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The efficacy and safety of acupuncture as an adjuvant treatment for acute pancreatitis: a protocol of systematic review and meta-analysis

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The efficacy and safety of acupuncture as an adjuvant treatment for acute pancreatitis: a protocol of systematic review and meta-analysis

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ABSTRACT

Introduction:

Acupuncture may be effective for acute pancreatitis. This systematic review aims to assess the efficacy and safety of acupuncture as an adjuvant treatment for acute pancreatitis.

Methods and analysis:

We will search PubMed, the Cochrane Central Register of Controlled Trials,

EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), Wan Fang Data and Chinese Science Journal Database (VIP) from inception to the present, to identify any eligible study. Only randomised controlled trials will be included. The selection of studies, data extraction and management will be completed by two reviewers, independently. The primary outcomes include the overall response rate, mortality during the treatment, transfer to the surgery or Intensive Care Unit (ICU) rate, gastrointestinal function and the Acute Physiology and Chronic Health Evaluation (APACHE) II scores. The secondary outcomes include the recovery time of blood amylase becoming normal, tumor necrosis factor α (TNF-α) counts, interleukin 6 (IL-6) counts, interleukin 10 (IL-10) counts, length of hospital stay and adverse events or reactions. RevMan 5.3 software will be used for statistical analyses. The risk of bias of included studies will be assessed by the Cochrane "risk of bias" tool.

Ethics and dissemination:

This study will not involve personal information. The ethical approval will not be required. The results will be published in a peer-reviewed journal. This protocol has been registered on PROSPERO (CRD42018115099).

Strengths and limitations of this study

- We will only include randomised controlled trials.
- Language and publication dates will not be restricted.
- We will attempt to contact the original researchers by e-mail to obtain any missing or inadequate data.
- We will conduct the sensitivity analysis to test whether the conclusions are robust.
- Different types of acupuncture therapy may lead to a large degree of heterogeneity.

Introduction

Acute pancreatitis (AP) is an inflammatory injury of the pancreas caused by edema, hemorrhage and necrosis associated with the digestion of pancreatic tissue [1]. AP is one of the most common acute abdominal diseases in clinical practice [1,2]. The mortality of AP is 2.1-7.8%, which takes up quite a lot of healthcare resources [3]. Despite the significant medical advancement in the last decade, the overall mortality of AP and SAP remains high [4-6]. The gastrointestinal disorder is a common clinical phenomenon in AP. Even in severe AP, bowel dysfunction, or failure, in the early stage of disease is quite common, which may lead to the translocation of inflammatory mediators and toxic products. This eventually causes systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) [7-9]. Therefore, improving the recovery of gastrointestinal function is of great significance for patients with AP [8,9]. A large amount of data supports the efficacy of acupuncture on gastrointestinal physiology, including: gastric acid secretion exercise, neurohormonal changes feelings and improving gastrointestinal function in patients with AP [10,11].

AP can cause severe abdominal pain, which makes it difficult for patients to recover. In severe cases, it affects heart function [12]. Effective pain relief can help patients recover and have shorter hospital stays. Opioids are safe and effective in treating AP patients. Compared with other analgesic drugs, opioids can reduce the need for supplemental analgesia [12]. However, frequent use of opioid analgesics may lead to opioid dependence [13,14]. One of the most important applications of acupuncture is for pain relief [15]. The analgesic effect of acupuncture is mainly achieved through the regulation of the central nervous system. Substances such as enkephalin, dynorphin, 5-hydroxytryptophan (5-HT), epinephrine, substance P and somatostatin produced in the spinal cord may contribute to acupuncture analgesic effects [16,17]. In this sense, acupuncture may be a suitable alternative to opioid analgesics in Oriental medicine because it is considered an effective analgesic therapy without dependence.

The morbidity and mortality of AP depend on the severity and balance of the

inflammatory response[18]. In the early stage of SAP, pancreatic enzymes are activated and released into the blood, which activate monocytes/macrophages and release a large number of pro-inflammatory cytokines, such as tumour necrosis factor (TNF-α), interleukin 6 (IL-6), etc. They can stimulate various inflammatory cells and an overactive pro-inflammatory response. This leads to an uncontrolled systemic response that ultimately results in SIRS and MODS [18,19]. IL-6 can not only directly damage vascular endothelial cells and activate inflammatory cells, but also worsen inflammatory reactions. However, the body's self-protection mechanism increases the anti-inflammatory factor interleukin 10 (IL-10) to inhibit the synthesis of the pro-inflammatory factors mentioned above, finally blocking or delaying the systemic inflammatory response. In addition, nuclear factor kB (NF-kB), a transcription factor, is known to be highly expressed in AP [20]. Studies have shown that inhibiting excessive inflammatory responses is the key to the treatment of AP. Changes in serum IL-6, IL-10 and concentrations can be used as indicators to judge the severity of AP and evaluate the prognosis [21]. The laboratory tests that have been proposed for the assessment of AP severity also include soluble intercellular adhesion molecule-1, acute phase proteins [C-reactive protein (CRP)] and so on [22,23].

Acupuncture can reduce elevated pro-inflammatory mediators in the process of inflammatory response, thus playing an anti-inflammatory role[24]. Animal experiments found that electroacupuncture could reduce TNF-α and IL-6 in rats. As a result, serum can alleviate local pancreatic injury and systemic inflammation [25-27]. It also increased serum IL-10 levels, and restored the balance between proinflammatory and anti-inflammatory cytokines. Another study showed that acupuncture might have therapeutic effect on AP through inhibition of NF-kB expression and a reduction in the release of pro-inflammatory cytokines [28-29]. Clinical evidence also supported the clinical effects of acupuncture on inflammatory responses. The study found that electroacupuncture could decrease TNF-α , IL-6, CRP and increase IL-10 values to reestablish the balance between proinflammatory and anti-inflammatory cytokines, and improve the inflammatory response of AP [30-32].

However, there is a lack of high quality evidence for acupuncture in the treatment of AP. Thus, this systematic review is conducted to assess the efficacy and safety of acupuncture as an adjuvant treatment for acute pancreatitis.

Methods

Criteria for including studies in the review

Types of studies

We will only include randomised controlled trials (RCTs) of acupuncture therapy for AP in any language or any publication. We will also remove low-quality studies without comparable baselines and re-used publications.

Types of participants

Participants diagnosed with AP according to the internationally acknowledged diagnostic criteria for AP were included. These criteria included: the revised Atlanta classification of AP; American clinical guide to AP; the clinical diagnostic criteria for acute pancreatitis developed by the pancreatic division of the surgery division of the Chinese medical association in 1996 or 2014; the diagnostic and therapeutic guidelines for severe acute pancreatitis in 2001; and the diagnostic and therapeutic guidelines for acute pancreatitis in China in 2004 [33-36]. All of the participants should accept acupuncture treatment and hospitalized within 48 hours of symptom onset. There is no restriction on age, gender or ethnicity of the enrolled subjects.

Types of outcome

The primary outcome

The primary outcomes include the overall response rate, mortality during treatment, transfer to the surgery or ICU rate, gastrointestinal function and the Acute Physiology and Chronic Health Evaluation (APACHE) II scores.

The total efficiency standard is based on the diagnostic standard which was included in the draft of diagnosis and treatment of acute pancreatitis [37], set by the pancreas group of the surgical society of China medical association in 2000. It is divided into four grades: cure, obvious effect, effective and ineffective. It can be also based on the 2002 edition of the guidelines for clinical research of traditional Chinese

medicine new drugs [32]. It is divided into three levels: obvious efficacy, effective efficacy and ineffective efficacy.

Mortality during treatment: SAP can often cause SIRS and the associated mortality rate ranges from 25 to 30% [34,35]. The mortality of acute pancreatitis is an important indicator of prognosis.

Transfer to the surgery or ICU rate: SAP is difficult to treat with conservative therapy in the general ward and therefore, requires transfer to ICU surgery. It can often cause SIRS and MODS.

Gastrointestinal function includes the effect on abdominal pain and distension, recovery time of bowel sound, recovery time of defecation and the time for resuming to diets (days).

APACHE II is a useful prognostic scoring system for predicting the severity of acute pancreatitis and can be of vital importance in determining the group of patients who have more chance of requiring tertiary care in the course of treatment. The disease requires early resuscitation and timely referrals, especially in developing countries with limited resources [38,39].

The secondary outcome

The secondary outcomes include: the recovery time of blood amylase becoming normal, TNF-α counts, IL-6 counts, IL-10 counts, length of hospital stay and adverse events or reactions.

Types of interventions

We will perform a systematic review and meta-analysis that includes all RCTs using acupuncture plus routine treatment (RT) in the treatment group and RT alone in the control group. RT comprises fluid resuscitation, use of antibiotics, nutritional support and mechanical ventilation when necessary.

Search strategy

Electronic searches

We will search the following electronic databases from their inception to the present: PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, Web

of Science, China National Knowledge Infrastructure (CNKI), Wan Fang Data and Chinese Science Journal Database (VIP).

The searching strategy for PubMed is listed in Table 1. Our study will not apply any language restrictions.

Searching other resources

Before searching additional resources, we will check the reference lists of identified relevant AP and reviews for other studies. Then we will contact experts in the field of pancreatitis to determine any additional study. The WHO International Clinical Trials Registry Platform (ICTRP), Chinese Clinical Trial Registry, Clinical Trials.gov will also be reviewed to determine planned, ongoing or unpublished researches. The Google Scholar website will be searched to identify any grey literature.

Table.1 PubMed search strategy

#1	pancreatitis [MeSH]
#2	acute pancreatitis [MeSH]
#3	pancreatitis, acute necrotizing [Abstract/Title]
#4	pancreatitis, alcoholic, cholelithic or familial hyperlipidemia [Abstract/Title]
#5	OR/1-4
#6	acupuncture [MeSH]
#7	acupuncture therapy [Abstract/Title]
#8	electroacupuncture [Abstract/Title]
#9	acupressure [Abstract/Title]
#10	elongated needle [Abstract/Title]
#11	fire needle[Abstract/Title]
#12	acupoint [Abstract/Title]
#13	warming needle [Abstract/Title]
#14	OR/6-13
#15	randomized controlled trial [pt]

#16	controlled clinical trial [pt]
#17	randomized [Abstract/Title]
#18	placebo [Abstract/Title]
#19	clinical trials as topic [Abstract/Title]
#20	randomly [Abstract/Title]
#21	trial [Abstract/Title]
#22	OR/15-21
#23	animals [MeSH] NOT humans [MeSH]
#24	#22 NOT #23
#25	#5 AND #14 AND #24

Data extraction and management

Selection of studies

Data screening and the selection process will be completed independently by two reviewers (CG and KZ). They will cross check their results with each other. When disagreements occur between them, a third reviewer (QLT) will make the final decision. Hard copies of all included studies will be obtained and read in full-text version. Details of the selection process will be shown in the PRISMA flow chart (Figure 1).

Data extraction and management

A piloted data extraction form that has been discussed and developed by all the reviewers will be assessed and extracted independently by two authors (QLT and KZ). The following information will be extracted from each included study: general information, details of study, study population, intervention characteristics and outcomes. Any disagreement in data extraction will be resolved by discussion or negotiation with a third arbitrator (CYL). If data presented in studies is unclear, missing or presented in a form that cannot be extracted, the authors of the study will retrieve the missing information from the corresponding authors.

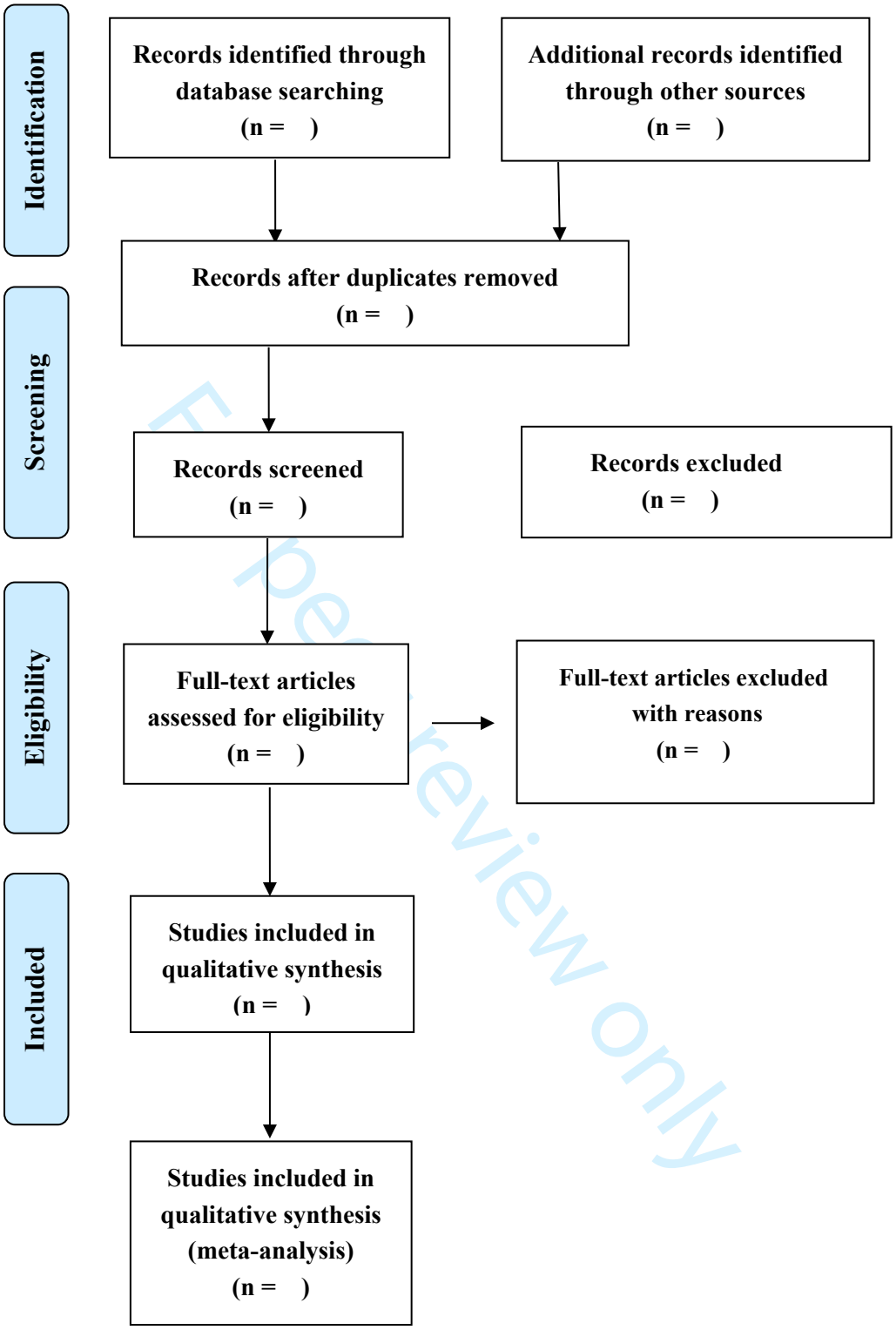

Figure 1 Study selection flow diagram.

Risk of bias assessment

Two reviewers (KZ and CYL) will individually assess the risk of bias using the Cochrane Collaboration's tool [40]. The following seven domains will be evaluated: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective outcome reporting; (7) other sources of bias. The studies will then be classified into three levels of bias as high, low and unclear. Any difference will be resolved by discussion.

Measurement of treatment effect

For continuous data, Mean Difference (MD) or Standard MD (SMD) will be used to measure the therapeutic effect with 95% confidence intervals (CIs). Risk ratios (RR) with 95% CIs will be calculated for dichotomous data.

Dealing with missing data

We will attempt to contact the original researchers by e-mail to obtain any missing or inadequate data if there is a lack of results in the included studies. We will also obtain data by phone. If we cannot obtain accurate data through the above methods, then we will exclude this study.

Assessment of heterogeneity

Heterogeneity will be analyzed through q-tests. When the P-value was below 0.1 or I^2 is greater than 50%, the studies will be considered to have the heterogeneity. In this condition, a subgroup analysis will be used to find the source of heterogeneity.

Assessment of reporting biases

We will assess publication bias using the funnel plot and Egger's test if more than 10 trials are included.

Data synthesis

The meta-analysis will be conducted using the Review Manager (RevMan) V.5.3 software. We will describe the effect size with RR for dichotomous data, and MD or SMD for continuous data. If I^2 is less than 50%, the fixed-effects model will be used for data synthesis. If I^2 is greater than 50%, we will combine the data using random-effect model. A narrative description of the results will be conducted when

the meta-analysis is not feasible.

Subgroup analysis

We will perform subgroup analysis to explore possible causes of heterogeneity if there are an adequate number of studies. Subgroup analysis will be conducted based on the type of acupuncture intervention (body acupuncture, electroacupuncture, fire needling, elongated needle, warming needling), acupuncture point (single or multiple points), the duration of treatment, age and gender if possible.

Sensitivity analysis

We will conduct sensitivity analysis to test whether the conclusions are robust compared to the decisions made during the review process. The main methods of sensitivity analysis include: changing the inclusion criteria, excluding low-quality studies, and using different statistical methods to analyze the same data. If the diametrically opposite conclusions are obtained even after the exclusion of significant differences, then it indicates high sensitivity and low reliability of the results. Care should be taken in interpreting the results and conclusions. It also suggests that there are important and potential bias factors related to the impact of interventions, and the source of controversy should be further clarified.

Assessment method of evidence quality

The quality of the evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE.) [41]. The evaluation items include risk of bias, inconsistency, indirectness, imprecision, publication bias. Two review authors (KZ and CG) will independently assess the quality of the evidence based on five levels of criteria. It will fall into one of four possible ratings: high, moderate, low and very low.

Ethics and dissemination

This study will not involve personal information from individuals or violate their personal rights. Therefore, ethical approval will not be required. The results will be published in a peer-reviewed journal. Due to the lack of relevant literature in this field, this paper will add more recent studies into the analysis to provide stronger evidence for acupuncture treatment of AP and guide clinical practice and acupuncture research.

Patient and Public Involvement

Patients' priorities, experience, and preferences were not involved in development of the research question, and outcome measures, the design of this study, or the recruitment to and conduct of the study. The results will be not disseminated to study participants.

Amendments

If the protocol is modified, then the information will be described in the final report.

Discussion

Acupuncture may be effective for AP. However, no systematic reviews on this topic have been published. This review will provide more convincing evidence on acupuncture for AP. This study has some potential limitations. Different types of acupuncture therapy may lead to a large degree of heterogeneity.

Protocol registration:

This protocol has been registered on PROSPERO (CRD42018115099).

Contributors

YL, JBZ and CZ conceived the study; these three authors provided general guidance to the drafting of the protocol. CG and KZ drafted the protocol. CYL designed the search strategy. CG, KZ, CYL and CZ drafted the manuscript. CG, KZ, CYL, CZ and QLT reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript.

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Competing interests: None declared.

Ethics approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: The final report of this systematic review will be published in a peer-reviewed scientific journal, and the data set will be made freely available.

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PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Page
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	12
Support:			
Sources	5a	Indicate sources of financial or other support for the revi	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report	5-6

		characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-8
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10

	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

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The efficacy and safety of acupuncture as an adjuvant treatment for acute pancreatitis: a protocol of systematic review and meta-analysis

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ABSTRACT

Introduction:

Acupuncture may be effective for acute pancreatitis. This systematic review aims to assess the efficacy and safety of acupuncture as an adjuvant treatment for acute pancreatitis.

Methods and analysis:

We will search PubMed, the Cochrane Central Register of Controlled Trials,

EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), Wan Fang Data and Chinese Science Journal Database from inception to June 30, 2019 to identify any eligible study. Only randomised controlled trials will be included. The selection of studies, data extraction and management will be completed by two reviewers independently. The primary outcomes include the overall response rate, mortality during the treatment, the proportion of patients with severe acute pancreatitis transferred to the Intensive Care Unit (ICU) or scheduled for surgery, gastrointestinal function and the Acute Physiology And Chronic Health Evaluation (APACHE) II scores. The secondary outcomes include visual analogue scale (VAS), the use of analgesics, the recovery time of blood amylase becoming normal, tumor necrosis factor α (TNF-α) counts, interleukin 6 (IL-6) counts, interleukin 10 (IL-10) counts, length of hospital stay and adverse events related to acupuncture (such as fainting, nausea, haematoma and local infection). RevMan 5.3 software will be used for statistical analyses. The risk of bias of included studies will be assessed by the Cochrane "risk of bias" tool.

Ethics and dissemination:

This study will not involve personal information. The ethical approval will not be required. The results will be published in a peer-reviewed journal. This protocol has been registered on PROSPERO (CRD42018115099).

Strengths and limitations of this study

- We will only include randomised controlled trials.
- Language and publication date will not be restricted.
- We will attempt to contact the original researchers by e-mail to obtain any missing or inadequate data.
- We will conduct the sensitivity analysis to test whether the conclusions are robust.
- Different types of acupuncture therapy may lead to a large degree of heterogeneity.

Introduction

Acute pancreatitis (AP) is an inflammatory injury of the pancreas caused by edema, hemorrhage and necrosis associated with the digestion of pancreatic tissue[1,2]. AP is one of the most common acute abdominal diseases in clinical practice[3,4]. Despite the rapid medical advancement in the last decade, the overall mortality of AP and severe acute pancreatitis (SAP) remains high[5-7]. The gastrointestinal disorder is a common clinical phenomenon in AP[8]. In the early stage of SAP, the bowel dysfunction is one of common symptoms, which may lead to the translocation of inflammatory mediators and toxic products. This eventually causes systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS)[9-11]. Therefore, improving the recovery of gastrointestinal function is very important for patients with AP. Some studies showed the efficacy of acupuncture for gastrointestinal disorders[12,13].

Opioids are safe and effective in treating AP patients. Compared with other analgesic drugs, opioids can reduce the need for supplemental analgesia[14]. However, frequent use of opioid analgesics may lead to opioid dependence[15]. One of the most important applications of acupuncture is for pain relief[16]. The analgesic effect of acupuncture is mainly achieved by the regulation of the central nervous system. Substances such as enkephalin, dynorphin, 5-hydroxytryptophan, epinephrine and somatostatin produced in the spinal cord may contribute to analgesic effects of acupuncture[17,18]. Acupuncture may be a suitable alternative to opioid analgesics because it is considered an effective analgesic therapy without dependence.

The morbidity and mortality of AP depend on the severity and balance of the inflammatory response[19]. In the early stage of SAP, pancreatic enzymes are activated and released into the blood, which activate monocytes/macrophages and release a large number of pro-inflammatory cytokines, such as tumour necrosis factor α (TNF-α), interleukin 6 (IL-6), etc. They can stimulate various inflammatory cells and cause an overactive pro-inflammatory response. This leads to an uncontrolled systemic response that ultimately results in SIRS and MODS[19,20]. IL-6 can not only directly damage vascular endothelial cells and activate inflammatory cells, but also

aggravate inflammatory reactions. However, the self-protection mechanism increases the anti-inflammatory factor interleukin 10 (IL-10) to inhibit the synthesis of the pro-inflammatory factors mentioned above, and finally reduces the systemic inflammatory response. Studies have shown that inhibiting excessive inflammatory responses is the key to the treatment of AP. Changes in serum IL-6 and IL-10 can be used as indicators to judge the severity of AP and evaluate the prognosis[21].

Acupuncture can reduce pro-inflammatory mediators in the process of inflammatory response[22]. An experiment found that electroacupuncture could reduce TNF-α and IL-6 in rats[23]. Another study showed that acupuncture might have therapeutic effects on AP by inhibiting nuclear factor κB expression and reducting the release of pro-inflammatory cytokines[24]. Some studies found that electroacupuncture could decrease TNF-α, IL-6, and increase IL-10 to reestablish the balance between pro-inflammatory and anti-inflammatory cytokines, and reduce the inflammatory response in AP[25-27].

To our knowledge, there is a lack of high-quality evidence on acupuncture in the treatment of AP. Thus, this systematic review aims to assess the efficacy and safety of acupuncture as an adjuvant treatment for acute pancreatitis.

Methods

Criteria for including studies in the review

Types of studies

We will only include randomised controlled trials (RCTs) of acupuncture therapy for AP regardless of any language or publication status. We will also remove studies without comparable baselines and duplicate publications.

Types of participants

Participants diagnosed with AP according to the internationally acknowledged diagnostic criteria for AP will be included. These criteria include: the revised Atlanta classification of AP, American clinical guideline for AP, the clinical diagnostic criteria for AP developed by the pancreatic division of the surgery division of the

Chinese medical association in 1996 or 2014, the diagnostic and therapeutic guideline for SAP in 2001, and the diagnostic and therapeutic guideline for AP in China in 2004[28-31]. All of the participants should receive acupuncture treatment and be hospitalised within 48 hours of symptom onset. There is no restriction on age, gender or ethnicity of the enrolled subjects.

Types of outcomes

The primary outcomes

The primary outcomes include the overall response rate, mortality during treatment, the proportion of SAP patients transferred to the Intensive Care Unit (ICU) or scheduled for surgery, gastrointestinal function and the Acute Physiology And Chronic Health Evaluation (APACHE) II scores.

The overall response rate is computed based on the diagnostic standard in the draft of diagnosis and treatment of acute pancreatitis proposed by the pancreas group of the surgical society of China medical association in 2000[32]. It is divided into four grades: cure, obvious effect, effective and ineffective. It can also be computed based on the 2002 edition of the guideline for clinical researches of traditional Chinese medicine new drugs[27]. It is divided into three levels: obvious effect, effective and ineffective.

The proportion of SAP patients transferred to the ICU or scheduled for surgery: It is difficult to treat SAP patients with conservative therapies in the general ward. SIRS and MODS could exacerbate SAP symptoms. Therefore, some SAP patients could be transferred to ICU or scheduled for surgery.

Gastrointestinal function includes abdominal pain and distension relief, recovery time of bowel sound, recovery time of defecation and time of resuming to diets (days).

APACHE II is a useful prognostic scoring system for predicting the severity of acute pancreatitis and can be of vital importance in determining the group of patients who have more chance of requiring tertiary care in the course of treatment[33,34].

The secondary outcomes

The secondary outcomes include visual analogue scale (VAS), the use of

analgesics, the recovery time of blood amylase becoming normal, TNF-α counts, IL-6 counts, IL-10 counts, length of hospital stay and adverse events related to acupuncture (such as fainting, nausea, haematoma and local infection).

Types of interventions

We will perform a systematic review and meta-analysis that includes all RCTs using acupuncture plus routine treatment (RT) in the treatment group and RT alone in the control group. RT includes fluid resuscitation, use of antibiotics, nutritional support and mechanical ventilation, etc.

Search strategy

Electronic searches

We will search the following electronic databases from inception to June 30, 2019: PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), Wan Fang Data and Chinese Science Journal Database. The searching strategy is available at appendix 1. No language or publication date will be restricted.

Searching other resources

The reference lists of identified relevant RCTs, comments, reviews and overviews will be screened for additional relevant articles. The World Health Organization International Clinical Trials Registry Platform (ICTRP), Chinese Clinical Trial Registry, Google Scholar and ClinicalTrials.gov will also be searched to identify any planned, ongoing or unpublished literature.

Data extraction and management

Selection of studies

The selection **of studies** will be completed independently by two reviewers (CG and KZ). They will check results with each other. When disagreements occur, a third reviewer (QLT) will make the final decision. Full-texts of all included studies will be read if necessary. Details of the selection process will be shown in the PRISMA flow chart (Figure 1).

Data extraction and management

A piloted data extraction form has been developed by reviewers. The following

information will be extracted from each included study independently by two authors (QLT and KZ): general information, study population, intervention characteristics and outcomes. Any disagreement will be resolved by discussion. If the information is unclear, missing or presented in a form that cannot be extracted, we will contact the corresponding author for additional information.

Risk of bias assessment

Two reviewers (KZ and CYL) will independently assess the risk of bias using the Cochrane 'risk of bias' tool[35,36]. This tool includes the following seven domains: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); (7) other bias. The risk of bias for each domain will be graded high, low or unclear based on the relevant information extracted from each eligible study. Any disagreement will be resolved by consensus.

Measures of treatment effect

For continuous data, Mean Difference (MD) or Standard MD (SMD) will be used to measure the therapeutic effect with 95% confidence intervals (CIs). Risk ratios (RR) with 95% CIs will be calculated for dichotomous data.

Dealing with missing data

We will attempt to contact the original researchers by e-mail to obtain any missing or inadequate data if possible. We will also obtain data by phone. If we cannot obtain accurate data through the above methods, we will exclude these studies.

Assessment of heterogeneity

The heterogeneity will be tested by the Chi-squared test or I^2 value. If the P value in Chi-squared test is less than 0.10 or I^2 is more than 50%, the heterogeneity across studies will be statistically significant. When the heterogeneity is identified, a meta-analysis with the random-effect model will be used to estimate overall treatment effect. Moreover, a subgroup analysis or meta-regression will be conducted to explore the causes of heterogeneity among results of studies.

Assessment of reporting biases

We will assess publication bias using the funnel plot and Egger's test if more than 10 trials are included.

Data synthesis

The meta-analysis will be conducted using the Review Manager (RevMan) V.5.3 software. We will describe the effect size with RR for dichotomous data, and MD or SMD for continuous data. If I^2 is less than 50%, the fixed-effects model will be used for data synthesis[37,38]. If I^2 is greater than 50%, we will combine the data using random-effects model[37,38]. A narrative description of the results will be conducted when the meta-analysis is not feasible.

Subgroup analysis

We will perform subgroup analysis to explore possible causes of heterogeneity if necessary. Subgroup analysis will be conducted based on the type of acupuncture intervention (body acupuncture, electroacupuncture, fire needling, elongated needle, warming needling), acupuncture point (single or multiple points), the duration of treatment, age and gender if possible.

Sensitivity analysis

We will conduct sensitivity analyses to test the robustness of pooled treatment effects. The following factors will be taken into consideration:

1. Impact of high or unclear risk of bias: excluding studies with high or unclear risk of bias for certain domain, such as random sequence generation;
2. Impact of selected models: fixed-effects model versus random-effects model.

If inconsistent results are identified, caution will be taken in interpreting results and drawing conclusions.

Assessment method of evidence quality

The quality of the evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[35]. The evaluation items include risk of bias, inconsistency, indirectness, imprecision, publication bias. Two authors (KZ and CG) will independently assess the quality of the evidence based on five levels of criteria. It will fall into one of four possible

ratings: high, moderate, low and very low.

Ethics and dissemination

This study will not involve personal information from individuals or violate their personal rights. Therefore, ethical approval will not be required. The results will be published in a peer-reviewed journal. Due to the lack of relevant systematic reviews in this field, this study will combine relevant RCTs to better explore evidence on acupuncture treatment for AP and guide clinical practice and acupuncture researches.

Patient and Public Involvement

Patients' priorities, experience, and preferences were not involved in development of the research question, and outcome measures, the design of this study, or the recruitment to and conduct of the study. The results will be not disseminated to study participants.

Amendments

If the protocol is modified, the information will be described in the final report.

Discussion

Acupuncture may be effective for AP. However, no systematic reviews on this topic have been published. This study will provide more convincing information on acupuncture for AP. This study has some potential limitations. Different types of acupuncture therapy may lead to a large degree of heterogeneity.

Protocol registration:

This protocol has been registered on PROSPERO (CRD42018115099).

Contributors

YL, JBZ and CZ conceived the study and provided general guidance to the drafting of the protocol. CG and KZ drafted the protocol. CYL designed the search strategy. CG, KZ, CYL, QLT and CZ drafted the manuscript. CG, KZ, CYL, CZ, JBZ, YL and QLT reviewed and revised the manuscript. All authors have read and approved the

final version of the manuscript.

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Competing interests: None declared.

Ethics approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: The final report of this systematic review will be published in a peer-reviewed scientific journal, and the data set will be made freely available.

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Figure legends:

Figure 1 Study selection flow diagram

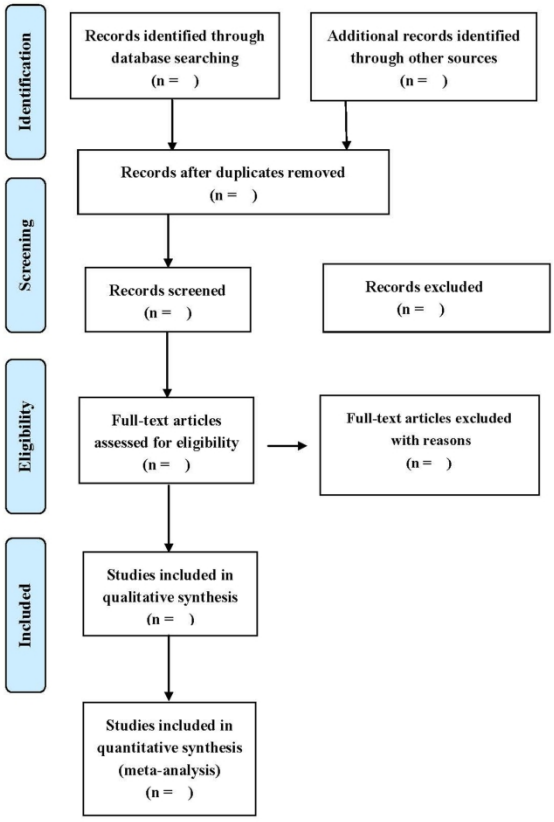

Figure 1 Study selection flow diagram

210x297mm (300 x 300 DPI)

Appendix 1.

PubMed Search strategy:

1. "acupuncture Therapy"[Mesh]
2. "acupuncture Analgesia"[Mesh]
3. "acupuncture, Ear"[Mesh]
4. " electroacupuncture "[Mesh]
5. " acupuncture points "[Mesh]
6. " meridians"[Mesh]
7. acupunctur*.tw
8. acupotom*.tw
9. (electroacupuncture OR electro-acupuncture).tw
10. acupoint*.tw
11. ((meridian OR non-meridian OR trigger) AND point*).tw
12. OR/1-11
13. "Pancreatitis/etiology"[Mesh:NoExp]
14. "Pancreatitis, Acute Necrotizing"[Mesh]
15. "Pancreatitis, Alcoholic"[Mesh]
16. acute pancreatitis.tw
17. alcoholic Pancreatitis.tw
18. acute pancreatitides.tw
19. cute pncretitis.tw
20. pancreatitis acuta.tw
21. SAP.tw
22. OR/13-21
23. randomized controlled trial.pt
24. controlled clinical trial.pt
25. randomized.tw
26. placebo.tw
27. "Clinical Trials as Topic"[Mesh]
28. Random* .tw
29. trial.tw
30. OR/23-29
31. Animals/ NOT humans/
32. 30 NOT 31
33. 12 AND 22 AND 32

EMBASE Search strategy:

1. 'acupuncture'/exp
2. ' acupuncture Analgesia '/exp
3. ' auricular acupuncture '/exp
4. ' electroacupuncture '/exp
5. acupunctur*: ti, ab
6. acupotom*: ti, ab
7. (electroacupuncture OR electro-acupuncture) : ti, ab
8. acupoint*: ti, ab
9. ((meridian OR non-meridian OR trigger) AND point*): ti, ab
10. OR/1-9
11. ' acute hemorrhagic pancreatitis '/exp
12. 'acute pancreatitis'/exp
13. ' alcoholic pancreatitis '/exp
14. 'acute pancreatitis': ti, ab
15. alcoholic NEAR/3 pancreatitis
16. acute NEAR/3 pancreatitides
17. ' cute pncretitis' ti, ab
18. ' pancreatitis acuta ' ti, ab
19. 'SAP': ti, ab
20. OR/11-19
21. randomized controlled trial/exp
22. 'randomized controlled trial (topic)'/exp
23. Placebo:ti,ab
24. random*:ti,ab
25. RCT:ti,ab
26. OR/21-25
27. (exp animal/ or exp animal experiment/ or nonhuman/) not exp human/
28. 26 NOT 27
29. 10 AND 20 AND28 AND [embase]/lim

Cochrane Central Register of Controlled Trials (CENTRAL) Search strategy:

1. MeSH descriptor: [acupuncture Therapy] explode all trees
2. MeSH descriptor: [acupuncture Analgesia] explode all trees
3. MeSH descriptor: [acupuncture, Ear] explode all trees
4. MeSH descriptor: [electroacupuncture] explode all trees
5. MeSH descriptor: [acupuncture points] explode all trees
6. MeSH descriptor: [meridians] explode all trees
7. acupunctur*:ti,ab,kw
8. acupotom*:ti,ab,kw
9. (electroacupuncture OR electro-acupuncture) :ti,ab,kw
10. acupoint*:ti,ab,kw
11. ((meridian OR non-meridian OR trigger) AND point*):ti,ab,kw
12. OR/1-11
13. MeSH descriptor: [Pancreatitis, Acute Necrotizing] explode all trees
14. MeSH descriptor: [Pancreatitis] this term only and with qualifier(s): [Etiology - ET]
15. MeSH descriptor: [Pancreatitis, Alcoholic] explode all trees
16. (acute near/3 pancrea*):ti,ab,kw
17. (necro* near/3 pancrea*):ti,ab,kw
18. (inflam* near/3 pancrea*):ti,ab,kw
19. ((interstitial or edema* or oedema*) near/2 pancrea*):ti,ab,kw
20. OR/13-19
21. MeSH descriptor: [Randomized Controlled Trial] explode all trees
22. MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees
23. randomized. ti,ab,kw
24. placebo. ti,ab,kw
25. randomly ti,ab,kw
26. OR/21-25
27. 12 AND 20 AND 26

Web of science Search strategy:

1. TS=((acute or necro* or inflam* or interstitial or edema* or oedema*) near/3 pancrea*)
2. TS=(alcoholic Pancreatitis OR acute pancreatitides OR pancreatitis acuta)
3. OR/1-2
4. TS=(*acupunctur* OR Acupoint*)
5. TS=random*
6. 3 AND 4 AND 5

China National Knowledge Infrastructure (CNKI) Search strategy:

(SU=急性胰腺炎 OR SU=胰腺 OR SU=胰腺炎) AND (SU=针刺 OR SU=针灸 OR SU=体针 OR SU=毫针 OR SU=毫针针刺 OR SU=电针 OR SU=温针灸 OR SU=温针 OR SU=火针 OR SU=燔针 OR SU=浮针 OR SU=耳针 OR SU=头针 OR SU=头皮针 OR SU=腹针 OR SU=腕踝针 OR SU=眼针)AND (SU=随机 OR FT=随机)

WANFANG data Search strategy:

主题:(针刺 OR 针灸 OR 体针 OR 毫针 OR 毫针针刺 OR 电针 OR 温针灸 OR 温针 OR 火针 OR 燔针 OR 浮针 OR 耳针 OR 头针 OR 头皮针 OR 腹针 OR 腕踝针 OR 眼针)*主题:(急性胰腺炎 OR 胰腺 OR 胰腺炎)*随机

Chinese Science Journal Database

(M=(急性胰腺炎+胰腺+胰腺炎))*(M=(针刺+针灸+体针+毫针+毫针针刺+电针+温针灸+温针+火针+燔针+浮针+耳针+头针+头皮针+腹针+腕踝针+眼针))*U=随机

PRISMA-P 2015 checklist

Section and topic	Item No	Checklist item	Page
Administrative information			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	9
Support:			
Sources	5a	Indicate sources of financial or other support for the revi	10
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	9
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report	4-6

		characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	6-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5-6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8

	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9