Original Article

Effects and safety of neostigmine for postoperative recovery of gastrointestinal function: a systematic review and meta-analysis

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Background: The purpose of this study was to evaluate the clinical effects and safety of neostigmine for the postoperative recovery of gastrointestinal function.

Methods: We performed a literature search of multiple databases [PubMed, Web of Science, Cochrane Library and China National Knowledge Internet (CNKI)] to retrieve studies comparing the postoperative gastrointestinal function of neostigmine and control groups. Review Manager 5.2 was applied for the analysis of heterogeneity, sensitivity, and bias.

Results: After screening the articles, 17 trials involving 1,589 postoperative patients that met the eligibility criteria were included. The results suggested that neostigmine improved the first passage of flatus [standard mean difference (SMD) =−3.00; 95% confidence interval (CI): (−4.03, −1.97); P<0.001), first defecation [SMD =−3.75; 95% CI: (−5.25, −2.24); P<0.001], time of bowel sound recovery [SMD =−3.42; 95% CI: (−4.49, −2.36), P<0.001], and gastrointestinal function recovery [risk ratio (RR) =1.84; 95% CI: (1.19, 2.86); P=0.007]. Compared to the control group, the neostigmine group had lower rates of abdominal distention [RR =0.39; 95% CI: (0.18, 0.87); P=0.02; I^2=76%] and overall adverse events [RR =0.49; 95% CI: (0.29, 0.82); P=0.007]. However, two groups had no difference in postoperative nausea and vomiting (PONV) [RR =0.50; 95% CI: (0.21, 1.23); P=0.13], and respiratory complications [RR =0.96; 95% CI: (0.20, 4.53); P=0.96]. Sensitivity and publication bias analyses showed that these results were robust and exhibited little publication bias.

Discussion: Small doses of neostigmine may promote the recovery of postoperative gastrointestinal function without obvious side effects.

Keywords: Neostigmine; gastrointestinal function; post-operation

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Introduction

Postoperative ileus (POI) is a common disease after gastrointestinal and other types of operations, such as orthopaedic, gynaecological, and urological surgeries, which leads to an increased incidence of several disease, hospitalization expenses, and 30-day readmission (1). In the past, it was generally believed that one of the normal compulsory physiological reactions of abdominal surgery is a certain degree of POI, and this reaction has no serious sequelae (2,3). However, POI could be caused by the inflammatory response in intestinal operation, which leads to the long-term inhibition of intestinal synergistic activity. The prolongation of intestinal obstruction will lead to patient discomfort and prolonged hospital stay. Prolonged POI is the main reason for the extended recovery period, protracted hospital stay, and increased medical expenses.

According to previous reports, the estimated incidence of POI in the United States in 2002 was approximately 17–80%, and the total hospital cost caused by POI was as high as US$1.46 billion (4).

The underlying mechanism of POI is multifactorial and not yet completely understood. The main risk factors of POI include fluid overload, neurohormonal dysfunction, gastrointestinal stretch, and inflammation (5). Activation of the sympathetic nervous system, release of inflammatory mediators and immigration of leucocytes into the intestinal wall, stimulation of opioid receptors due to perioperative opioid usage, and edema of the intestinal wall due to fluid overload are considered the causes of postoperative gastrointestinal dysmotility (4). By introducing enhanced recovery after surgery (ERAS) protocols, laparoscopic procedures, and epidural anaesthesia, the incidence of POI may be reduced (6-8). However, it remains a problem in daily postoperative care. Therefore, prokinetic drugs, such as neostigmine, are widely administered in surgical wards. Neostigmine is a water-soluble, ionized compound that inhibits acetylcholinesterase (AChE). Its indication in FDA is to reverse the effect of non-depolarizing neuromuscular blockers after surgery. The drug is usually administered by intravenous injection, and the main route of excretion is the kidney. Neostigmine should be used with caution in patients with coronary heart disease, arrhythmia, recent acute coronary syndrome and myasthenia gravis (9). It was reported that neostigmine was used to treat POI in several disease types patients (10).

The previous studies had little analysis on neostigmine for postoperative recovery of gastrointestinal function, meanwhile there are several studies about the effect of neostigmine on POI; yet, there are few comprehensive reviews in this field. We conducted this meta-analysis to assess the safety and efficacy of neostigmine for the recovery of postoperative gastrointestinal function.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3291).

Methods

Literature search strategy

A comprehensive literature search was conducted to retrieve eligible studies published between January 2000 and 2021 in the following electronic databases: PubMed, Web of Science, Cochrane Library and China National Knowledge Internet (CNKI). The keywords used included neostigmine, gastrointestinal function, and postoperative ileus or POI.

We used the Boolean operators "and" and "OR" to expand the search scope by combining the set words and strings. A comprehensive search of trials without language or publication status restrictions was performed. We then performed data extraction; one of us (Li) performed all of the data extraction, and two of us (Liao and Ouyang) conducted independent verification.

Study selection

The inclusion criteria were specified according to the population, interventions, comparisons, outcomes, and setting/study design (PICOS) reporting structure, and were as follows: (I) language was restricted to English or Chinese publications; (II) patients received neostigmine; (III) studies focused on the gastrointestinal function of patients; (IV) study type is randomized control trials (RCTs); and (V) articles with sufficient data provided by means of indicators with standard deviation.

Studies were excluded according to the following criteria: (I) studies lacking available data; (II) non-Chinese or English articles; (III) duplicates, reviews, letters, case reports, comments, or editorials; (IV) studies involving simple descriptions without comparison; and (V) articles with an absence of key information.

Data extraction and quality assessment

Two reviewers independently screened the titles, abstracts, and full texts of the potentially eligible studies, and resolved disagreements through discussion. We used structured data tables to extract the required data elements from each trial, including baseline characteristics, sample size, and interventions used. The validity of eligible RCTs was assessed using the Cochrane risk of bias tool in Review Manager 5.2 (Cochrane Collaboration, 2020). Egger's tests and funnel plots were planned to evaluate the risk of bias across studies.

Statistical analysis

We assessed the efficacy and safety of neostigmine for the postoperative recovery of gastrointestinal function by pooling the standard mean difference (SMD) or risk ratios (RRs) using the DerSimonian-Laird random-effects model

from RCTs and non-randomized studies, respectively.

Standardized differences were calculated based on the mean differences (control *vs.* neostigmine) of the several indicators (end of treatment) means and standard deviations. Heterogeneity was assessed by calculating the Cochrane Q statistics and I^2 statistics. If there was no statistical heterogeneity among the included studies, the fixed effect model was used for meta-analysis; otherwise, the random effect model was applied. The Egger's test and a funnel plot were used to examine potential publication bias. Sensitivity analysis was further conducted to evaluate the robustness of the findings through exponential tilting. The Review Manager (Version 5.2, Cochrane Collaboration, 2011) was used to estimate the impact of the results in the selected report. To measure the consistency of the effect size, SMD and RR were used. I^2 statistics was used to test the heterogeneity. If I^2>50%, it meant that there was a certain degree of heterogeneity among the studies, and the random effect model would be used for analysis; if I^2≤50%, it meant that there was no heterogeneity or less heterogeneity between the studies, and the fixed effect model would be used for analysis.

Results

Search process

A literature search in four databases identified 862 unique studies and 77 were retrieved for full-text assessment. After the removal of ineligible design, insufficient data files, and reviews, we conducted further screening. We screened the titles and abstracts of these articles and removed non-related articles. Finally, 17 publications remained for further screening.

A total of 17 studies met the inclusion/exclusion criteria and were included in the present meta-analysis (*Figure 1*).

Characteristics of included studies

The detailed characteristics of these 17 eligible studies were summarized in *Table 1* (9-25). For each RCT, the following characteristics were collected: first author, publication year, number of patients in each group, interventions in this meta-analysis, gender and age distribution of participants, and any related results. These studies included a total of 1,608 patients who received surgeries. The included studies were published in the Chinese or English languages.

Quality assessment results

The risk-of-bias assessment for each of the included studies was summarized in *Figure 2*. There was a high risk of selection bias, performance bias, and detection bias in five different studies (*Figure 2*).

A summary of the risk-of-bias assessment for each study is shown in *Figure 3*. The Begg's tests showed that there was no publication bias in our study (P=0.45).

Results of heterogeneity test

Primary outcomes

Heterogeneity analysis about first passage of flatus

Thirteen studies including 589 patients in the neostigmine group and 572 patients in control group were involved in the heterogeneity analysis of the first passage of flatus (*Figure 4*). All 13 studies showed statistically significant differences of the first flatus passage between the neostigmine and control groups. The times of the first passage of flatus in the neostigmine group were shorter than those of the control group [SMD =−3.00; 95% confidence interval (CI): (−4.03, −1.97); overall P<0.001; P for heterogeneity <0.001; I^2=98% using random effect model].

Heterogeneity analysis regarding first defecation between the neostigmine and control groups

Six articles were included in this analysis. The heterogeneity test results showed that the random effect model was needed to analyze the data (P of heterogeneity <0.001; I^2=98%; P of overall effect <0.001). The overall effect of first defecation was significant and the SMD was −3.75 with 95% CI: (−5.25, −2.24), showing that the neostigmine group had earlier first defecation than control group (*Figure 5*).

Heterogeneity analysis regarding the time of bowel sound recovery in the neostigmine and control groups

As shown in *Figure 6*, 10 included studies were involved in the analysis of bowel sound recovery time between the neostigmine and control groups. The bowel sound recovery time of the neostigmine group was less than that of the control group [SMD =−3.42; 95% CI: (−4.49, −2.36); P<0.001; I^2=97%].

Secondary outcomes

Heterogeneity analysis regarding the gastrointestinal function recovery between the neostigmine and control groups

Five articles were included in the analysis of gastrointestinal

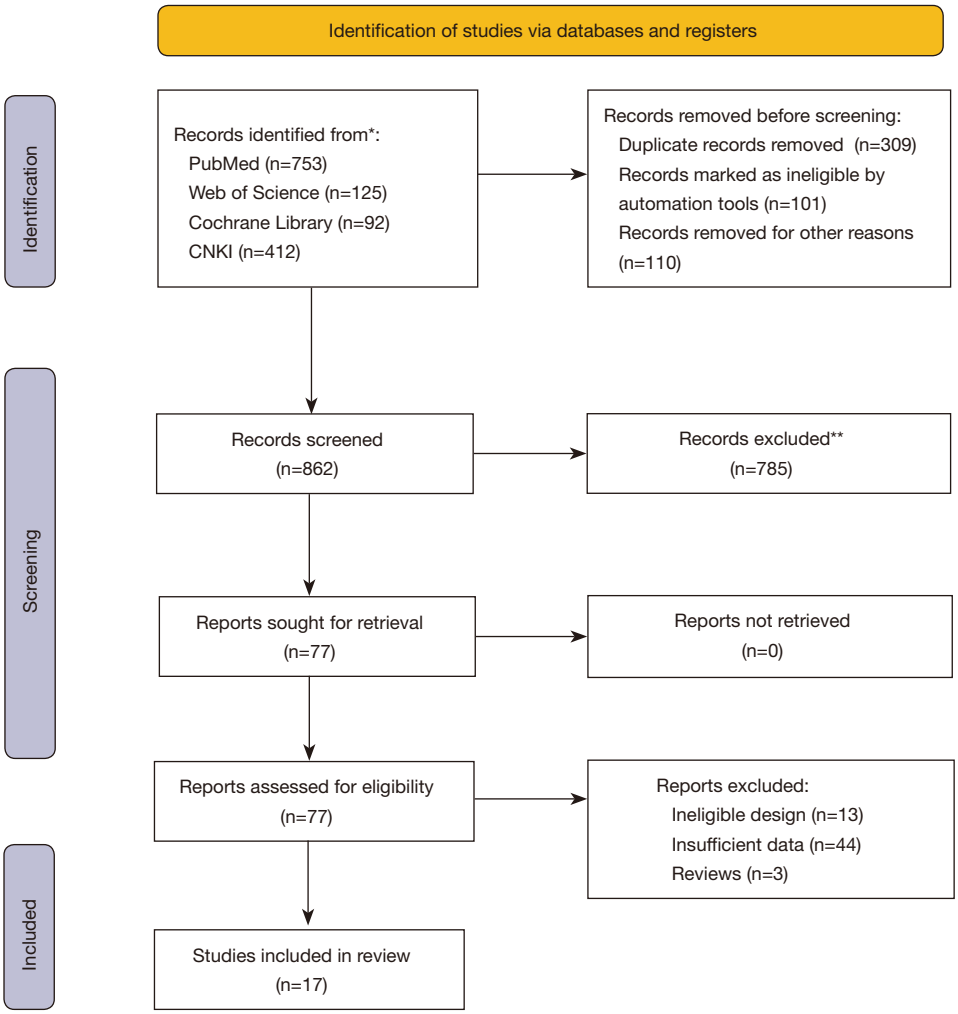

Figure 1 Literature selection flow chart. CNKI, China National Knowledge Internet. *, consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **, if automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. From: Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. For more information, visit: http://www.prisma-statement.org/.

function recovery between the neostigmine and control groups. The heterogeneity test results showed that random effect model was needed to analyze the data (P of heterogeneity <0.001; I^2=90%; P of over effect =0.007). The overall effect of gastrointestinal function recovery was significant; the overall RR was 1.84 with 95% CI: (1.19, 2.86). The gastrointestinal function recovery of the neostigmine group was superior to that of the control group (*Figure* 7).

Heterogeneity analysis regarding the adverse events between the neostigmine and control groups

The adverse events (e.g., nausea, vomiting, abdominal distention, respiratory complications) in the two arms were compared by overall analysis and further subgroup analysis (*Figure 8*). In the overall analysis, the rate of adverse events was markedly different between the neostigmine and control groups [RR =0.49; 95% CI: (0.29, 0.82); P=0.007; I^2=75%], and the control group had higher rates of adverse

Table 1 Baseline data of included studies

Study	Year	Groups	Dosage of neostigmine	Treatment	Sex (male/female)	Age (years), mean ± SD	N
Caliskan	2008	Neostigmine	1 μg/kg	Epidural catheter	17/1	57±8	18
		Control	–	Normal saline	16/0	63±7	16
Chen	2012	Neostigmine	1 mg	Acupoint injection	19/16	47.3±12	35
		Control	–	Vitamin B1 by acupoint injection	21/14	45.5±11	35
Chen	2020	Neostigmine	1–2 mg	Acupoint injection + conventional therapy	36/16	54.4±11.4	52
		Control	–	Conventional therapy	37/18	55.3±9.4	55
Feng	2014	Neostigmine	1 mg	Acupoint injection + conventional therapy	21/14	45.2±7.2	35
		Control	–	Conventional therapy	19/16	46.2±6.2	35
Gao	2013	Neostigmine	0.5 mg	Acupoint injection	12/8	45±18	20
		Control	–	Conventional therapy	11/9	45±23	20
Geng	2019	Neostigmine	1 mg	Acupoint injection	25/16	42.2±13.3	41
		Control	–	Conventional therapy	22/19	41.2±13.7	41
Jiang	2001	Neostigmine	1 mg	Epidural catheter	0/20	–	20
		Control	–	Normal saline	0/20	–	20
Qiu	2015	Neostigmine	2 mg	Acupoint injection	18/22	43.2±5.8	40
		Control	–	Conventional therapy	19/21	43.3±5	40
Shao	2014	Neostigmine	1 mg	Acupoint injection	24/8	67.3±10.3	32
		Control	–	Conventional therapy	26/6	63.1±9.9	32
Wu	2010	Neostigmine	0.5 mg	Acupoint injection	17/13	41.6±12.3	30
		Control	–	Kaiselu	18/12	41.6±12.3	30
Wu	2019	Neostigmine	1 mg	Acupoint injection	16/14	57±18	30
		Control	–	Normal saline	16/14	57±18	30
Xi	2015	Neostigmine	2 mg	Acupoint injection	16/14	54±14	30
		Control	–	Conventional therapy	15/15	54.2±13.1	30
You	2018	Neostigmine	1 mg	Acupoint injection	50/17	–	67
		Control	–	Conventional therapy	37/16	–	53
Zeng	2015	Neostigmine	1 mg	Acupoint injection	45/30	53.5±6.3	75
		Control	–	Conventional therapy	–	–	75
Zhang	2012	Neostigmine	1 mg	Acupoint injection	24/22	63	46
		Control	–	Conventional therapy	22/23	61	45
Zhang	2021	Neostigmine	1 mg	Intramuscular injection	0/120	28.7±2.2	120
		Control	–	Conventional therapy	0/120	29.2±2.1	120
Zhu	2006	Neostigmine	1 mg	Analgesic pump	0/126	–	126
		Control	–	Analgesic pump	0/114	–	114

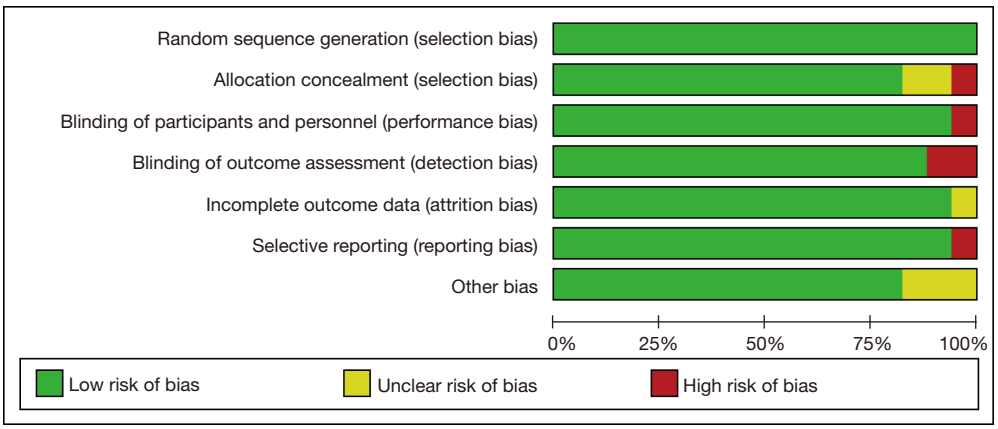

Figure 2 Quality assessment of the studies in this meta-analysis. High, low, and unclear risk of bias were marked in red, green, and yellow, respectively.

events rate than the neostigmine group.

In the subgroup analysis, there was no significant difference in the rates of nausea, vomiting, and respiratory complications between the neostigmine and control groups [nausea and vomiting: RR =0.50 with 95% CI: (0.21, 1.23), P=0.13 and I^2=82%; respiratory complications: RR =0.96 with 95% CI: (0.20, 4.53), P=0.96 and I^2=0%]. The abdominal distention rate of the neostigmine group was lower than that of the control group [RR =0.39; 95% CI: (0.18, 0.87); P=0.02; I^2=76%].

Results of sensitivity analysis and publication bias

The meta-analysis results showed that the heterogeneity of flatus passage was high (I^2=98%). As shown in *Figure 9*, the heterogeneity of the flatus passage might be attributed to the differences between different studies. When You's research in 2018 (21) was removed, the I^2 value changed from 98% to 96%. This showed that the results of this paper were stable.

Funnel plots of the first passage of flatus in the neostigmine and control groups were constructed. Thirteen studies were included in the plot. The results showed that the funnel plot had good symmetry and little publication bias (*Figure 10*). The result of Begg's test suggested that no significant evidence of potential publication bias existed (z=1.83; P=0.24). The result of Egger's test also suggested that no significant evidence of potential publication bias existed (t=2.54; P=0.35).

Discussion

Postoperative intestinal obstruction refers to the obstruction and intolerance of oral intake caused by factors that interfere with the normal coordination of the gastrointestinal tract to promote sporting activities. Neostigmine is often prescribed for patients with symptoms of POI to promote gastrointestinal function recovery after abdominal surgery. In this study, we reviewed the efficacy and safety outcomes of neostigmine in patients with POI.

Thirteen studies reported the time to first passage of flatus, and all 13 studies showed that patients prescribed with Neostigmine had a shorter time to first passage of flatus. Six studies reported the first defecation postoperatively, and the analysis of 10 involved studies showed that bowel sound recovery time in the neostigmine group was lower than that of the control group. In the enteric nervous system, AChE inhibitors can prevent the degradation of acetylcholine (ACh) and increase the utilization of ACh, thereby increasing gastrointestinal movement. It was reported that neostigmine has successfully treated POI, intestinal pseudo-obstruction, refractory constipation, spinal injury-induced constipation, and opioid-induced constipation in cancer patients (26-29). In a randomized trial, 21 patients with acute colonic pseudo-obstruction were assigned to treatment with either neostigmine or a placebo. Prompt decompression was observed in 11 patients who received neostigmine compared with none who received the placebo (30). Neostigmine has

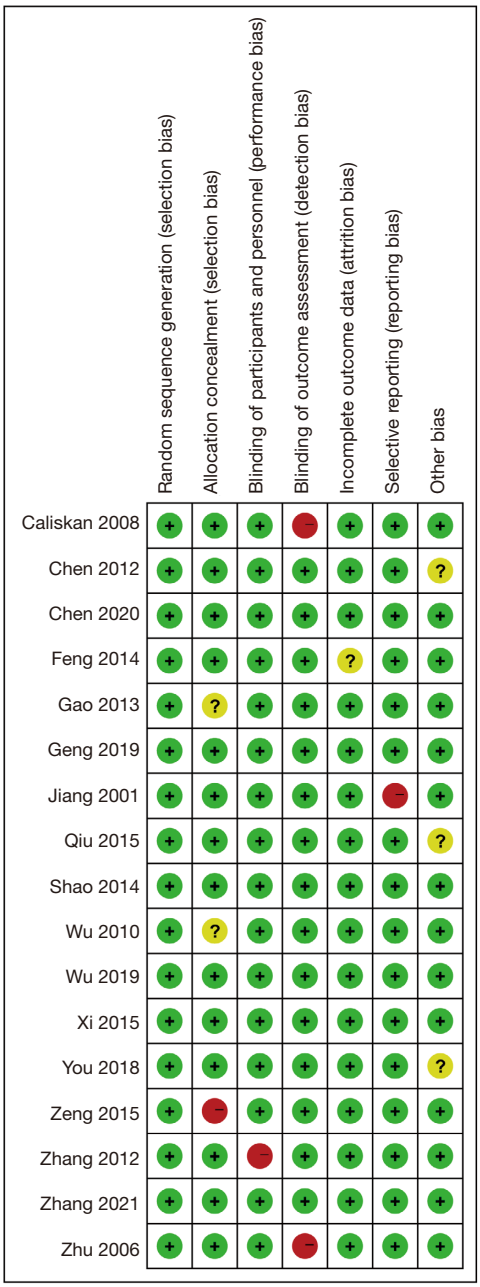

Figure 3 Risk of bias summary of the included studies.

a strong excitatory effect on gastrointestinal and bladder smooth muscle, and can promote the peristalsis of stomach, intestine and colon.

In the secondary outcomes, we analyzed the adverse events associated with neostigmine. The analysis of all 17 studies showed no difference in the occurrence of postoperative nausea and vomiting (PONV) and respiratory complications between the neostigmine and control groups, indicating that neostigmine can be well tolerated and safely prescribed. A previous meta-analysis on neostigmine as a neuromuscular blocking antagonist after anesthesia also found no significant increase in the risk of vomiting (31). Parthasarathy *et al.* (32) reported that neostigmine could also improve symptoms of irritable bowel syndrome, help

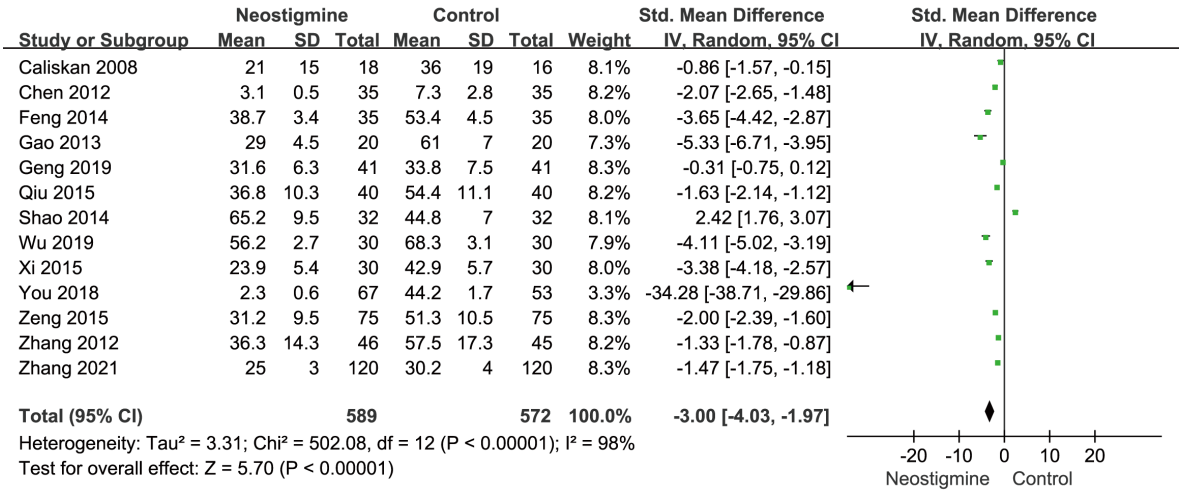

Figure 4 Forest plot: comparison of the first passage of flatus between the neostigmine and control groups.

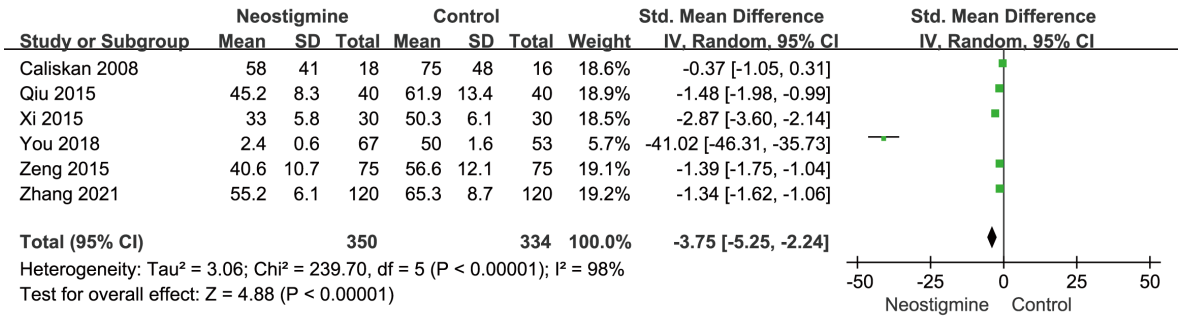

Figure 5 Forest plot: comparison of the first defecation between the neostigmine and control groups.

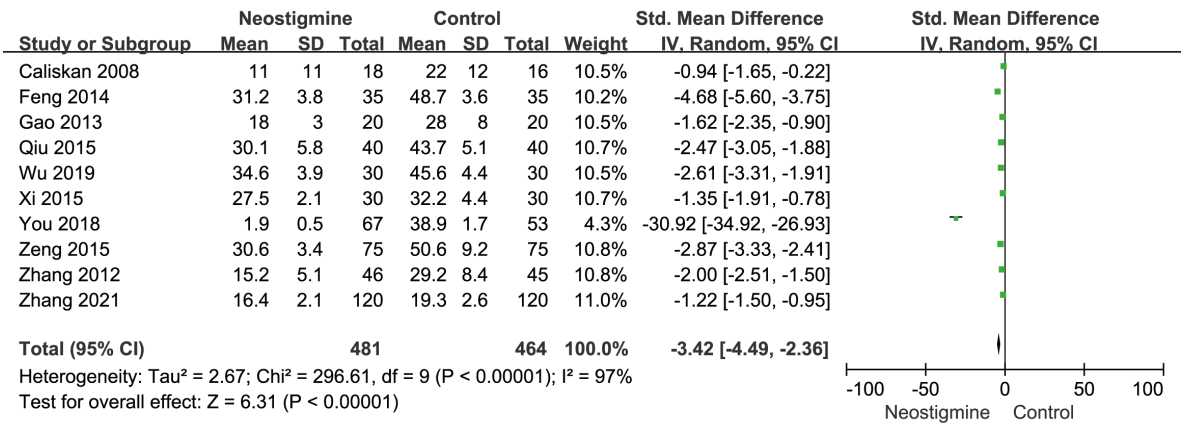

Figure 6 Forest plot: comparison of the time of bowel sound recovery between the neostigmine and control groups.

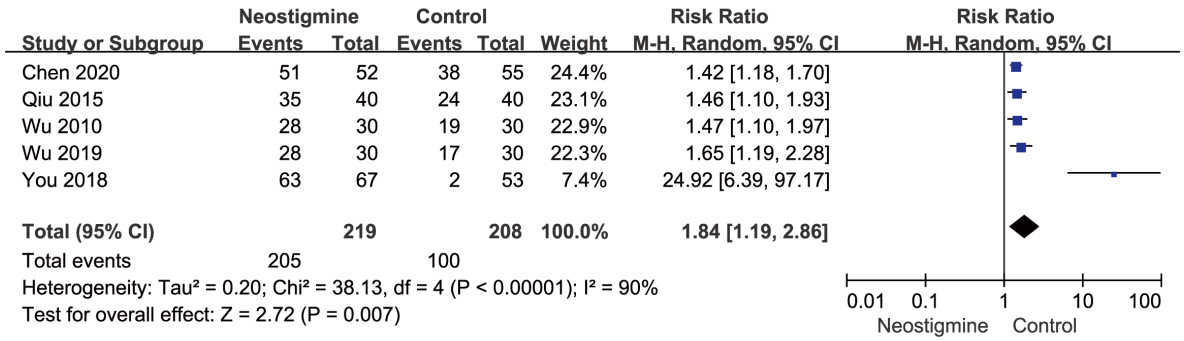

Figure 7 Forest plot: comparison of the first passage of gastrointestinal function recovery between the neostigmine and control groups.

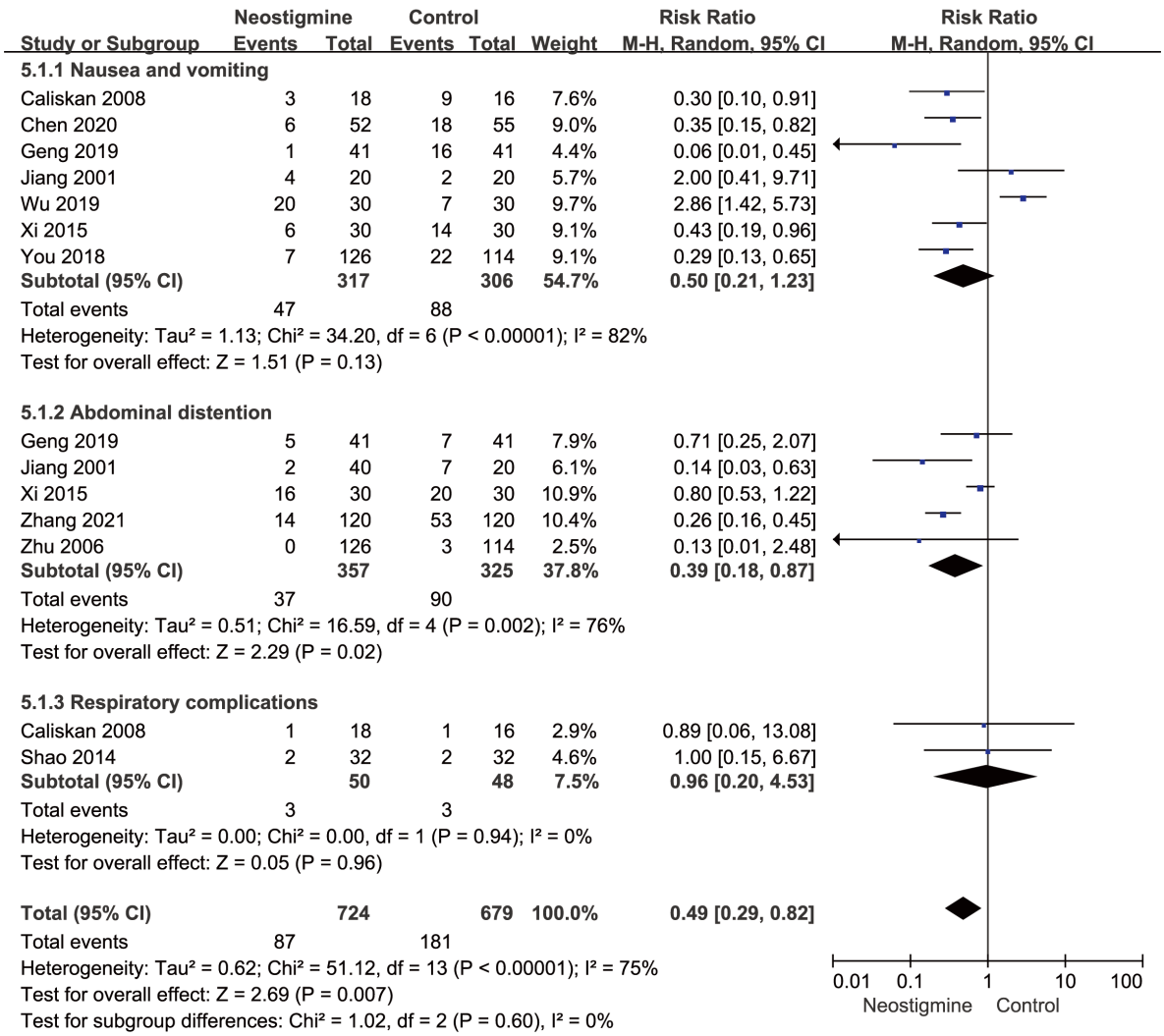

Figure 8 Forest plot: comparison of the adverse events between the neostigmine and control groups.

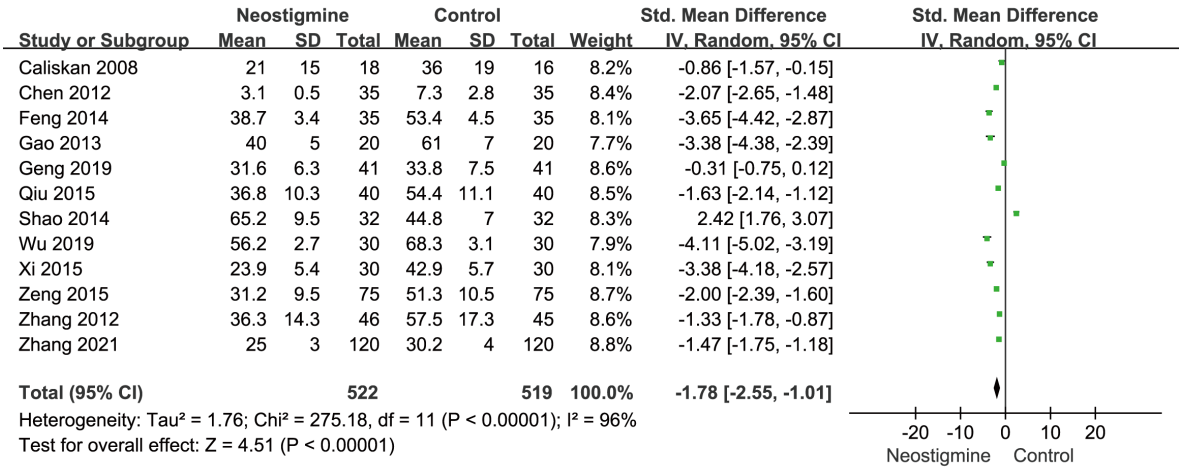

Figure 9 Sensitivity analysis forest plots of the first passage of flatus between the neostigmine and control groups.

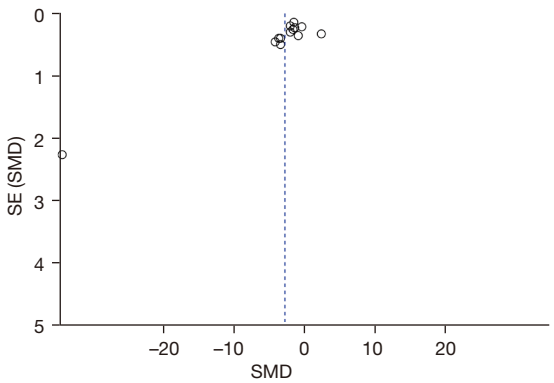

Figure 10 Funnel plot for publication bias in the first passage of flatus.

intestinal gas discharge, and reduce abdominal symptoms and abdominal distension, which is consistent with our results.

Although most included trials are of small, the funnel plot results showed good symmetry and little publication bias. Also, the Begg's test results also suggested that no significant evidence of potential publication bias existed.

In conclusion, prokinetic agents to decrease POI are commonly used in post-surgical management, and neostigmine is effective and safe for accelerating gastrointestinal function recovery after surgeries, acting to prevent and alleviate symptoms of POI without additional side effects. Our findings should be understood with caution due to the small sample sizes of the included studies. A large number of trials involving a large study population and high methodological quality are required to further confirm the beneficial effects of neostigmine.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-3291

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-3291). 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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