Neostigmine for the treatment of acute pancreatitis: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Acute pancreatitis (AP) is a common disease with substantial mortality. Gut dysfunction may result in abdominal compartment syndrome (ACS) and delay enteral nutrition, worsening AP condition. Neostigmine is used as a prokinetic drug for the treatment of AP. But there are no recommendations from guidelines due to the lack of evidence. Therefore, we plan to conduct a systematic review and meta-analysis to explore the efficacy and safety of neostigmine for AP, aiming to provide current evidence for clinical practice.

Methods and analysis We prepared this protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols. We will search the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, Wanfang, conference proceedings and ongoing trials registers for eligible studies comparing neostigmine plus conventional therapy with conventional therapy. Primary outcomes include new-onset ACS and serious adverse events caused by neostigmine. Evaluation of the risk of bias, heterogeneity and quality of evidence will follow recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. Trial sequential analysis will be used to control the risk of random errors and assess conclusions in the meta-analysis.

Ethics and dissemination Ethics approval is unnecessary as the systematic review is based on published studies. Study findings will be published in a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THE STUDY

⇒ To the best of our knowledge, this study will be the first systematic review and meta-analysis about efficacy and safety of neostigmine for the treatment of patients with acute pancreatitis.

⇒ Randomised controlled studies and observational studies will be included to obtain sufficient data and adequate statistical power for the meta-analysis.

⇒ This study has a clear objective with art methods for data collection, quality evaluation and quantitative synthesis.

⇒ The major limitations may be attributed to small sample size of included studies and unexpected heterogeneity from observational study designs.

INTRODUCTION

Acute pancreatitis (AP) is a sudden inflammatory process of the pancreas, often involving nearby tissues or other organs, causing local or systemic complications and even death. It is one of the most common causes of gastroenterology-related hospitalisation, and the annual incidence of AP has increased in past decades. AP can be classified as mild AP (MAP), moderately severe AP (MSAP) and severe AP (SAP) according to the Revised Atlanta Classification. Gut dysfunction, mostly presented as bowel obstruction, is common in AP especially SAP. It often aggravates intra-abdominal hypertension (IAH) and may develop into abdominal compartment syndrome (ACS). In addition, gut dysfunction also limits the use of enteral nutrition which has been demonstrated to lower the rate of mortality, infection, multiple organ failure and surgical intervention. Therefore, the concept as ‘gut rousing’ has been proposed to maintain gut function. However, there are currently no effective evidence-based strategies except supportive treatment in clinical practice.

Neostigmine is a reversible acetylcholinesterase inhibitor. Its distribution and elimination half-lives are 3.4 and 77 min, respectively. After neostigmine administration, increased acetylcholine stimulates both nicotinic and muscarinic receptors. Therefore, neostigmine is usually used to reverse the effects of non-depolarising muscle relaxants at the end of an operation with a dose-dependent effect and ceiling effect. Adverse effects of neostigmine include bradycardia, salivation, nausea and vomiting due to overstimulation of cholinergic nerves. Arrhythmia and bronchospasm can also occur in severe cases.

In addition, based on its pharmacology, neostigmine can act as an enhancer of intestinal peristalsis, contributing to the passage...
of flatus and defecation. Neostigmine has been proven to induce colonic decompression in pseudo-obstruction effectively, and is recommended for colonic obstruction and IAH with poor response to other measures.\(^8\)\(^\rightarrow\)\(^20\) Currently, international clinical guidelines have not attached importance to this drug, and no systemic review has addressed this topic.\(^21\)\(^\rightarrow\)\(^24\) Therefore, this systemic review and meta-analysis aim to assess the efficacy and safety of neostigmine for the treatment of AP.

Neostigmine, as a prokinetic drug, seems to play an essential role in the treatment of AP, especially when gut dysfunction occurs. However, its clinical effect remains unclear according to previous studies, including the latest one published in March 2022.\(^18\)\(^\rightarrow\)\(^20\) Currently, international clinical guidelines have not attached importance to this drug, and no systemic review has addressed this topic.\(^21\)\(^\rightarrow\)\(^24\) Therefore, this systemic review and meta-analysis aim to assess the efficacy and safety of neostigmine for the treatment of AP.

**METHODS**

This protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (online supplemental table 1) (PRISMA-P Checklist). This systematic review has been registered on the PROSPERO database (CRD42022369536).\(^25\) We will timely update any revision of this protocol and the review process on the PROSPERO registration. We will conduct this systemic review based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.\(^26\) The planned start and end date of the study are 1 March 2023 and 1 May 2023, respectively.

**Criteria for considering studies for this review**

**Types of studies**

Our review will include randomised controlled trials (RCTs), quasi-RCTs and observational studies (cohort and case–control). A quasi-RCT is a trial in which allocation methods of included participants are not truly random. Other types of studies, such as case series, case reports, reviews and abstract conferences will be excluded. Studies without sufficient data, primary data or full text were also excluded, neither were duplicate publications.

**Types of participants**

Our review will include adults (aged over 18 years) with AP irrespective of the severity (MAP, MSAP and SAP). Participants with contraindications to neostigmine, pregnancy or lactation will be excluded. The diagnosis of AP is established when two of the three features are presented: (a) typical abdominal pain as acute onset of a persistent, severe, epigastric pain, often radiating to the back; (b) serum amylase or lipase activity with at least three times greater than the upper limit of normal and (c) radiological findings of AP on transabdominal ultrasonography, contrast-enhanced CT or MRI.\(^3\)

**Types of interventions**

Studies comparing neostigmine plus conventional therapy versus conventional therapy are eligible. Conventional therapy includes fluid management (early fluid resuscitation and volume control) for IAH, analgesics, nutrition support, symptomatic treatment, gastrointestinal decompression, if necessary, and Chinese medicine components such as rhubarb and Glauber’s salt.\(^1\)\(^\rightarrow\)\(^27\)

**Types of outcomes measures**

Studies reporting at least one of the following outcomes will be included.

**Primary outcomes**

1. Efficacy outcome: new-onset ACS, defined as a sustained IAP >20 mm Hg with organ failure after treatment, assessed for 4 weeks.\(^8\)
2. Safety outcome: serious adverse events occurred during the use of neostigmine (nervous system dysfunction such as ataxia, convulsions, coma, slurred speech, anxiety or fear, malignant arrhythmia, bronchospasm or other abnormality not characteristic of AP).\(^28\)

**Secondary outcomes**

1. Deterioration of IAH: IAP rebounds ≥5 mm Hg or increases to ≥20 mm Hg after treatment within 7 days after treatment.\(^20\)
2. Intestinal function recovery time: time interval from treatment onset to the tolerance of enteral nutrition.
3. In-hospital mortality.
4. Multiple organ failure within 7 days after treatment.
5. Radiological or endoscopic interventions after treatment during hospitalisation.
6. Operative intervention after treatment during hospitalisation.
7. Length of hospital stay.
8. Length of intensive care unit.

**Search methods for identification of studies**

We will conduct the literature search in the following databases up to the formal search date: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, China National Knowledge Infrastructure, Chinese Biomedical Literature Database and WanFang Database. Designed search strategies are shown in online supplemental table 2. In addition, we will also search other databases such as conference proceedings for relevant abstracts, WHO International Clinical Trials Registry Platform (https://www.who.int/ictrp/en/) and US National Institutes of Health Ongoing Trials Register (https://clinicaltrials.gov/). There will be no restrictions on study type, language or publication type. The reference lists of all included primary studies and reviews will be checked for additional studies.

**Data collection and analysis**

**Selection of studies**

Two reviewers will independently screen titles and abstracts of all potential studies from the literature search and retrieve the qualified articles. Then, they will screen the full text and identify eligible studies. Reasons for exclusion will be recorded. Discussions will resolve
disagreements, and a third author will be consulted if necessary. If information is insufficient to include or exclude a study, we will attempt to contact study authors. We will identify and exclude duplicates and multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review.

Data extraction and management
Two reviewers will independently extract data and record details from included studies using a standardised data extraction form. Disagreements were resolved through consensus. The following study characteristics will be extracted:
1. Methods: for example, study design, number of study centres and location, study setting, withdrawals and study date.
2. Participants: for example, numbers, mean age, age range, sex, severity and type of AP, inclusion criteria and exclusion criteria.
3. Interventions: for example, intervention, comparison, co-interventions and number of participants of each group.
4. Outcomes: primary and secondary outcomes, time points reported.
5. Notes: additional information (funding, conflicts of interest and trial registration).

Assessment of risk of bias in included studies and certainty of the evidence
Two reviewers will independently assess the risk of bias for each study and record it in a table. Conflicts were resolved through consensus or by involving a third author if necessary. RCTs and quasi-RCTs will be assessed using items in the Cochrane Collaboration’s tool, while non-RCTs (observational cohort and case-control studies) will be assessed using the Newcastle-Ottawa Scale.

We applied the grading of recommendations assessment, development and evaluation framework to assess the certainty of evidence on main outcomes, including primary outcomes and several important secondary outcomes such as deterioration of IAH, intestinal function recovery time, in-hospital mortality and multiple organ failure.

Trial sequential analysis
Trial sequential analysis will be used to control the risk of random errors and assess the conclusions in the meta-analysis. Based on previous clinical experience and RCTs in this field, we will use an anticipated relative risk reduction (RRR) of 20.0% with a power of 80% to calculate the required sample size and assess the clinical significance of primary outcomes in our meta-analysis according to the position of cumulative Z curve with conventional boundary, trial sequential monitoring boundary and futility boundary.

Measures of treatment effect
We will perform the meta-analysis using RevMan (V.5.4.1) for the statistical analysis. We will use mean differences with 95% CIs to calculate effect sizes for continuous data. To pool results in a consistent format, we will transform the median, the minimum and maximum values, and the first and third quartiles to mean value and SD. For dichotomous data, we will calculate risk ratios (RRs) with 95% CIs. As for observational studies, we will use adjusted effect estimates rather than unadjusted estimates if available.

Dealing with missing data
We will contact investigators or study sponsors for missing data if possible. Otherwise, we will impute missing data using established methods, including informative missing RRs for dichotomous outcomes and difference of means for continuous outcomes. Furthermore, we plan to assess our imputations by sensitivity analysis.

Assessment of heterogeneity
We will use the I² statistic to measure heterogeneity among trials in each analysis. I² ≥60% is considered evidence of moderate to substantial levels of heterogeneity. If I² >80% (substantial heterogeneity), we will not perform the meta-analysis but present results using forest plots without pooled estimates.

Assessment of reporting bias
We will use funnel plots to measure reporting bias if there are more than 10 included studies. Egger’s test will determine the statistical significance of the reporting bias, and p <0.05 is considered statistically significant. If the number of included studies is less than 10, we will assess reporting bias qualitatively based on research characteristics.

Data synthesis
If there are not sufficient included studies, we will provide a narrative description of the study results rather than a meta-analysis. If at least two studies are identified for inclusion, we will perform a meta-analysis using RevMan (V.5.4.1) for statistical analysis as described above.

Subgroup analysis and investigation of heterogeneity
If sufficient data are available, a subgroup analysis will be conducted to explore potential reasons for heterogeneity. If possible, the following effect modifiers will be included: age, sex, dosage or duration of neostigmine, timing from qualifying event treatment, rate of fluid resuscitation and the severity of AP.

Sensitive analysis
When heterogeneity of results is substantial, we will perform sensitivity analyses based on primary outcomes by excluding studies at high risk of bias or with imputed outcomes.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.
DISCUSSION

Considering that only a small group of RCTs were identified through an experimental search, we will also include non-randomised studies to obtain adequate statistical power to evaluate the outcomes, especially for rare complications. Moreover, data from observational studies are more approximate to real-world practice. We will draw conclusions based on findings from the quantitative and narrative synthesis of studies included in this review. The findings are expected to address important questions about the efficacy and safety of neostigmine for patients with AP, providing a reference for clinical practice and future studies.

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Contributors
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Supplemental material
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REFERENCES


