Original Article

Efficacy and safety of neostigmine for neuromuscular blockade reversal in patients under general anesthesia: a systematic review and meta-analysis

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Background: Since the antagonistic effect of neostigmine on muscle relaxation is still controversial, this study aimed to evaluate the efficacy and safety of neostigmine for the reversal of neuromuscular blockade in patients recovering from general anesthesia.

Methods: Multiple databases, including PubMed, Web of Science, the Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI), were electronically searched up to August 2021. Relevant studies on the use of neostigmine for neuromuscular blockade reversal in patients under general anesthesia were retrieved. Two reviewers independently screened and extracted data from the retrieved studies, and assessed their risk of bias. Review Manager 5.2 was used to evaluate the efficacy and safety of neostigmine based on the included articles. Heterogeneity and related subgroup, sensitivity, and bias analyses were carried out.

Results: The analysis included 14 studies involving 2,109 patients, including 1,209 in the neostigmine group and 990 in the control group. Results from the random-effects model showed that neostigmine reduced the length of stay in the post-anesthesia care unit [mean difference (MD) =−17.73; 95% confidential interval (CI): −22.06 to −13.41; P<0.0001], the time to recovery of train-of-four ratio ≥0.9 (MD =−16.60; 95% CI: −23.67 to −9.52; P<0.0001), and the extubation time (MD =−16.69; 95% CI: −28.22 to −5.17; P=0.005). However, no difference was observed in adverse events between the neostigmine and control groups [odds ratio (OR) =0.97; 95% CI: 0.84–1.12; P=0.71]. Subgroup analyses adjusted for the dosage of neostigmine had no effect on the above results.

Conclusions: Neostigmine can effectively and safely enhance neuromuscular recovery from non-depolarizing muscle relaxants in patients under general anesthesia.

Keywords: Neostigmine; neuromuscular blockade; anesthesia

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Introduction

The proportion of the global population that receives surgical procedures under anesthesia is increasing annually. The development of short-acting anesthetics has provided opportunities for enhanced recovery after surgery (1). Most anesthesia procedures involve the intraoperative use of muscle relaxants to ensure optimal surgical conditions, facilitate tracheal intubation while decreasing the potential for vocal cord trauma, and allow full control of the patient's respiratory function. These compounds also reduce the

occurrence of intraoperative adverse events (2). However, surgical patients often face high risks of developing postoperative complications, including pain, nausea and vomiting, and impaired pulmonary function.

Pulmonary function impairment resulting from inadequate neuromuscular recovery following general anesthesia can contribute to critical respiratory events in the post-anesthesia care unit (PACU). Postoperative residual neuromuscular blockade, which is associated with adverse patient outcomes, persists with an unacceptably high incidence (3). The neuromuscular block should be routinely monitored in order to guide the administration of muscle relaxant doses and determine the adequacy of reversal. Ali *et al.* (4) introduced train-of-four (TOF) nerve stimulation in the early 1970s. Four super-maximum stimuli were emitted every 0.5 seconds (2 Hz), and the muscle response to the fourth stimulus was compared with that to the first stimulus. The attenuation of muscle contractility caused by repetitive nerve stimulation provides a basis for evaluating neuromuscular block reversal (5). Devices providing digital readings of the TOF ratio (TOFR) should be considered. Viby-Mogensen *et al.* (6) defined a TOFR of 0.7 as a 42% residual block incidence after using long-acting neuromuscular blocking drugs.

Among patients who received muscle relaxants during surgery, residual neuromuscular block (defined as TOF ratio <0.9) commonly occurs during endotracheal extubation or the PACU stay, with an incidence of 88% and 83%, respectively (7). Reports suggests that residual neuromuscular block is associated with clinical complications, including hypoxemia, shortness of breath, upper respiratory tract disease, dysphagia, hypercapnia, slurred speech, blurred vision, and general discomfort (8-12).

Neostigmine is a quaternary ammonium compound with a strong alkaline carbamoyl group. Neostigmine binds to the anion site of acetylcholinesterase and is then transferred to the esterification site and hydrolyzed. It is mainly used to reverse muscle relaxants, at an intravenous dose of 0.05 to 0.07 mg/kg. Its onset of action is generally evident within 1 min, with the peak effect occurring within 10 min. Neostigmine has a duration of action of 20 to 30 min, and an elimination half-life of approximately 77 min (13).

Kopman *et al.* (14) suggested that the TOFR should above 0.9 and close to 1, and found that the weakness of neck and jaw muscles was significantly underestimated when the TOFR reached 1. Their observations remind us to not only to rely on the TOFR but to also evaluate the individual patient, as the effects of muscle relaxants can vary widely. Patients with TOF ratio less than 0.90 had an increased risk of hypoxic events, impaired respiratory control during hypoxia, airway obstruction, aspiration, postoperative pulmonary complications and myasthenia (2). Neostigmine can shorten time to recovery of TOFR ≥0.9 may help to decrease the incidence of postoperative complications.

Neostigmine has imperative research significance for the reversal of neuromuscular blockade after anesthesia. However, there is still doubt about the effects of neostigmine for reversal of neuromuscular blockade (7). To evaluate the efficacy and safety of neostigmine for neuromuscular blockade reversal during recovery from general anesthesia, this meta-analysis compared the typical postoperative recovery indicators including length of PACU stay, time to recovery of TOFR ≥0.9, extubation time, and adverse events between the neostigmine and control groups. In this research, we included 5 new trials published after 2016 and update the meta-analysis about the efficacy and safety of neostigmine for neuromuscular blockade reversal in patients under general anesthesia. In addition, we divided three clinical effects based on the patients' age and further analyzed safety according to the adverse events details.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/atm-21-5667).

Methods

Literature search strategy

Two investigators (JWT and ZXT) independently searched the PubMed, Web of Science, Cochrane Library, and CNKI (Chinese National Knowledge Infrastructure) databases for relevant studies. The search terms and related variants used included "neostigmine", "neuromuscular blockade" or "nerve block", and "general anesthesia". The reference lists and citations of retrieved studies were manually searched to identify additional studies of interest. A comprehensive search was performed to identify all relevant studies regardless of language or publication status (published, unpublished, in the press, and ongoing) up to August 2021.

Study selection

Two investigators (JWT and ZXT) independently reviewed all potentially relevant manuscripts. Cases of disagreement

or uncertainty were resolved by a third investigator (BLL). The initial stage of study included reviewing article titles and abstracts. The following articles were excluded at this stage: (I) studies not written in English or Chinese; (II) non-original research studies; (III) conference abstracts or presentations; and (IV) duplicate studies.

The second stage of study included full-text reviews, and the selection of articles against the inclusion and exclusion criteria. The studies included in this systematic review and meta-analysis met the following inclusion criteria: (I) published in peer-reviewed journals; and (II) reported outcome measures relating to neostigmine. The exclusion criteria comprised the following: (I) studies with non-RCT methodology; (II) studies involving patients not under general anesthesia; and (III) studies without fully available or any relevant clinical outcome measures. Reviews, qualitative studies, animal trials, and laboratory studies were also excluded.

Data extraction

Two investigators (JWT and ZXT) independently extracted the data and evaluated the quality of all eligible studies. The quality of the included studies and validity of the extracted data were then verified independently. Differences between the investigators were resolved through discussion or by a third investigator (BLL) if necessary. The extracted data were as follows: first author, year of publication, location, income level, study population, study design, and study participant characteristics (sample size, age, and sex).

Assessment of methodological quality

The RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Demark) was employed for the assessment of selection bias, performance bias, attrition bias, and reporting bias, and to generate risk of bias tables. The risk of bias and quality of each included article were independently assessed by two reviewers using Cochrane risk assessment tool (JWT and ZXT), who assessed each risk of bias item as "low", "high", or "unclear". Any discrepancies between the two reviewers were resolved by a consulting group comprising two experts in anesthesia specialty (BLL and DXM). Publication bias was determined based on visual symmetry of funnel plots, with asymmetry suggesting possible publication bias.

Statistical analysis

Data were pooled, and mean difference [MD, with 95% confidence interval (CI)] was used for continuous outcomes including the length of PACU stay, time to recovery of TOFR ≥0.9, and extubation time. Odds ratios (ORs) were used for dichotomous variables including postoperative nausea and vomiting (PONV), bradycardia, pain, and hypoxemia. Heterogeneity was assessed using the P value and I-square (I^2) statistic in the pooled analyses, and these two parameters represent the percentage of total variation across studies. If the P value was less than 0.1 or the I^2 value exceeded 50%, the summary estimate was analyzed by random-effects model; otherwise, a fixed-effects model was applied. Potential publication bias was assessed by Begg's funnel plot and Egger's linear regression test. The existence of publication bias was indicated by a P value <0.05. Additionally, a scenario sensitivity analysis was conducted to evaluate the robustness of the results. All statistical analyses were carried out with Review Manager 5.2 (The Cochrane Collaboration).

Results

Search process

Through a search of multiple databases, a total of 855 articles were identified for initial screening. Then, on the basis of their titles and abstracts, 779 of these studies were excluded. The full texts of the remaining 76 studies were carefully examined according to the inclusion and exclusion criteria. Finally, 14 comparative studies were included for meta-analysis. The study selection flow chart is shown in *Figure 1*.

Characteristics of the included studies

Table 1 details the main characteristics of the 14 studies included in the meta-analysis (15-28). The mean ages of participants in the studies ranged from 7.3 to 73.3 years old, and the proportion of male participants ranged from 0% to 63.5%. The follow-up duration lasted from 1 to 3 years. The 14 studies were RCTs or retrospective trials and involved a total of 2,199 patients, of whom 1,209 patients received neostigmine and 990 received control drugs.

Results of quality assessment

The risk of bias and quality of the included studies were

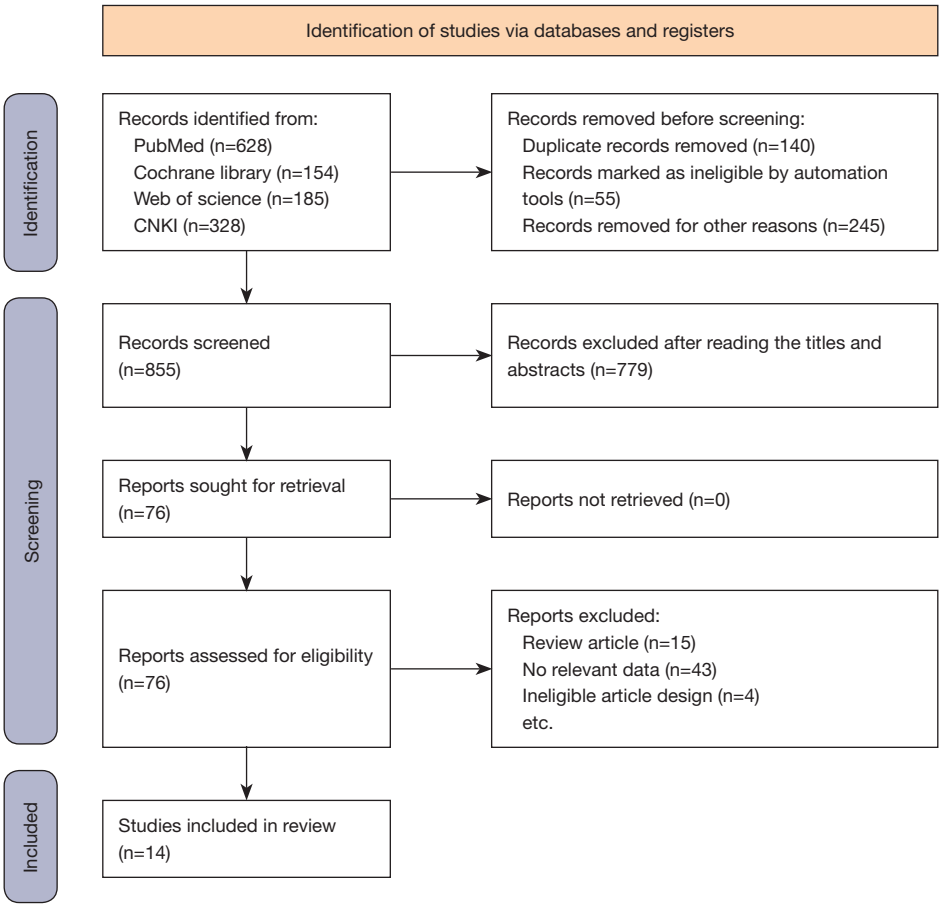

Figure 1 Flow chart of the study selection process for the meta-analysis.

evaluated. The results of quality evaluation showed the studies to have low risk of bias (*Figure 2*). As shown in *Figure 3*, only one study had high selection bias (22), one had high attrition bias (15), one had high reporting bias (18), and two had other biases (17,22). Overall, these results evidenced the good quality of the included studies.

Results of meta-analysis

Length of PACU stay

Five studies examined the difference in the length of PACU stay between the neostigmine and control groups. Meta-analysis by random-effects model showed that patients in the neostigmine group had a shorter PACU stay than those in the control group (MD =–17.73; 95% CI: –22.06 to –13.41; P<0.0001; I^2=92%; *Figure 4*). Subgroup analysis based on the dosage of neostigmine indicated that compared to that in the control group, the length of PACU stay was significantly shortened in both the neostigmine ≥40 μg/kg (MD =–18.11; 95% CI: –23.16 to –13.05; P<0.0001; I^2=94%) and neostigmine <40 μg/kg (MD =–16.03; 95% CI: –26.51 to –5.55; P=0.003; I^2=83%) groups.

Time to recovery of TOFR ≥0.9

Seven studies reported the time to recovery of TOFR ≥0.9. Meta-analysis showed that the time to recovery of TOFR ≥0.9 in the neostigmine group was shorter than that in the control group (MD =–16.60; 95% CI: –23.67 to –9.52; P<0.0001; I^2=100%; *Figure 5*). In the subgroup analysis, compared to the time to recovery of TOFR ≥0.9 in the control group, the time to recovery of TOFR ≥0.9 was significantly shortened in both the neostigmine ≥40 μg/kg (MD =–16.19; 95% CI: –24.27 to –8.11; P<0.001; I^2=98%) and neostigmine <40 μg/kg (MD =–16.61; 95% CI: –26.11 to –7.12; P=0.0006; I^2=100%) groups.

Table 1 Characteristics of the included studies

Study	Year	Country	Groups	Dosage of neostigmine (μg/kg)	Sex (male/female)	Age (years)	n	Years of onset
Chen	2014	China	Neostigmine 3	20	11/9	70.1±5.6	20	February 2013 to September 2013
			Neostigmine 2	10	10/10	71.1±5.2	20	
			Neostigmine 1	5	12/8	70.2±4.9	20	
			Control	0	9/11	72.0±6.2	20	
Chen	2019	China	Neostigmine	40	87/75	72.0±9	162	–
			Control	0	93/72	73.0±10	165	
Choi	2016	Korea	Neostigmine 3	40	–	–	28	–
			Neostigmine 2	20	–	–	28	
			Neostigmine 1	10	–	–	28	
			Control	0	–	–	28	
Di	2014	China	Neostigmine	20	0/59	37.7±6.1	59	February 2011 to August 2013
			Control	0	0/59	39±7.8	59	
Li	2010	China	Neostigmine	40	5/9	38.6±5.9	14	August 2009 to January 2010
			Control	0	6/8	39.5±9.7	14	
Li	2012	China	Neostigmine	35	27/23	7.5±0.2	50	–
			Control	0	26/24	7.3±0.3	50	
Liu	2015	China	Neostigmine	50	0/100	38.2±6.9	100	August 2012 to August 2013
			Control	20	0/100	38.2±6.9	100	
Naguib	2000	Saudi Arabia	Neostigmine 3	50	–	–	8	–
			Neostigmine 2	20	–	–	8	
			Neostigmine 1	10	–	–	8	
			Control	5	–	–	8	
Xu	2011	China	Neostigmine 3	50	7/8	50.7±8.8	15	–
			Neostigmine 2	30	8/7	50.1±10.1	15	
			Neostigmine 1	10	7/8	52.0±10.0	15	
			Control	0	8/7	55.7±9.0	15	
Xu	2020	China	Neostigmine	40	261/161	54±12	422	September 2016 to June 2019
			Control	0	254/146	55±9	400	
Yao	2021	China	Neostigmine	20	7/4	45.6±9.1	11	–
			Control	0	7/12	49.9±14.1	19	
Zhou1	2015	China	Neostigmine 4	50	–	–	10	–
			Neostigmine 3	30	–	–	10	
			Neostigmine 2	20	–	–	10	
			Neostigmine 1	10	–	–	10	
			Control	0	–	–	10	
Zhou2	2015	China	Neostigmine	40	–	–	60	January 2013 to January 2015
			Control	0	–	–	60	
Zhu	2020	China	Neostigmine 2	40	21/19	73.3±6.2	40	September 2018 to January 2020
			Neostigmine 1	20	20/18	72.5±6.1	38	
			Control	0	22/20	72.9±4.9	42	

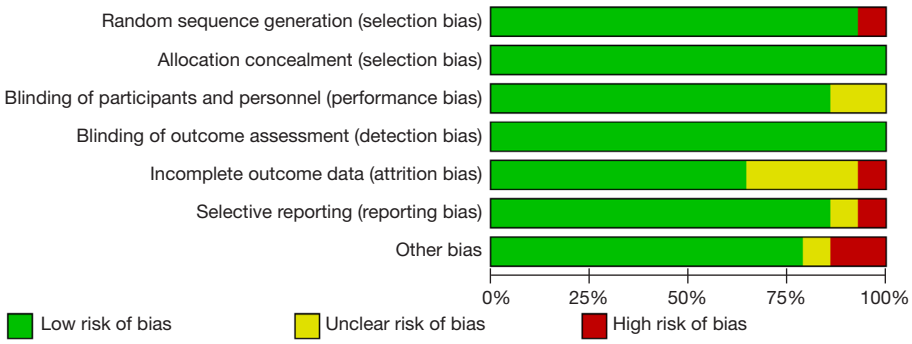

Figure 2 Summary of quality assessment of the included studies. Red, yellow, and green indicate high, unclear, and low risk of bias, respectively.

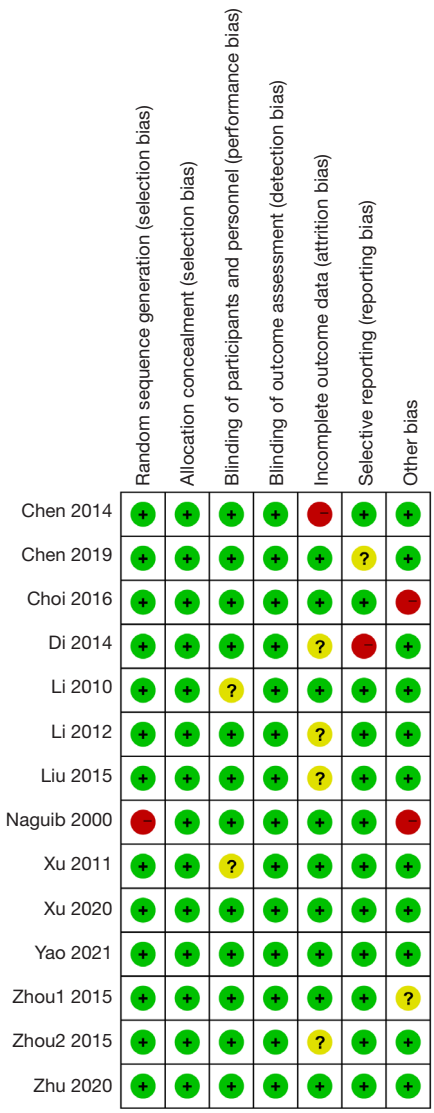

Figure 3 Summary of the risk of bias assessment according to the Cochrane Collaboration's tool. Red, yellow, and green indicate high, unclear, and low risk of bias, respectively.

Extubation time

Five studies compared the extubation time between the neostigmine and control groups. The extubation time in the neostigmine group was significantly shorter than that in the control group (MD =−16.69; 95% CI: −28.22 to −5.17; P=0.005; I^2=100%; *Figure 6*). However, in the subgroup analysis, the extubation time showed no differences in the neostigmine ≥40 μg/kg (MD =−22.08; 95% CI: −51.97 to 7.81; P=0.15; I^2=99%) and neostigmine <40 μg/kg (MD =−13.84; 95% CI: −28.10 to −0.42; P=0.06; I^2=100%) groups compared with the control group.

Adverse events

Seven studies reported adverse events in the neostigmine and control groups, and the forest plot is presented in *Figure 7*. There was no difference in the overall incidence of adverse events between the neostigmine and control groups (OR =0.97; 95% CI: 0.84–1.12; P=0.71; I^2=34%). In the subgroup analysis, the incidence of PONV in the neostigmine group was higher than that in the control group (OR =1.30; 95% CI: 1.03–1.65; P=0.03; I^2=0%). However, there were no differences observed in other adverse events, including bradycardia (OR =1.12; 95% CI: 0.44–2.88; P=0.81; I^2=57%), pain (OR =0.82; 95% CI: 0.65–1.03; P=0.09; I^2=0%), and hypoxemia (OR =0.79; 95% CI: 0.59–1.07; P=0.13; I^2=0%).

Results of sensitivity and publication bias analysis

The length of PACU stay was reported in five studies, and the pooled result showed that it was shortened by neostigmine (MD =−17.73; 95% CI: −22.06 to −13.41; P<0.0001; I^2=92%; *Figure 4*). A sensitivity analysis was performed by removing Xu *et al.*'s study (23), which reduced the I^2 statistic from 92% to 86% (*Figure 8*), thus indicating

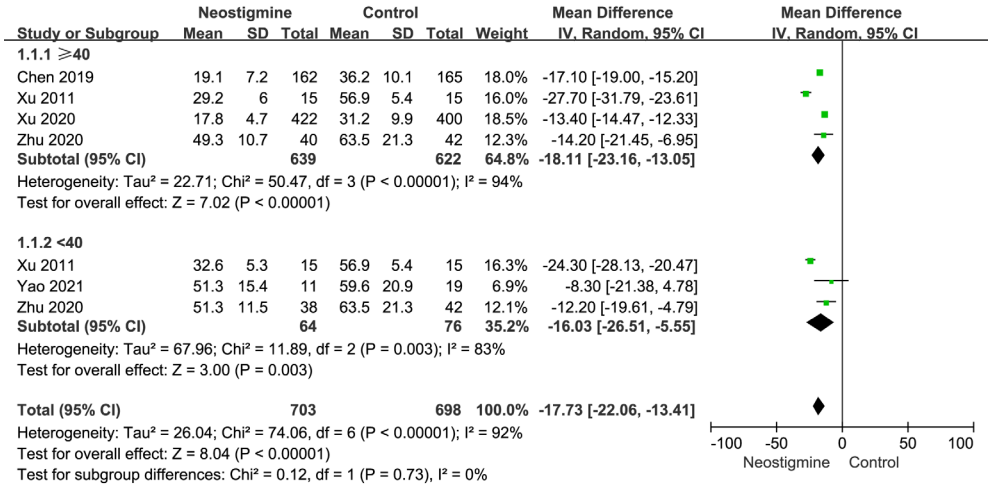

Figure 4 Forest plots of the length of stay in the post-anesthesia care unit (PACU).

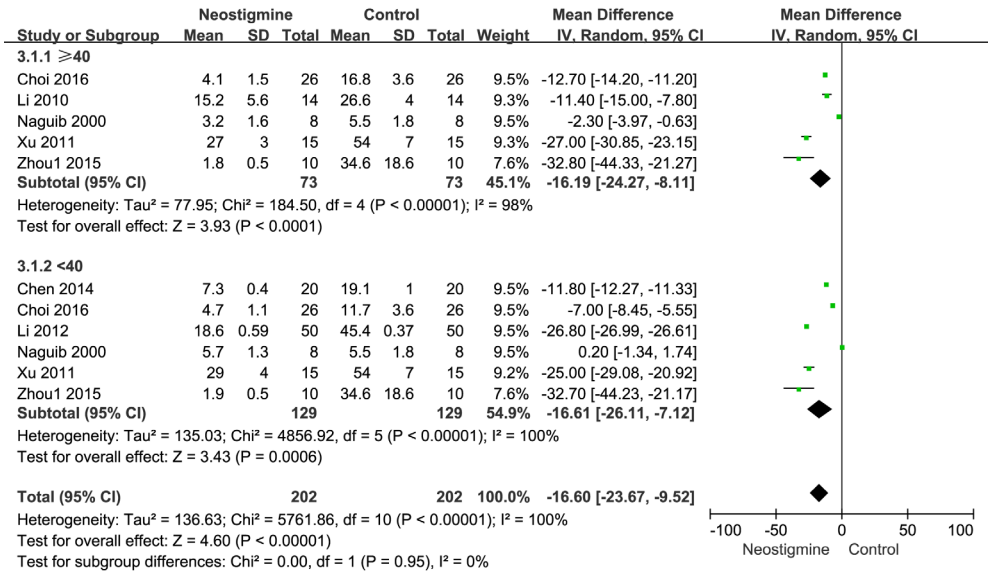

Figure 5 Forest plots for time to recovery of train-of-four ratio (TOFR) ≥0.9.

that the results of the included articles were robust.

A funnel plot was created to evaluate the publication bias for the length of PACU stay. The shape was symmetrical and the P value of the Egger's test was 0.482, which indicated that no significant publication bias existed in this meta-analysis (*Figure 9*).

Discussion

Muscle relaxants mainly act on the neuromuscular junctions, and vary in the mode, duration, and intensity of blockade. Non-depolarizing muscle relaxants competitively occupy receptors on the motor endplates in place of acetylcholine, exerting muscle relaxing effects. At the end of surgery, muscle relaxation can be reversed with neostigmine, which restores the binding of acetylcholine to receptors on the motor endplate, thereby reversing the neuromuscular block (29).

In this meta-analysis, neostigmine was found to significantly shorten both the length of stay in the PACU and the extubation time (P<0.05). These results, which are consistent with the results of Lu's research (30), suggest that

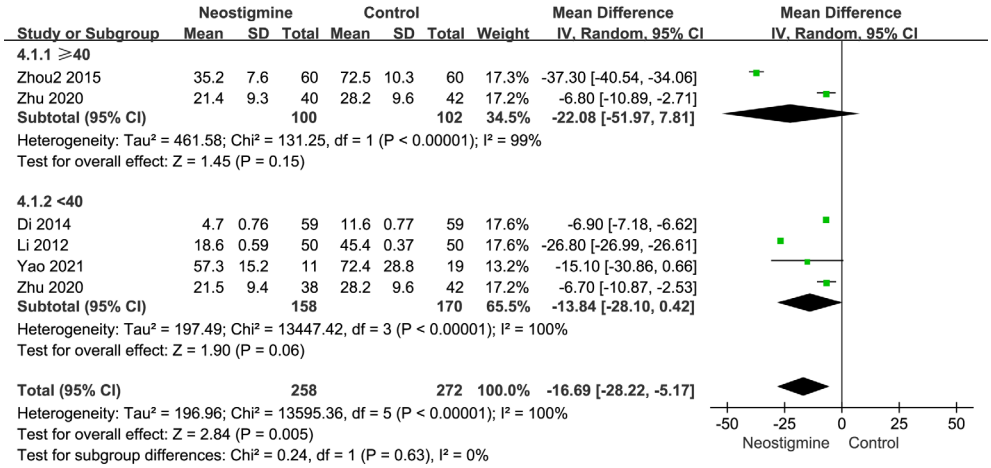

Figure 6 Forest plot of the extubation time.

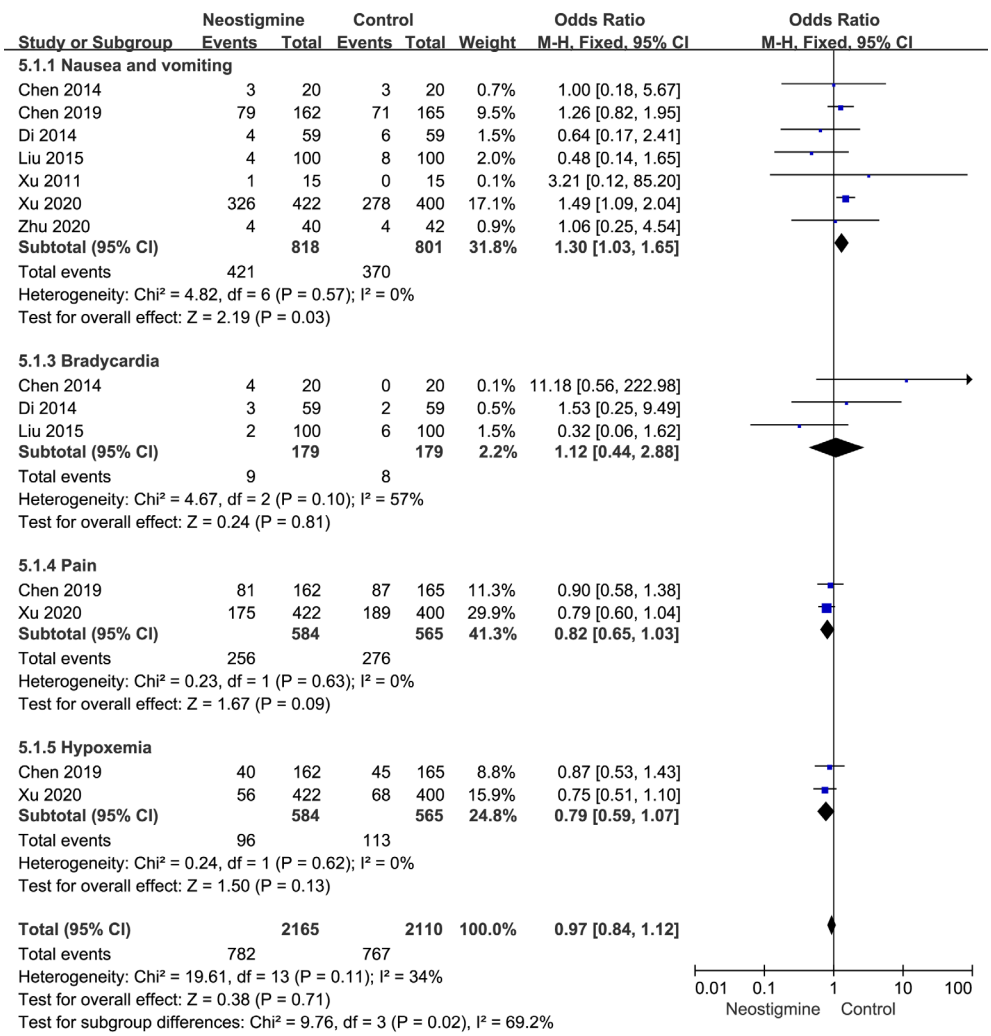

Figure 7 Forest plot of adverse events.

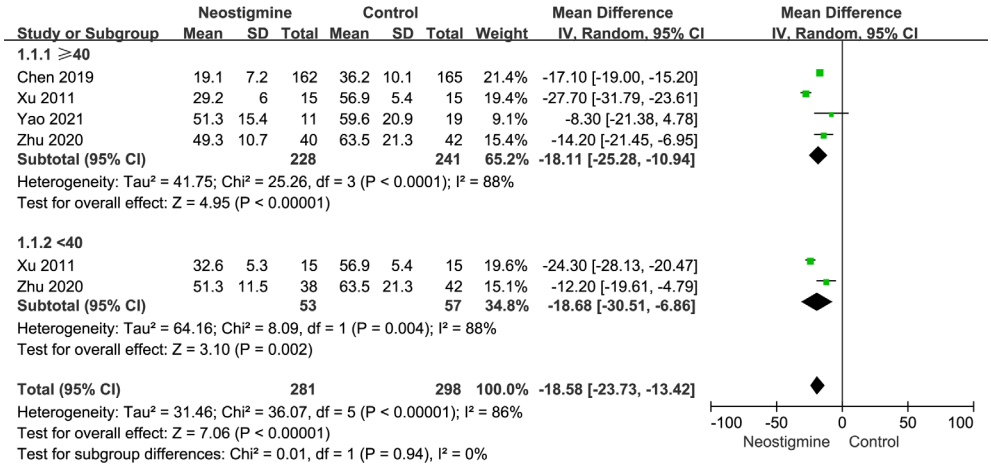

Figure 8 Sensitivity analysis forest plots of the length of stay in the post-anesthesia care unit (PACU).

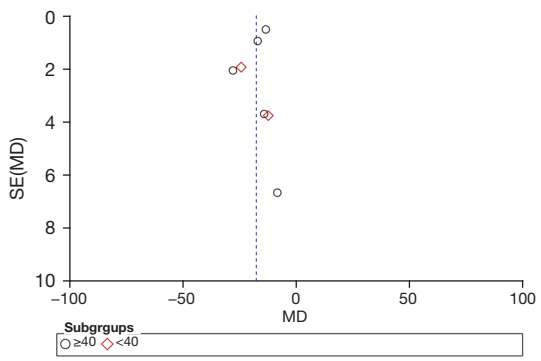

Figure 9 Publication bias funnel plot for the length of stay in the post-anesthesia care unit (PACU).

neostigmine can accelerate the rehabilitation of patients. Further, regardless of whether the dose was high or low, patients who received neostigmine had a short PACU stay.

TOF is a medical test used to assess the degree of paralysis. The TOF value can precisely reflect the degree of muscle relaxation, and has been widely applied clinically to assess the degree of intraoperative and postoperative residual muscle relaxation. When non-depolarizing muscle relaxants are used, neuromuscular monitoring is essential throughout the whole anesthesia process. Recovery of the TOFR to 0.7 has been reported to provide insufficient confirmation of the complete recovery of the swallowing muscles and upper respiratory tract; instead, a TOFR of 0.9 should be taken as confirmation of complete recovery before extubation (31). This meta-analysis showed that neostigmine can enhance the recovery of the TOFR, which is also in consistent with Lu's research findings (30). In the low-, medium-, and high-dose subgroups, neostigmine significantly shortened the time to recovery of TOFR ≥0.9. When the dose of neostigmine was increased from 20 to 40 μg/kg, the recovery of muscle relaxation was significantly accelerated, but with an increase to 60 μg/kg, only the time to recovery of TOFR ≥0.7 was shortened, with limited clinical significance (32).

In this meta-analysis, we found that neostigmine did not cause an increase in postoperative total adverse events such as bradycardia, hypoxemia, and postoperative pain. Neostigmine can mitigate hypoxemia; however, no significant difference between the neostigmine and control groups was observed in this analysis, which may be attributable to the limited number of studies included that reported this outcome. The relationship between neostigmine and the incidence of PONV remains controversial (33,34). Although this meta-analysis showed that neostigmine elevated the risk of PONV, further study is needed to confirm this observation. Also, the use of muscle relaxants during anesthesia has been reported to be associated with an increased risk of postoperative pulmonary complications (2). Together, these observations serve as a reminder that neuromuscular monitoring and reversal agents may reduce the risk of postoperative pulmonary complications.

This study has some potential limitations that should be mentioned. First, significant heterogeneity existed between the studies, and the small sample sizes of each study did not allow for meta-regression or additional sensitivity analyses; instead, a random-effects model was applied for

meta-analysis. Second, included quantitative researches on neostigmine is insufficient. Further, the included studies were mostly performed in Asia, and there was a lack of relevant studies from other geographical areas. Neither of these factors is conducive to the wider generalization of our conclusions. In addition, the comparison between Neostigmine and Sugammadex is not conducted, which could be analyzed in the future. To conduct more in-depth scientific research on this topic, more studies from non-Asian countries and more quantitative analyses should be conducted in future.

In conclusion, this comprehensive meta-analysis of 14 studies has demonstrated that neostigmine is safe and effective for neuromuscular blockade reversal in patients recovering from general anesthesia. Neostigmine shortened the length of stay in the PACU, the extubation time, and the time to recovery of TOFR ≥0.9, with limited overall incidence of adverse events.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-5667

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-5667). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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