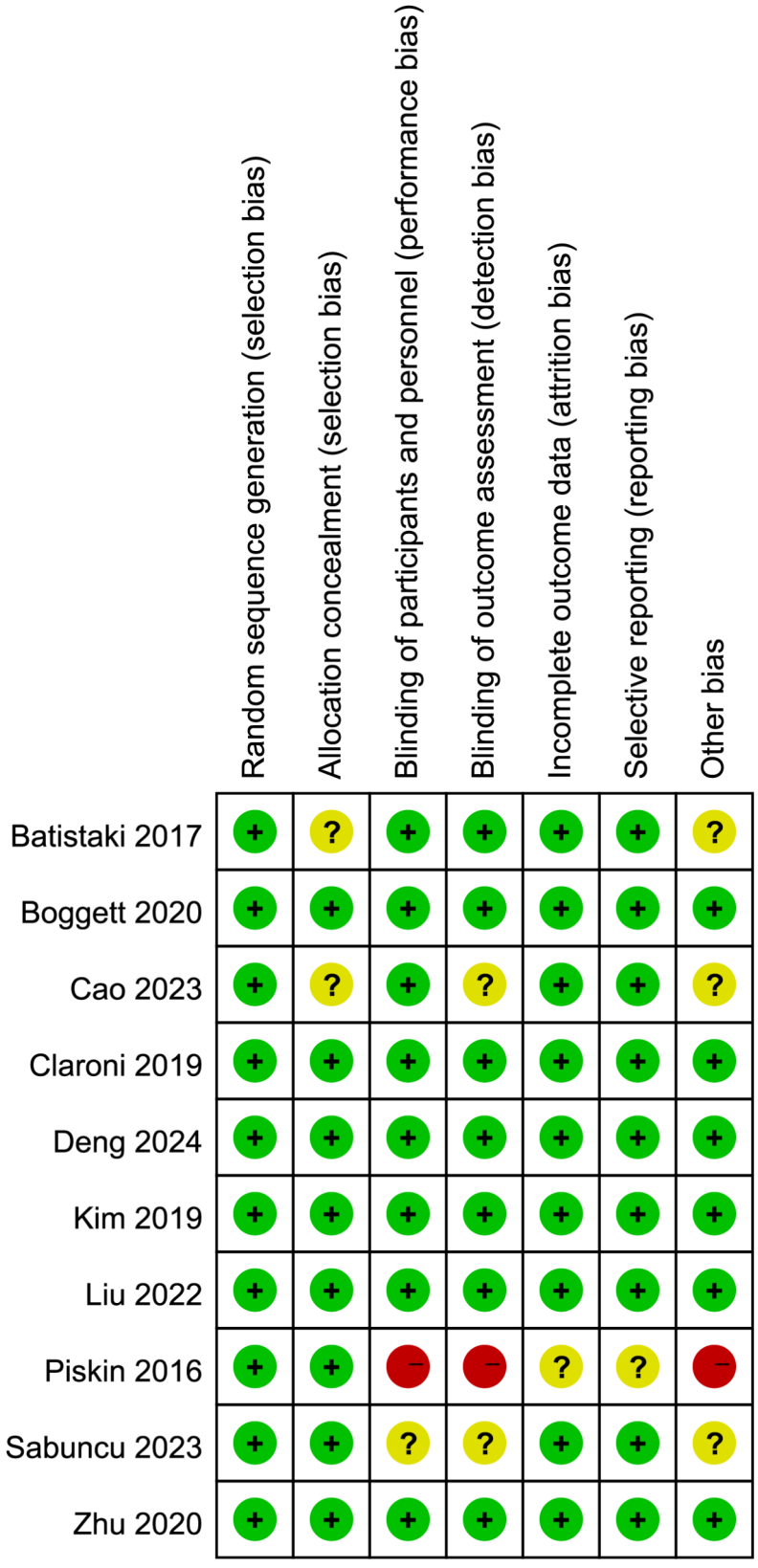

Fig. 2 Assessment of risk of methodological bias in the included studies

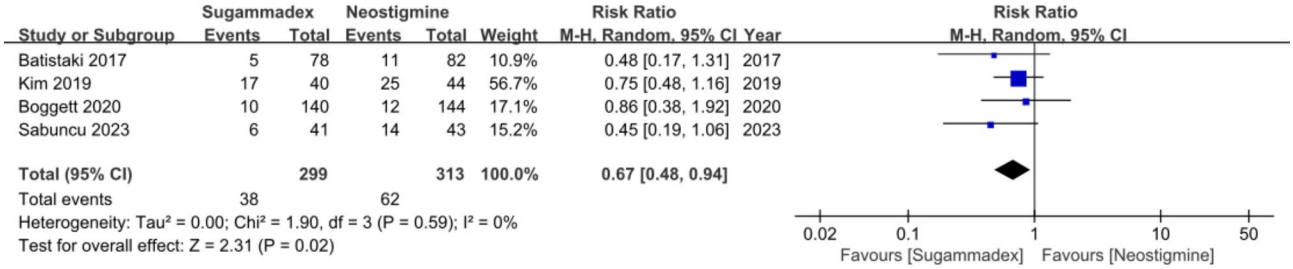

Fig. 3 Forest plot of PND (Sugammadex vs. Neostigmine)

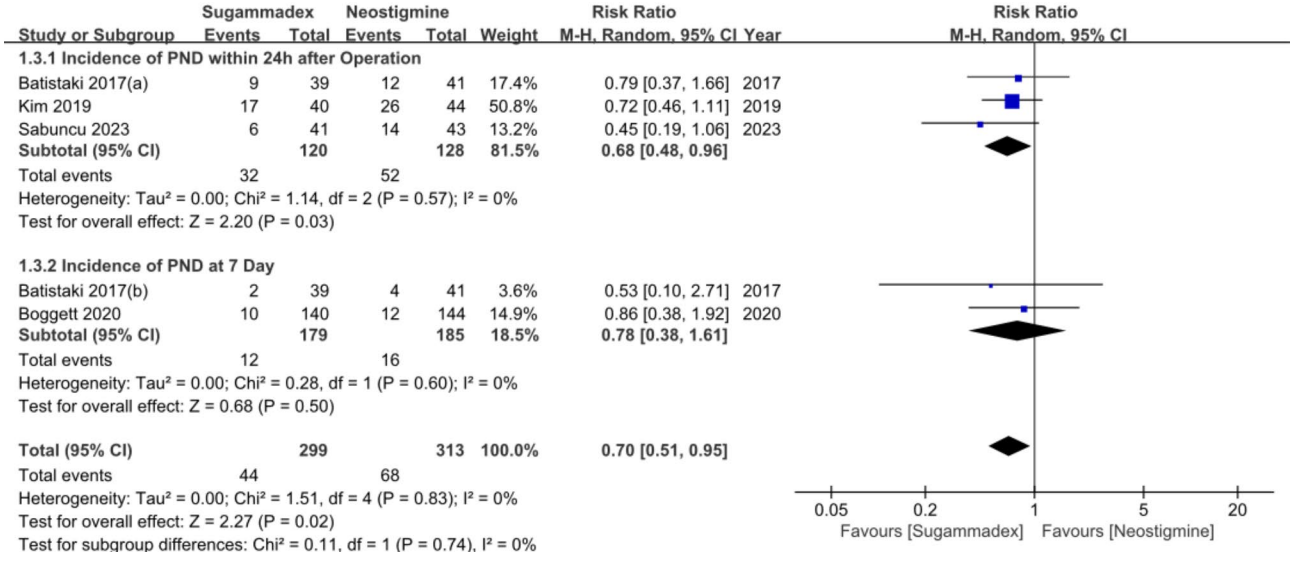

Fig. 4 Subgroup analyses for PND by different time points (24 h or 7days postoperatively) (Sugammadex vs. Neostigmine)

group. In the first analysis, we observed a statistically significant subgroup effect of evaluated time points on the incidence of PND. Three studies [25, 27, 32]showed that sugammadex may reduce the incidence of PND at 24 h postoperatively (RR 0.68; 95%CI: 0.48–0.96; $I^2 = 0\%$; $P = 0.03$) (Fig. 4). However, an analysis of two trials [25, 28] focusing on PND at 7 days postoperatively revealed no significant disparity between sugammadex and neostigmine (RR 0.78; 95%CI: 0.38–1.61; $I^2 = 0\%$; $P = 0.50$) (Fig. 4). No studies reported PND at 3 days following surgery. In the second analysis, we did not conduct a subgroup analysis based on age groups (younger vs. older patients), as the majority of patients (about 86%) in the sugammadex group were younger, and there was no clear age definition for the remaining 14% of patients.

Furthermore, we performed a post hoc subgroup analysis of trials utilizing different anticholinergic drugs (atropine or glycopyrrolate) across four studies (2 RCTs with atropine [25, 32], $n = 244$; 2 RCTs with glycopyrrolate [27, 28], $n = 368$), which revealed a significant subgroup effect of atropine on PND (RR 0.47; 95%CI: 0.24–0.95; $I^2 = 0\%$; $P = 0.03$) (Fig. 5).

Secondary outcome

Given that monitoring muscle relaxation and antagonizing residual muscle relaxation are already routine practices in clinical anaesthesia, the secondary outcome events will exclusively present the results of sugammadex and neostigmine, excluding studies involving a placebo.

MMSE score

Two studies ($n = 247$) [24, 25] reported preoperative MMSE scores, while four studies ($n = 440$) [24–26, 32] reported postoperative MMSE scores. The pooled results indicated no significant difference in preoperative or postoperative MMSE scores between sugammadex and neostigmine (Supplementary Fig. S2).

Recovery time

Two studies ($n = 196$) [24, 26] reported the time taken for patients administered NMBRs to reach a TOF ≥ 0.9. Sugammadex significantly shortened the time of TOF ≥ 0.9 compared to neostigmine (MD -4.52; 95%CI: -5.04 to -3.99; $I^2 = 80\%$; $P < 0.01$; Moderate quality) (Supplementary Fig. S3). One study found that sugammadex resulted in a shorter postoperative extubation time

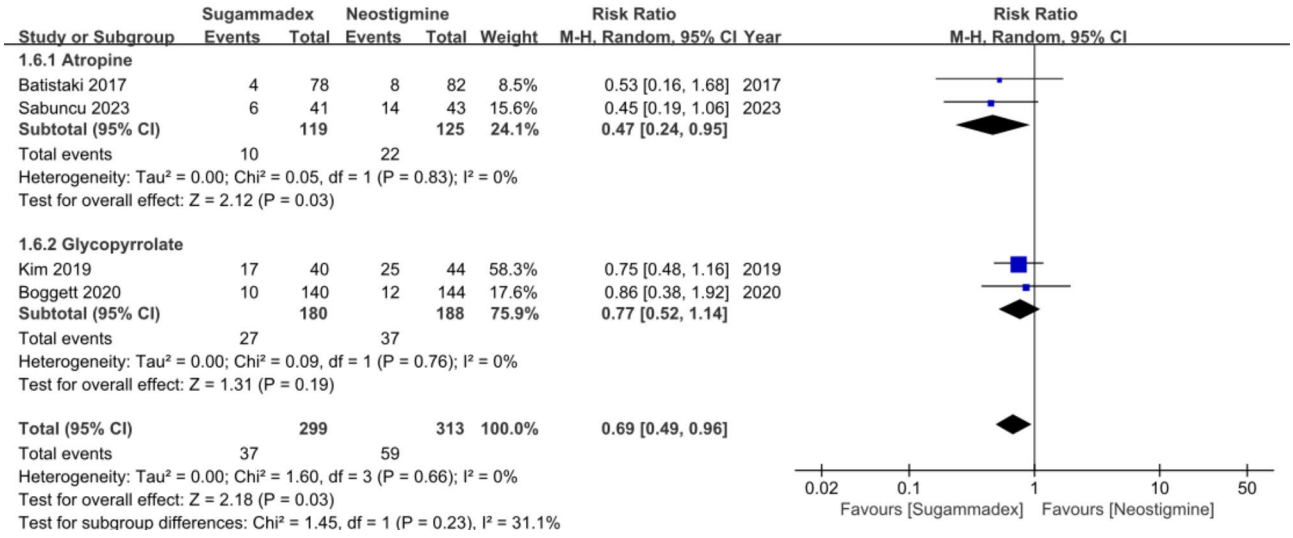

Fig. 5 Subgroup analyses for PND by atropine or glycopyrrolate

compared to neostigmine(7.85 1.26 vs. 6.28 1.33, $P<0.05$) [27].

PONV

Two studies [26, 27] reported the effects of NMBRs on PONV. The pooled analysis of these RCTs ($n=193$) revealed no significant difference in the risk of PONV(RR 0.86; 95%CI: 0.48–1.56; $I^2=0\%$; $P=0.63$; moderate quality) (Supplementary Fig. S4).

Length of stay

One study compared the effects of NMBRs on PACU LOS and found no difference [28]. Additionally, three RCTs ($n=619$) [25, 26, 28] recorded hospital LOS and indicated that the use of sugammadex does not affect hospital LOS compared to neostigmine (MD 0.06; 95%CI: -1.06 to 1.19; $I^2=78\%$; $P=0.91$; very low quality) (Supplementary Fig. S5).

Other outcomes

Of all the studies we included, however, no study reported postoperative anaesthetic awakening time, hospitalisation costs, or postoperative mortality rates.

Publication bias

Publication bias assessment was not performed for any of the outcomes included in this meta-analysis due to the limited number of datasets.

Sensitivity analysis

Sensitivity analyses, employing a leave-one-out approach to examine the robustness of the results, showed inconsistency in the PND outcomes within 7 days post-surgery (Supplementary Fig. S8).

Assessment of pooled effect estimates

Details regarding our GRADE assessment of pooled effect estimates can be found in Supplementary Table S2.

Discussion

In this systematic review and meta-analysis, we identified 10 RCTs, including 1705 patients, that reported on the effects of perioperative NMBRs on postoperative neurocognition. Two primary types of NMBRs were compared: neostigmine and sugammadex. The moderate certainty evidence indicates that sugammadex significantly reduces the risk of PND within 7 days compared to neostigmine when used to reverse residual neuromuscular blockade in patients undergoing non-cardiac surgery. Furthermore, in the subgroup of RCTs analyzed, patients who received sugammadex exhibited a 34.3% lower risk of PND at 24 h postoperatively. Nonetheless, the pooled data showed that the use of sugammadex may be associated with a reduced time of TOF ≥ 0.9. There was no statistically significant difference in the length of hospital or PONV between these reversal approaches.

Our meta-analysis revealed that the administration of sugammadex resulted in improved cognitive function within the first 24 h after surgery. This finding is significant given the importance of optimizing patient brain function and recovery during this vulnerable period. Several factors may explain the beneficial impact of sugammadex on early postoperative cognitive function. First, sugammadex reduces postoperative pulmonary complications across various surgical procedures by adequately reversing residual neuromuscular blockade after anaesthesia, preventing the incidence of hypoxia [34–37]. Impaired postoperative pulmonary function and hypoxia have also been associated with a higher risk of PND [38, 39]. Second, sugammadex offers

a better quality of recovery compared to neostigmine, as it increases postoperative gastrointestinal motility [40] and improves postoperative weakness [41] Third, sugammadex mitigates brain oxidative stress and neuroinflammation, inhibiting the release of malondialdehyde and myeloperoxidase, promoting the release of anti-inflammatory cytokines [15, 42]. Overall, the multimodal protective effects of sugammadex appear to collectively enhance postoperative physical comfort, facilitating cognitive function during the critical postoperative recovery period. The reasons for the benefits of sugammadex on PND not extending to seven days remain unclear but may be related to the drug's short half-life and the dosing regimens employed.

We included placebo studies to determine whether any differences in the effects on PND or PONV could be attributed to a negative impact of neostigmine rather than a positive effect of sugammadex. Our findings suggest that the use of neostigmine may not be associated with PND within 7 days postoperatively when compared to placebo. However, results from the subgroup analysis (Supplementary Fig. S6) are consistent with a recent RCT, which revealed that postoperative neostigmine use is associated with a reduction in PND at 24 h postoperatively compared to placebo [33]. As a quaternary ammonium compound, neostigmine does not readily cross the BBB and remains in the peripheral compartment when administered via non-central routes. It is speculated that peripheral neostigmine could enter the central nervous system through the compromised BBB, increasing the level and duration of acetylcholine in the brain, and amplifying the activity of the cholinergic anti-inflammatory pathway to exert cognition protective effects [43]. Our study demonstrated that neostigmine could reduce the incidence of early PND when compared to placebo, but the protective benefits were diminished when compared to sugammadex. Based on these results, we think that the protective effects of NMBRs may be primarily be attributed to the improved overall quality of postoperative recovery [44–46].

Another key finding of our study was that atropine has significant subgroup effects on PND. Anticholinergics, such as atropine and glycopyrrolate, are commonly used to counteract the muscarinic effects of ACEIs. Compared to the atropine-neostigmine combination, the glycopyrrolate-neostigmine pairing has been shown to provide a more stable cardiovascular profile in elderly patients when reversing residual neuromuscular blockade [47]. The latest clinical guidelines for postoperative neurocognitive disorders recommend minimizing the anticholinergic burden in patients as a non-invasive preventive measure [6, 48]. However, anticholinergic agents can cross the BBB and interfere with normal brain function. Amirreza and colleagues evaluated the cognitive effects of individual anticholinergic drugs through a meta-analysis of 38 studies [49]. They found that glycopyrrolate was not associated with significant cognitive impairment, but the results regarding atropine were inconsistent [49]. This aligns with our subgroup analysis. However, this result needs to be confirmed through further clinical trials due to the limited sample size in our study.

Prior systematic reviews have identified that old age is a risk factor for PND [50, 51]. Interestingly, our results indicate that neostigmine primarily enhances cognitive function in older patients rather than in younger ones (Supplementary Fig. S7). This phenomenon may be attributed to the diminished functional reserve of the elderly brain, which is affected by various factors, thereby demonstrating greater therapeutic potential [52]. However, no study to evaluate the influence of sugammadex on PND in elderly patients. Therefore, there is a need to design rigorous randomized trials in the future to determine the effect of sugammadex on perioperative neurocognitive function in these patients.

Current clinical guidelines recommend the use of neuromuscular transmission monitoring to ensure reversal of TOF ≥ 0.9 before extubation and to guide the use of reversal agents [53]. The implementation of this monitoring is crucial as anticholinergics themselves can induce muscle weakness when reversing patients in whom spontaneous recovery has started [54]. Our results indicate that sugammadex could accelerate the recovery speed of TOF. This result further suggests that sugammadex possesses a stronger ability than neostigmine to reverse residual muscle blockade [46].

This systematic review has several strengths related to its rigor. Notably, only randomized studies were included, which minimizes potential confounding factors frequently present in observational and retrospective data. Additionally, we assessed the risk of bias for the included studies and appraised the quality of evidence for each outcome using the GRADE framework. However, our review has several limitations that must be acknowledged. First, the included RCTs are small and primarily conducted at single centers. Meanwhile, 40% of the included studies exhibited a medium to high risk of bias, which may impact the quality of our study. Among these, one RCT was classified as having a high risk of bias related to blinding, which is particularly important when considering subjective outcomes. However, this study used MMSE scores as the outcome measure rather than incidence, so it does not affect the main research conclusion of our study. Additionally, we employed a leave-one-out approach to examine the robustness of the results when conducted a quantitative analysis of MMSE scores, which revealed consistent results.(Supplementary Fig. S2)Second, the diversity of surgical procedures is notable, and no cardiac surgery was reported. Nevertheless, an

observational study found that postoperative cognitive improvement was greater with sugammadex treatment than with neostigmine in patients undergoing aortic valve replacement [42]. Third, the use of different cognitive scales (CAM, MMSE, PQRS) across studies complicates direct comparisons of results. Fourth, without conducting a network meta-analysis, we are unable to examine the effect of sugammadex on PND in comparison to placebo. Finally, we just followed up for only seven days after surgery, a duration that might not sufficiently reflect the long-term recovery process.

Conclusions

In conclusion, moderate certainty of evidence in our meta-analysis revealed that the use of sugammadex could result in improved early perioperative neurocognitive function and shortened the duration of TOF > 0.9. It may provide a greater protective effect than neostigmine in preventing PND when used to reverse neuromuscular blockade. Furthermore, the absence of an increase in adverse events supports the safety profile of sugammadex in perioperative settings. However, a large, definitive randomized trial is necessary to confirm these findings regarding cognitive function using unified diagnostic criteria, particularly in higher-risk patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03019-9.

Supplementary Material 1: Supplementary data

Supplementary Material 2: PRISMA checklist

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Author contributions
Study conception and design: HW, YLL, XHLLiterature search: HW, LW1, FLMData acquisition and analysis: HW, LW1, FLMQuality review: HW, LW1, FLMData analysis and interpretation: HW, XXW, YQW, LW2Manuscript preparation: all authorsFinal approval of the version to be published: all authors.

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Data availability
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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