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Acupuncture for stable angina pectoris: a systematic review protocol

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Abstract

Introduction:

Previous reviews indicate that the effect of acupuncture for stable angina pectoris (SAP) remains controversial. Many trials published in the past five years may possibly change this situation, however an updated systematic review is not available. We, therefore, designed this study to update, as well as comprehensive resources to systematically assess the efficacy and safety of acupuncture for treating SAP.

Methods and analysis:

Nine online databases will be searched without language or publication status restrictions from their inception to September 2017. Randomized controlled trials enrolling stable angina patients receiving acupuncture therapy versus a control group will be deemed eligible. Selection of studies, data extraction, and risk of bias assessment will be carried out by two independent reviewers. Data synthesis will be performed in RevMan 5.3 software by using either a fixed effect model or random effect model, depending on the heterogeneity test. Evidence quality evaluation will be conducted by using the GRADE system. The efficacy-effectiveness spectrum for each included trial will be rated by using the RITES tool. Outcomes of interest include the improvement of weekly angina attacks and reduction of nitroglycerin medication use after receiving acupuncture treatment, the incidence of cardiovascular events, heart rate variability, pain intensity measured by a VAS, total workload and exercise duration at peak exercise, safety, and adverse events. Meta-analysis will be conducted if no considerable heterogeneity is detected. The results will be presented as risk ratios with 95% CIs for dichotomous data and weighted mean differences (WMD) or standardized mean difference (SMD) with 95% CIs for continuous data.

Ethics and dissemination:

This systematic review does not involve private information from individuals or endanger their rights, and therefore does not necessarily require ethical approval. The results may be published in a peer-reviewed journal or disseminated in relevant conferences.

Registration:

PROSPERO registry ID: CRD42015016201 (http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015016201)

Strengths and limitations of this study

- This study will update the evidence base of acupuncture for stable angina pectoris as many clinical trials have been published in the past 5 years, despite previous systematic reviews being conducted;
- Rating the efficacy-effectiveness spectrum of included trials undertaken within this systematic review has the potential to indicate how close current evidence is to 'real-world' practice;
- Several clinical outcomes have been used in published trials, therefore a pooled analysis of all included studies may not be possible; however, subgroup analyses will be performed according to different outcomes.

Background

Stable angina pectoris (SAP) is a prevalent cardiovascular disease that greatly endangers a patient's life quality and longevity. It is a clinical syndrome involving temporary hypoxic myocardial ischemia and features sensations of burning, severe pain, pressure and other forms of discomfort in the left anterior chest region. In the U.S., SAP affects more than 7.8 million people and is reported to have an incidence of more than 0.5 million cases per year[1]. For the European population, its incidence is estimated to be 10%-20% of people aged 65 to 74 years[2]. Within China, the prevalence is 2.4% among males and 3.2% among females[3], which makes it a serious public health problem. Current treatment options for SAP are diverse, generally including lifestyle modification and risk factors elimination, pharmacological management and revascularization according to the 2013 ESC guidelines on the management of stable coronary artery disease[4].

Though many therapeutic interventions are available to patients, the management of SAP is not satisfactory. Most patients continue to suffer from SAP or the side effects brought by modern drugs[5]. Non-pharmacological therapies as secondary options are frequently chosen by patients. Acupuncture, as a major component of traditional Chinese medicine, has been extensively used by clinicians for management of acute attacks and for prophylaxis of SAP since ancient times[6 7]. Technologically, the clinical practice of acupuncture involves a series of procedures that entail the insertion of filiform needles into designated acupuncture points and followed by different needle manipulation techniques. Clinical observations and expert opinions claimed that acupuncture has potential to reduce disease duration, angina attack frequency and nitroglycerin consumption, and improve cardiac work capacity[8-11]. Basic studies also suggest that acupuncture may exert myocardial protection and vascular dilation effect against cardiac ischemia and reperfusion by inhibiting the beta(1)-adrenoceptor signalling pathway and regulating myocardial enzyme action[12-17]. Therefore, acupuncture has the potential to be an effective supplementary treatment option for SAP.

The effect of acupuncture for SAP however are still controversial from the perspective of evidence-based medicine. Several systematic review have been conducted to assess the clinical benefits of acupuncture therapy for SAP; but all of them, even including the latest one which reviewed studies before 2013, still found inconclusive conclusions concerning the effect of acupuncture for treating SAP, due to poor quality trials[18-20]. Recently, it has noticed with great interest that a rough estimation of at least 10 clinical studies have been

published or conducted in recent 5 years[6 21-29]. These studies have the great potentials to change the current evidence base of acupuncture for SAP. However, at present there exists no updated systematic review or study protocol published for this question, which gives us the unique opportunity to re-evaluate this question. We therefore conceived this systematic review to update the most recent evidence to determine the effectiveness and safety of acupuncture for patients with SAP. This systematic review aims to use the most comprehensive and up-to-date resources to assess the effectiveness and safety of acupuncture for treating SAP.

Methods

Criteria for considering studies for this review

Types of studies

The review will include randomized controlled trials (RCTs) that were reported in any language. Completed or ongoing trials will be included in this review. Trials using two-arm or three arm parallel design will be included. Cross-over trials and Quasi-RCTs will be excluded. Any study with a sample size of less than 10 participants will also be excluded from this review.

Types of participants

Trials including participants that fulfil the following criteria will be included: 1) study participants meet the definition, diagnostic criteria of stable angina pectoris of stable coronary heart disease[30-33]. All eligible study participants will be included in this review regardless of their age, race or gender. Trials including study participants who are not appropriate to receive acupuncture therapy, such as pregnant or lactating women and other severe diseases will be excluded.

Types of interventions

The interventions considered in the studies have to involve needle insertion at acupuncture points, pain points or trigger points, and have to be described as acupuncture. Adjunct therapy with acupuncture that are additive to the active treatment will be included in this study. However, other methods of stimulating acupuncture points without needle insertion (such as moxibustion, laser stimulation, massage or

transcutaneous electrical nerve stimulation), will be excluded. Studies that compare the efficacy of different forms of acupuncture shall be excluded as it is not the focus of this review.

Types of comparator(s)/control

The following control group will be considered:
1. acupuncture versus sham devices (interventions mimicking 'verum' acupuncture/treatment, but deviating in at least one aspect considered important by acupuncture theory, such as skin penetration or non-acupoint location);
2. acupuncture versus routine care;
3. acupuncture versus conventional drugs;
4. acupuncture in addition to active treatment against an active treatment alone.
Studies that only compared different forms of acupuncture and compared acupuncture with other complementary and alternative therapeutics shall be excluded.

Types of outcome measures

Primary outcomes

The numbers of weekly angina attacks and nitroglycerin use in during a period of at least two weeks following randomization.

Secondary outcomes

1. Cardiovascular events;
2. ECG changes (mainly ST-segment depression);
3. heart rate variability;
4. angina pain intensity (assessed by VAS);
5. affective emotions (assessed by SAS and SDS);
6. total workload (in Met-minutes) and exercise duration (in seconds) at peak exercise;
7. overall tolerability[34];
8. overall acceptability[34];

Search methods for identification of studies

Electronic searches

Nine electric databases will be searched from their inception to July, 2017: MEDLINE, Ovid, EMBASE, Cochrane Library, the Allied and Complementary Medicine Database (AMED), Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Wanfang Database, the Chongqing VIP Chinese Science and Technology Periodical Database (VIP). Only randomized controlled trials that evaluate the effect of acupuncture by comparing with the aforementioned comparator controls will be included. There will be no language restriction to the included trials. The following Medical Search Headings (MeSH) will be used: stable angina pectoris, stable angina, angina pectoris, angina, acupuncture, acupuncture therapy, electroacupuncture, electroacupuncture therapy, manual acupuncture, acupoint, randomized controlled trial, randomized controlled, randomized, controlled, clinical trial, comparative study, prospective study. Chinese translations of these searching terms will be used for the Chinese database. The searching strategy for MEDLINE is listed in Table 1. The search strategy will be modified according to the Cochrane Handbook for Systematic Reviews[35] for other databases.

Searching other resources

Ongoing trials with unpublished data will be retrieved from the following clinical trial registries: the NIH clinical registry-clinicaltrials.gov (https://www.clinicaltrials.gov/), the International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/), the Australian New Zealand Clinical Trials Registry(http://www.anzctr.org.au/) and the Chinese clinical registry(http://www.chictr.org/en/). The reference list of all identified publications including relevant systematic reviews and meta-analysis will be reviewed to further identify additional trials. Useful but incomplete data of certain trials will be obtained for data synthesis from the contact trial personnel.

Data collection and analysis

Selection of studies

The search results will be imported from the original database to an external citation management software (Endnote X7.1). According to inclusion criterion, two reviewers (M Yang and M Sun) will independently assess the eligibility of retrieved studies. For preliminary study selection, only title and abstract will be reviewed to exclude obvious inappropriate publications. Unmatched studies will be removed to a trash box in the software. The reasons for exclusion will be recorded in an excel dataset. The next step is to further evaluate the included studies by reading their full-text version. The reference

list will be checked by the two reviewers to identify potentially missing trials. The selection results will be cross-checked by the two reviewers. Any disagreement shall be resolved by consensus. Further argument will be arbitrated by a 3rd reviewer (T Du). Each eligible trial will be assigned a study ID which is a formatted as: First name of the 1st author +space +Year of publication (e.g. Yang 2017).

Data extraction and management

Two reviewers (L Long and Z Shen) will independently double-check the eligibility of the included study and extract data by entering details into a predefined data acquisition form. This acquisition form will include four main domains, including citation information (title, author list, source of publication, year of publication, first author's name and affiliation, country, and sponsor), design (design, participants, trial methods, duration, interventions details, care-giver information), results (outcome measures, adverse events) and conclusion. Any discrepancy noticed in the process of data cross checking will be resolved through discussion and a third reviewer's (L Lao) suggestion.

Assessment of risk of bias in included studies

The risk of bias for each included trial will be evaluated by employing the Cochrane Collaboration's tool for assessing risk of bias in randomized trials[36]. Two reviewers (M Yang and T Du) will input relevant details of each trial into the RevMan software[37] (Version 5.3) and assess the trial for at least six domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, Selective reporting, and other bias if necessary). For each domain, the trial will be rated as high, unclear, or low risk of bias. A trial that is rated high risk of bias in one or more domains will be considered as 'high risk', while a low risk of bias in all domains will be rated as 'low risk'. If one or more 'unclear risk' of bias in each domain occurs it will be rated as 'unclear risk'[38]. The contact person or corresponding author will be contacted in circumstances where basic information is missing for the risk of bias assessment. Similarly, rating results will be cross-checked and discrepancies will be resolved through discussions and arbitration of a third reviewer (F Liang).

Measures of treatment effect

Data in terms of efficacy will be synthesized and statistically analyzed in RevMan 5.3. Dichotomous data will be analyzed by using a risk of ratio (RR) with 95% CIs. For

continuous outcomes, data will be analyzed by using a weighted mean difference (WMD) or a standard mean difference (SMD) with 95% CIs. To be clear, the WMD will be used for the same scale or same assessment instrument; while SMD will be used for different assessment tools.

Unit of analysis issues

The unit of each outcome from different trials will be transformed to the International System of Units before statistical analysis.

Dealing with missing data

Whether the data was missing on purpose or 'at random' it will be pre-determined by contacting the corresponding author or relevant author. Available data will be analyzed following confirmation by investigators that the data was missing 'at random'[35]. If not, a request for missing data from the original investigators of the trial will be sent, or the contact person recorded in the trial registry if necessary. In circumstances of no reply from the authors or contact person, we will impute the missing data with replacement values, treating these as if they were observed. The last observation carried forward (LOCF) imputation methods will be used to assume a missing value and then an intention-to-treat (ITT) analysis will be performed. Moreover, if possible, we will perform the sensitivity analyses to assess how sensitive results are to reasonable changes in the assumptions that are made. Potential impact of the effect of missing data on the final findings of the review will be addressed in discussion.

Assessment of heterogeneity

The Chi-square statistics will be performed in the forest plot using RevMan 5.3, to observe the existence of statistical heterogeneity and a *P* value less than 0.10 will be considered significant according to Cochrane Handbook[35]. Moreover, the I^2 value will be calculated to quantify impact of the statistical heterogeneity on the meta-analysis. The Cochrane handbook classified the I^2 values into four categories: 0-40%, might not be important; 30-60%, indicates moderate heterogeneity; 50-90%, represents substantial heterogeneity; 75-100%, suggests considerable heterogeneity.

Assessment of reporting biases

The funnel plot will be generated to observe the reporting bias when the number of included trials is over 10[35].

Data synthesis

Clinical data will be imported into the RevMan software (version 5.3) to perform data synthesis. Data will be synthesized and analyzed depending on the level of statistical heterogeneity. If the heterogeneity tests show little or no statistical heterogeneity in these trials, the fix effect model will be used for the pooled data. If a significant heterogeneity is detected (if the I^2 value is no less than 50%), the random effect model will be used for data synthesis. If there is considerable heterogeneity in the trials, meta-analysis will not be performed. In this case, we will try to identify the source of heterogeneity from both clinical and methodological aspects and a narrative, qualitative summary will be provided.

Subgroup analysis and investigation of heterogeneity

If data is available, a subgroup analysis will be conducted according to variations in characteristics of trial participants and acupuncture treatments. When considerable heterogeneity is detected in a previous analysis, a subgroup analysis will be performed if necessary.

Sensitivity analysis

Sensitivity analysis will be used to monitor the robustness of the primary decision made in the process. In this review, we will consider several decision nodes within the process of the systematic review to implement a sensitivity review, such as small-studies, methodological weakness, missing data, etc. The sensitivity analysis that will be performed in this review will involve undertaking two steps as suggested by the Cochrane handbook: first, including all studies as the primary meta-analysis does and second, including those that are definitely known to be eligible. The results of sensitivity analysis will be presented in summary tables. The risk of bias in the review process, as indicated by the results of sensitivity analysis, will be discussed.

Other analysis

Consideration will be given to using a meta-regression analysis to investigate the impact of the year of publication on the outcome estimates.

Evidence quality evaluation

Reviewers will use the online Grading of Recommendations Assessment Development and Evaluation (GRADE) application, the GRADEpro (https://gradepro.org/), to independently assess the quality of evidence for each outcome[39]. Evidence quality will be rated 'high', 'moderate', 'low' or 'very low' according to the GRADE rating standards[40] [41]. The quality of evidence of a specific study will be assessed depending on the appropriateness of study design, soundness of implementation, directness and precision of evidence, consistency or homogeneity of the results and other biases. The summary of findings (SoF) table will be generated and included in the final report.

Efficacy-effectiveness spectrum analysis

Because systematic reviews can include both explanatory trials and pragmatic trials for data synthesis, it is important for clinicians and researchers to know the nature of evidence. Therefore to analyze the efficacy-effectiveness spectrum of each included trial the RITES (Rating of Included Trials on the Efficacy-effectiveness Spectrum) scale[42]will be used. Four domains will be assessed to justify the efficacy-effectiveness spectrum for each trial, including participant characteristics, trial setting, flexibility of interventions and clinical relevance of interventions.

Ethics and dissemination

This review does not involve private information from individuals or compromise their rights, and therefore does not require ethical approval. The results may be published in a peer-reviewed journal or disseminated at relevant conferences. Due to the paucity of related publications in the field, this review article will, by adding more recent studies in analysis, provide more robust evidence of acupuncture therapy for treating stable angina, and lead to informed clinical practice and acupuncture research.

Acknowledgements

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Contributions of authors

MY conceived the review protocol and drafted the manuscript. LL, QW, DL and FL revised the study design. TD, MS, FL and HL participated in the design of the search strategy and data extraction dataset. MY, TD, MS and ZS formed the data synthesis and analysis plan. In practice, FL and LL will monitor each procedure of the review and are responsible for the quality control. All authors have read and approved the publication of the protocol.

Competing interest

None declared.

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Table

Table 1 Search Strategy in MEDLINE

#1	randomized controlled trial [pt]
#2	controlled clinical trial [pt]
#3	randomized [tiab]
#4	placebo [tiab]
#5	clinical trials as topic [mesh: noexp]
#6	randomly [tiab]
#7	trial [ti]
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	animals [mh] NOT humans [mh]
#10	#8 NOT #9
#11	angina, stable [mesh]
#12	chronic stable angina pectoris [tiab]
#13	stable angina pectoris [tiab]
#14	chronic stable angina [tiab]
#15	stable angina [tiab]
#16	angina pectoris [ti]
#17	angina [ti]
#18	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	acupuncture [mesh]
#20	acupuncture therapy [mesh]
#21	electroacupuncture [tiab]
#22	electroacupuncture therapy [tiab]
#23	manual acupuncture [tiab]
#24	dry needle [tiab]
#25	acupoint [tiab]
#26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27	#10 AND #18 AND #26

#28	remove duplicates from #27

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

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	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
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	11
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	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
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 characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
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	7
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)	7
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, 9
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	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 I^2, Kendall's τ)	9-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	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, 11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Acupuncture for stable angina pectoris: a systematic review protocol

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Abstract

Introduction:

Previous reviews indicate that the effect of acupuncture on stable angina pectoris (SAP) remains controversial. The results of trials published in the past five years may possibly change this situation, but an updated systematic review is not available. We therefore designed this study to systematically assess the efficacy and safety of acupuncture for treating SAP.

Methods and analysis:

Nine online databases will be searched without language or publication status restrictions from their inception to September 2017. Randomised controlled trials that include stable angina patients receiving acupuncture therapy versus a control group will be deemed eligible. The selection of studies, data extraction, and risk of bias assessment will be carried out by two independent reviewers. Data synthesis will be performed using RevMan 5.3 software with either a fixed effects model or random effects model, depending on the heterogeneity test. Evidence quality will be evaluated using the GRADE system. The efficacy–effectiveness spectrum for each included trial will be rated using the Rating of Included Trials on the Efficacy-effectiveness Spectrum (RITES) tool. Outcomes of interest include the improvement of weekly angina attacks and reduction of nitroglycerin medication use after receiving acupuncture treatment, the incidence of cardiovascular events, heart rate variability, pain intensity measured on a visual analogue scale, total workload and exercise duration at peak exercise, safety, and adverse events. A meta-analysis will be conducted if no considerable heterogeneity is detected. The results will be presented as risk ratios with 95% confidence intervals (CIs) for dichotomous data and weighted mean differences or standardised mean differences with 95% CIs for continuous data.

Ethics and dissemination:

This systematic review will not involve private information from individuals or endanger their rights, and therefore does not necessarily require ethical approval. The results may be published in a peer-reviewed journal or disseminated in relevant conferences.

Registration:

PROSPERO registry ID: CRD42015016201 (http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015016201)

Strengths and limitations of this study

- Although systematic reviews of acupuncture for stable angina pectoris have been conducted previously, this study will update the evidence base by including many clinical trials that have been published in the past 5 years.
- Rating the efficacy–effectiveness spectrum of trials included in the systematic review has the potential to indicate how close current evidence is to 'real-world' practice.
- As several clinical outcomes have been used in published trials, a pooled analysis of all included studies may not be possible; however, subgroup analyses will be performed according to different outcomes.

Background

Stable angina pectoris (SAP) is a prevalent cardiovascular disease that greatly compromises a patient's life quality and longevity. It is a clinical syndrome involving temporary hypoxic myocardial ischemia and features sensations of burning, severe pain, pressure and other forms of discomfort in the left anterior chest region. In the U.S., SAP affects more than 7.8 million people and is reported to have an incidence of more than 0.5 million cases per year[1]. In the European population, its incidence is estimated to be 10% to 20% of people aged 65 to 74 years[2]. Within China, the prevalence is 2.4% among males and 3.2% among females[3], which makes it a serious public health problem. According to the 2013 European Society of Cardiology (ESC) guidelines on the management of stable coronary artery disease[4], current treatment options for SAP are diverse, generally including lifestyle modification and elimination of risk factors, pharmacological management and revascularisation.

Although many therapeutic interventions are available to patients, the management of SAP is not satisfactory. Most patients continue to suffer from SAP or the side effects of their medications[5]. Non-pharmacological therapies as secondary options are frequently chosen by patients. Acupuncture, a major component of traditional Chinese medicine, has been extensively used by clinicians for the management of acute attacks and for prophylaxis of SAP since ancient times[6,7]. The clinical practice of acupuncture involves a series of procedures that entail the insertion of filiform needles into designated acupuncture points, followed by different needle manipulation techniques. Clinical observations and expert opinions suggest that acupuncture has the potential to reduce disease duration, angina attack frequency and nitroglycerin consumption, and improve cardiac work capacity[8-11]. Studies suggest that acupuncture may exert a myocardial protection and vascular dilation effect against cardiac ischemia and reperfusion by inhibiting the beta (1)-adrenoceptor signalling pathway and regulating myocardial enzyme action[12-17]. Therefore, acupuncture has the potential to be an effective supplementary treatment option for SAP.

However, the effect of acupuncture for SAP is still controversial from the perspective of evidence-based medicine. Several systematic reviews have been conducted to assess the clinical benefits of acupuncture therapy for SAP, but all of them, including the most recent, which reviewed studies before 2013, were inconclusive due to poor-quality trials[18-20]. Recently, it has been noticed with great interest that a rough estimation of at least 10 clinical studies have been published or conducted in the past 5 years[6,21-29]. These studies have great potential to change the current evidence base of acupuncture for SAP. However, at present there exists no updated systematic review or study protocol published on this question. We thus have a unique opportunity to re-evaluate the issue and conceived this systematic review to determine the effectiveness and safety of acupuncture for patients with SAP based on the most comprehensive and up-to-date resources.

Methods

Criteria for including studies in the review

Types of studies

The review will include randomised controlled trials (RCTs) that were reported in any language. Completed and ongoing trials will be included. Trials using a two-arm or three-arm parallel design will be included. Crossover trials and quasi-RCTs will be excluded. Any study with a sample size of less than 10 participants will also be excluded from this review.

Types of participants

Trials including participants that meet the diagnostic criteria of stable angina pectoris of stable coronary heart disease will be included[30-33]. All eligible study participants will be included in this review regardless of their age, race or gender. Trials including study participants who are not appropriate to receive acupuncture therapy, such as pregnant or lactating women and those with additional severe diseases will be excluded.

Types of interventions

The interventions considered in the studies must involve needle insertion at acupuncture points, pain points or trigger points, and be described as acupuncture. Adjunct therapy with acupuncture that is additive to the active treatment will be included in this review. However, other methods of stimulating acupuncture points without needle insertion (such as moxibustion, laser stimulation, massage or transcutaneous electrical nerve stimulation) will be excluded. Studies that compare the efficacy of different forms of acupuncture will be excluded as this is not the focus of the review.

Types of comparator(s)/control

The following control groups will be considered:
1. acupuncture versus sham devices (interventions mimicking 'verum' acupuncture/treatment, but deviating in at least one aspect considered important by acupuncture theory, such as skin penetration or non-acupoint location);
2. acupuncture versus routine care;
3. acupuncture versus conventional drugs;
4. acupuncture in addition to active treatment versus active treatment alone.

Studies that only compare different forms of acupuncture or compare acupuncture with other complementary and alternative therapeutic interventions shall be excluded.

Types of outcome measures

Primary outcomes

The number of weekly angina attacks and nitroglycerin use during a period of at least two weeks following randomisation.

Secondary outcomes

1. Cardiovascular events;
2. ECG changes (mainly ST-segment depression);
3. heart rate variability;
4. angina pain intensity (assessed by VAS);
5. affective emotions (assessed by SAS and SDS);
6. total workload (in Met-minutes) and exercise duration (in seconds) at peak exercise;
7. overall tolerability[34];
8. overall acceptability[34];

Search methods for identification of studies

Electronic searches

The following databases will be searched from their inception to September 2017: MEDLINE, Ovid, EMBASE, Cochrane Library, the Allied and Complementary Medicine Database (AMED), Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Wanfang Database, the Chongqing VIP Chinese Science and Technology Periodical Database (VIP). Only randomised controlled trials that evaluate the effect of acupuncture in comparison with the aforementioned comparator controls will be included. There will be no language restriction on the included trials. The following medical search headings (MeSH) will be used: stable angina pectoris, stable angina, angina pectoris, angina, acupuncture, acupuncture therapy, electroacupuncture, electroacupuncture therapy, manual acupuncture, acupoint, randomised controlled trial, randomised controlled, randomised, controlled, clinical trial, comparative study, prospective study. Chinese translations of these search terms will be used for the Chinese databases. The searching strategy for MEDLINE is listed in Table 1. The search strategy will be modified according to the Cochrane Handbook for Systematic Reviews[35] for other databases.

Searching other resources

Ongoing trials with unpublished data will be retrieved from the following clinical trial registries: the NIH clinical registryclinicaltrials.gov (https://www.clinicaltrials.gov/), the International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/), the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/) and the Chinese clinical registry(http://www.chictr.org/en/). The list of all identified publications including

relevant systematic reviews and meta-analyses will be reviewed to further identify additional trials. Useful but incomplete data will be obtained for data synthesis from the contact trial personnel.

Data collection and analysis

Selection of studies

The search results will be imported from the original databases to Endnote X7.1. Two reviewers (M. Yang and M. Sun) will independently assess the eligibility of the retrieved studies according to the inclusion criteria. For preliminary study selection, only the title and abstract will be reviewed to exclude obviously inappropriate publications. Unmatched studies will be removed to a trash box in the software. The reasons for exclusion will be recorded as an Excel dataset. The next step will be to further evaluate the included studies by reading their full-text version. The reference list will be checked by the two reviewers to identify potentially missing trials. The selection results will be cross-checked by the two reviewers. Any disagreement will be resolved by consensus. Further argument will be arbitrated by a third reviewer (T. Du). Each eligible trial will be assigned a study ID formatted as follows: Surname of the first author + space + year of publication (e.g., Yang 2017).

Data extraction and management

Two reviewers (H Long and Z Shen) will independently double-check the eligibility of the included studies and extract data by entering details into a predefined data acquisition form. This acquisition form will include four main domains: citation information (title, author list, source of publication, year of publication, first author's name and affiliation, country, and sponsor), design (design, participants, trial methods, duration, intervention details, care-giver information), results (outcome measures, adverse events) and conclusion. Any discrepancy noticed in the process of data cross-checking will be resolved through discussion and the suggestion of a third reviewer (L. Lao).

Assessment of risk of bias in included studies

The risk of bias for each included trial will be evaluated using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials[36]. Two reviewers (M. Yang and T. Du) will input the relevant details of each trial into the RevMan software[37] (Version 5.3) and assess the trial for at least six domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias if necessary). For each domain, the trial will be rated as high, unclear, or low risk of bias. A trial that is rated high risk of bias in one or more domains will be rated as 'high risk', while a low risk of bias in all domains will be rated as

'low risk'. If there is low or unclear risk of bias for all key domains, the trial will be rated as 'unclear risk'[36]. The contact person or corresponding author will be contacted if basic information is missing for the risk of bias assessment. The rating results will be cross-checked and discrepancies resolved through discussions and the arbitration of a third reviewer (F. Liang).

Measures of treatment effect

Efficacy data will be synthesised and statistically analysed in RevMan 5.3. Dichotomous data will be analysed by using a risk ratio (RR) with 95% CIs. For continuous outcomes, data will be analysed by using a weighted mean difference (WMD) or a standard mean difference (SMD) with 95% CIs. The WMD will be used for the same scale or same assessment instrument; SMD will be used for different assessment tools.

Unit of analysis issues

The units of each outcome from different trials will be converted to the International System of Units before statistical analysis.

Dealing with missing data

Whether the data was missing on purpose or 'at random' will be pre-determined by contacting the corresponding author or relevant author. Available data will be analysed following confirmation by investigators that the data was missing 'at random'[35]. If not, a request for missing data will be sent to the original investigators of the trial, or the contact person recorded in the trial registry. In case of no reply from the authors or contact person, we will impute the missing data with replacement values, treating these as if they were observed. The last observation carried forward (LOCF) imputation method will be used to assume a missing value and then an intention-to-treat (ITT) analysis will be performed. Moreover, if possible, we will perform sensitivity analyses to assess how sensitive the results are to reasonable changes in the assumptions that are made. The potential impact of the effect of missing data on the final findings of the review will be addressed in the discussion.

Assessment of heterogeneity

Chi-square tests will be performed in the forest plot using RevMan 5.3, to investigate the statistical heterogeneity and a *P* value of less than 0.10 will be considered significant, in line with the Cochrane Handbook[35]. Moreover, the I^2 value will be calculated to quantify the impact of the statistical heterogeneity on the meta-analysis. The Cochrane Handbook classifies the I^2 values into four categories: 0–40%, might not be important; 30–60%, indicates moderate heterogeneity; 50–90%, represents substantial heterogeneity; 75–100%, suggests considerable heterogeneity.

Assessment of reporting biases

A funnel plot will be generated to observe the reporting bias when more than 10 trials are included 10[35].

Data synthesis

Clinical data will be imported into RevMan software (version 5.3) to perform data synthesis. Data will be synthesised and analysed depending on the level of statistical heterogeneity. If the heterogeneity tests show little or no statistical heterogeneity in these trials, the fixed effects model will be used for the pooled data. If significant heterogeneity is detected (if the I^2 value is no less than 50%), the random effects model will be used for data synthesis. If there is considerable heterogeneity in the trials, meta-analysis will not be performed. In this case, we will try to identify the source of heterogeneity from both clinical and methodological aspects and a narrative, qualitative summary will be provided.

Subgroup analysis and investigation of heterogeneity

If data is available, a subgroup analysis will be conducted according to variations in the characteristics of the trial participants and acupuncture treatments. When considerable heterogeneity is detected in a previous analysis, a subgroup analysis will be performed if necessary.

Sensitivity analysis

Sensitivity analysis will be used to monitor the robustness of the primary decision made in the review process. We will consider several decision nodes within the process of the systematic review to implement a sensitivity review, such as small studies, methodological weaknesses, and missing data. The sensitivity analysis will involve two steps, as suggested by the Cochrane Handbook: first, including all studies as the primary meta-analysis does and second, including those that are definitely known to be eligible. The results of the sensitivity analysis will be presented in summary tables. The risk of bias in the review process, as indicated by the results of the sensitivity analysis, will be discussed.

Other analysis

Consideration will be given to using a meta-regression analysis to investigate the impact of the year of publication on the outcome estimates.

Evidence quality evaluation

The reviewers will use the online Grading of Recommendations Assessment Development and Evaluation (GRADE) application, GRADEpro (https://gradepro.org/), to independently assess the quality of evidence for each outcome[38]. Evidence quality will be rated 'high', 'moderate', 'low' or 'very low' according to the GRADE rating standards[39 40]. The quality of evidence of a specific study will be assessed according to the appropriateness of the study design, soundness of implementation, directness and precision of evidence, consistency or homogeneity of the results and other biases. A summary of findings (SoF) table will be generated and included in the final report.

Efficacy–effectiveness spectrum analysis

Because systematic reviews can include both explanatory trials and pragmatic trials for data synthesis, it is important for clinicians and researchers to know the nature of the evidence. Therefore, to analyse the efficacy–effectiveness spectrum of each included trial the RITES (Rating of Included Trials on the Efficacy–Effectiveness Spectrum) scale[41]will be used. Four domains will be assessed to justify the efficacy–effectiveness spectrum for each trial: participant characteristics, trial setting, flexibility of interventions and clinical relevance of interventions.

Ethics and dissemination

This review will not involve private information from individuals or compromise their rights, and therefore does not require ethical approval. The results may be published in a peer-reviewed journal or disseminated at relevant conferences. Due to the paucity of related publications in the field, this review article will, by adding more recent studies into the analysis, provide more robust evidence of acupuncture therapy for treating stable angina, and lead to informed clinical practice and acupuncture research.

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Contributions of authors

MY conceived the review protocol and drafted the manuscript. LL, QW, DL and FL revised the study design. TD, MS, FL and HL participated in the design of the search strategy and data extraction dataset. MY, TD, MS and ZS formed the data synthesis and analysis plan. In practice, FL and LL will monitor each procedure of the review and are responsible for the quality control. All authors have read and approved the publication of the protocol.

Competing interest

None declared.

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Table

Table 1 Search Strategy in MEDLINE

#1	randomized controlled trial [pt]
#2	controlled clinical trial [pt]
#3	randomized [tiab]
#4	placebo [tiab]
#5	clinical trials as topic [mesh: noexp]
#6	randomly [tiab]
#7	trial [ti]
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	animals [mh] NOT humans [mh]
#10	#8 NOT #9
#11	angina, stable [mesh]
#12	chronic stable angina pectoris [tiab]
#13	stable angina pectoris [tiab]
#14	chronic stable angina [tiab]
#15	stable angina [tiab]
#16	angina pectoris [ti]
#17	angina [ti]
#18	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	acupuncture [mesh]
#20	acupuncture therapy [mesh]
#21	electroacupuncture [tiab]
#22	electroacupuncture therapy [tiab]
#23	manual acupuncture [tiab]
#24	dry needle [tiab]
#25	acupoint [tiab]
#26	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27	#10 AND #18 AND #26
#28	remove duplicates from #27

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

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	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
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	11
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	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
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 characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
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	7
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)	7
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, 9
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	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 I^2, Kendall's τ)	9-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	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, 11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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