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Safety and efficacy of Acupuncture for Varicocele-Induced Male Infertility: A systematic review protocol

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These authors have contributed equally to this work.

Strengths and limitations of this study

►This protocol aims to provide patients, clinical practitioners and policy makers with more evidence on the efficacy and safety of acupuncture in the treatment of varicocele.

►The data extraction and management, assessment of risk of bias sections will be carried out by two or more researchers independently.

►The non-inclusion of studies published in languages other than English and Chinese may result in limitations related to publication bias.

►Multiple types of acupuncture therapies may increase the risk of heterogeneity.

ABSTRACT

Introduction

Varicocele (VC) is a common clinical disease in andrology. There are a lot of ways for VC treatment, and surgery is the most common one, but the benefits of surgical repair can be very slightly. There is a growing exploration of complementary therapies in clinical research on acupuncture for VC, but there is no relevant systematic review and meta-analysis to assess the efficacy and safety of acupuncture for VC.

Methods and analysis

All relevant publications published from inception through February 2022 will be searched in four English-language databases (Embase, Cochrane Library, Pubmed, Web of Science) and four Chinese-language databases (China National Knowledge Infrastructure, China Science and Technology Journal Database, Chinese

Biomedical Literature Database and Wanfang Data). Randomized controlled trials (RCTs) in English and Chinese concerned with acupuncture for patients with Varicocele will be included. The input clinical data will be processed by the Review Manager software (RevMan).The literature will be appraised with the Cochrane Collaboration risk of bias tool. The Grading of Recommendations Assessment, Development and Evaluation system (GRADE system) will be used to evaluate the quality of evidence.

Ethics and dissemination

This study is a secondary study based on clinical studies so it does not relate to any individual patient information and will not infringe the rights of participants. Hence no ethical approval is required. The results will be reported in peer-reviewed journals or disseminated at relevant conferences.

Registration number:

INTRODUCTION

Varicocele (VC) is regarded as the abnormal dilation of the internal testicular vein and pampiniform venus plexus within the spermatic cord, which is one of the most common causes of male infertility. It accounts for 35% of patients with primary infertility and up to 81% in secondary infertility.[1]

In addition to affect fertility, VC may also cause symptoms such as enlargement of the scrotum, swelling, dull aching pain and cramping in the lower abdomen, which can be exacerbated by prolonged standing, walking or heavy physical work. Several theories explain the role of varicocele in terms of pathophysiology, including altered testicular blood flow, increased temperature, oxidative stress, development of anti-sperm antibodies, reflux of adrenal and gonadal hormone metabolites and alterations in the hypothalamic-pituitary-gonadal axis.[2] The precise mechanism by which VC potentially affects spermatogenesis remains unclear,[3 4] but some recent documents allows for the conclusion that VC can injure fertility by affecting testicular histology, sperm function, semen quality and reproductive hormones.[4-6] Currently surgery remains the main treatment option for VC, which includes surgical treatment and interventional treatment. Surgical treatments for VC include the traditional inguinal or high retroperitoneal ligation, laparoscopic repair and microsurgical repair via an inguinal or subinguinal incision and embolization.[7-9] However there is some possibility of recurrence and complications with different surgical techniques (Table 1). The recurrence rates vary with the technique of varicocele repair from 0% to 35% and the incidence of post-operative hydrocele formation varies from 0% to 25%.[10 11] For patients with mild symptoms, conventional medications such as clomiphene citrate and levocarnitine are often used. These drugs mainly work by promoting sperm maturation, improving semen quality and dilating blood vessels. However it do not fundamentally address the anatomical basis of the disease, so the overall outcome is often unsatisfactory.[12-15] Therefore complementary therapies need to be pursued and developed. Acupuncture is well known as a safe and low side effect therapy, which has already been

widely used in the treatment of VC. The incidence of adverse reactions to acupuncture is significantly lower than using other drugs or other conventional medical procedures under the same conditions, which is one of the significant advantages of acupuncture.[16] Specific acupuncture methods that have been used clinically include manual acupuncture, electro-acupuncture, needle warming moxibustion and needle pricking, etc. Acupuncture treatment for VC may have a therapeutic effect on VC by lowering the scrotal skin temperature of the patient,[17] inhibiting the patient's oxidative stress process,[18 19] and improving the patient's neuroendocrine function by affecting the patient's serum testosterone (T) and follicle-stimulating hormone (FSH),[20-22] increase the blood flow and vasodilatory elasticity of spermatic veins in patients with VC infertility and reduce the viscosity of blood flow, thus improving blood circulation and relieving VC.[23]

At present, there are a certain number of documents on acupuncture treatment of VC. These experimental and theoretical studies on the improvement of treating VC by acupuncture can provide preliminary evidence that acupuncture is effective in treating varicocele-induced male infertility, but the systematic review is still lacking. Therefore, this paper is to evaluate the safety and efficacy of acupuncture in the treatment of VC.

Table 1 Postoperative spontaneous pregnancy rates, recurrence rates, hydrocele formation rates among the techniques

Technique	Spontaneous pregnancy rate	Recurrence rate	Hydrocele formation rate	Advantages	Disadvantages
Palomo[24-27]	37.69%	14.97%	8.24%	Good for pain relief shorter surgery time.	Highest recurrence rate and hydrocele formation rate.
Laparoscopic varicocelectomy[24 26-28]	30.07%	4.3%	2.84%	Suitable for bilateral varicocele and recurrent varicocele. Less invasive surgery, faster recovery and fewer complications.	May cause damage to intestines and blood vessels. Requires high level of surgical skills, anaesthesia and is more expensive.
Radiologic embolization[24 27 29 30]	33.2%	12.7%	0%-12%	Less damage and faster recovery. No accidental injury to the internal spermatic artery.	Potential risks of radiation exposure, misplaced embolism and displacement of embolic agents.
Mcroscopic inguinal (Ivanissevich) [24 31-33]	36%	2.63%	7.3%	More effective in improving sperm concentration.	Increased chance of arterial and lymphatic vessel damage, requiring more surgical skill.
Microsurgical varicocelectomy[9 28 34 35]	41.97%	1.05%-2.60%	0.44%	Relatively good efficacy and low recurrence and complication rates.	Less than 40% of infertile couples achieve spontaneous pregnancy after microsurgical

				Better control of post-operative pain.	varicocelectomy, and most of them still require additional interventions such as advanced assisted reproductive technologies (ARTS).
Subinguinal microsurgical varicocclectomy[30 33 36]	42.8%,	0.8%,	0.6%	The "gold standard" for the treatment of varicocele.	Most patients still need the help of advanced ARTS, such as the costly intracytoplasmic sperm injection (ICSI).

Patients, intervention, comparison and outcome strategy

Patients participants have been diagnosed with varicocele infertility, no restrictions on age, race, onset time.

Intervention: acupuncture (manual acupuncture, electro-acupuncture, warming needle moxibustion , auricular acupuncture and needle pricking)

Comparison: sham acupuncture, varicocelectomy, conventional drugs, Chinese herbal medicine.

Outcome A routine semen analysis (sperm concentration, motility and progression), the pregnancy rates, the reproductive endocrine hormone level (FSH, LH, PRL, et al.), the maximum internal diameter of spermatic vein (D_R) during calm breathing under color Doppler ultrasound, Determination of seminal plasma and trace elements (SOD, Zn, Cd), Adverse events of acupuncture interventions.

METHODS AND ANALYSIS

Study registration

Inclusion/ exclusion criteria for study selection

Type of studies

Inclusion criteria are as follow: (a) randomized controlled trials; (b) articles published in the English or Chinese will be included.

Exclusion criteria are as follow: (a) Case reports, animal studies; (b) Meta-analysis and systematic review, narrative review, overviews and conference abstract; (c) Studies in which the required data were unavailable.

Types of participants

Male participants have been diagnosed with varicocele infertility, no restrictions on race.

Inclusion criteria are as follow: (a) aged 22~50; (b) had unprotected, regular intercourse at least 1 year with a healthy partner; (c) had a unilateral clinical varicocele (Grade I–III).

Exclusion criteria are as follow: (a) Patients who had received acupuncture treatment or had taken Chinese herbal medicine in the previous three months; (b) bleeding disorders, genetic abnormalities, chronic inflammatory diseases and severe chronic diseases including cancer; (c) female partner was documented with infertility(including ovulatory, uterine, cervical dysfunction and pathology changes).

Types of interventions

Acupuncture therapy (manual acupuncture, electro-acupuncture, warming needle moxibustion , auricular acupuncture and needle pricking) versus sham acupuncture, varicocelectomy, conventional drugs or Chinese herbal medicine. Treatment groups using therapies other than acupuncture and moxibustion would be excluded. There is no restriction on the frequency of treatment.

Types of outcome measures

Primary outcome

A routine semen analysis (sperm concentration, motility and progression)

Secondary outcomes

1. The pregnancy rates.
2. The reproductive endocrine hormone level (FSH, LH, PRL, et al.).
3. The maximum internal diameter of spermatic vein (D_R) during calm breathing under color Doppler ultrasound.
4. Determination of seminal plasma and trace elements (SOD, Zn, Cd).
5. Adverse events of acupuncture interventions.

Search strategy

All relevant publications published from inception through February 2022 will be searched in four English-language databases (Embase, Cochrane Library, Pubmed, Web of Science) and four Chinese-language databases (China National Knowledge Infrastructure, China Science and Technology Journal Database, Chinese Biomedical Literature Database and Wanfang Data). Search for the following terms, "varicocele," "acupuncture therapy," and "randomized controlled trial". Languages are limited to English and Chinese literature. Our researchers will then screen this literature in EndNote software. The recommended full search strategy for PubMed is shown in Table 2.

Table 2 Search strategy for Pubmed database

Query	Search term
#1	Varicocele [MeSH]
#2	Varicoceles [MeSH]
#3	#1 OR #2
#4	Acupuncture [MeSH]
#5	Acupuncture [title/abstract] OR Pharmacoacupuncture [title/abstract] OR Acupotomy[title/abstract] OR Acupotomies [title/abstract] OR Needle [title/abstract] OR Needling[title/abstract] OR Dry-needling[title/abstract] OR Body-acupuncture [title/abstract] OR Electro-acupuncture [title/abstract] OR Auricular acupuncture [title/abstract] OR Manual acupuncture[title/abstract] OR Warming needle moxibustion [title/abstract] OR Warm acupuncture[title/abstract] OR Needle pricking[title/abstract]
#6	#4 OR #5
#7	Random?ed controlled trial[MeSH]
#8	#3 AND #6 AND #7

Searching other resources

The unpublished or ongoing randomized clinical trials will be searched on the International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, PROSEPERO and Chinese Clinical Registry (CHICTR). In addition, relevant references also need to be searched.

Data collection and analysis

Literature screening and data extraction

First, in accordance with the search strategy, two independent researchers imported the acquired articles into endnote and read through the titles and abstracts to identify articles that met the filtering criteria. Then the sieved literature will be read in full by two researchers for a further screening. If there is a discrepancy of opinion between the two researchers, a group discussion will be held and an experienced researcher and corresponding author will be invited to arbitrate the final

decision. Articles that have been excluded will be marked with their exclusion. The flow chart and selection process is shown in Figure 1.

The following data will be extracted separately by the two researchers, including: title, first author, year of publication, country, participants (number, age), random method, blinding, treatment group, control group, follow-up, outcome, results, adverse events, etc. If there are any missing details, our researcher will contact the corresponding author to make up for the lacking.

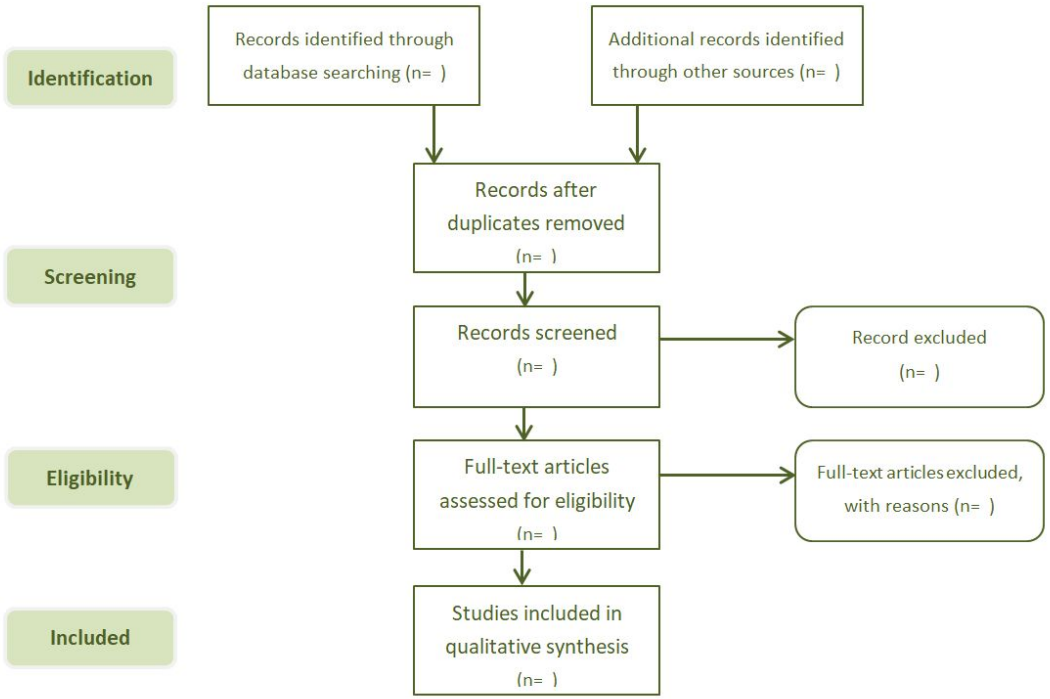

Figure 1 Flow diagram of the trial selection process.

Assessment of risk of bias

Two researchers will independently conduct risk of bias assessments for this study with Cochrane risk of bias (ROB) tool, and the sources of the seven types of bias (selection bias, performance bias, detection bias, attrition bias and reporting bias) will be assessed, with each type to be classified into one of the three levels (low, high and unclear risk of bias). At the end the eligible articles will be classified as low, high or unclear risk of bias based on the aggregation of all seven types of bias. The differences between the two researchers will be eventually arbitrated by the corresponding author.

Measures of treatment effect

If heterogeneity is low, then the fixed-effect model will be selected; instead, the random-effects model will be selected. Heterogeneity will always be present regardless of the sample size of the study, so we will switch our focus from examining the presence of heterogeneity to assessing the impact of heterogeneity on the meta-analysis. Our researchers will explore the sources of heterogeneity in four dimensions: population, intervention, outcome, study design and implementation, and will explain heterogeneity through subgroup analysis, meta-regression or sensitivity analysis.

Unit of analysis issues

In Unit of analysis issues, the level of randomization occurring will be fully considered in the light of the aggregated data.

Dealing with missing data

As noted above, if there is any necessary missing data, our researcher will contact the corresponding author to fill in the blanks. If missing data is not available, then sensitivity analysis will be conducted to address the issue of missing data and this issue will be addressed in the discussion section.

Assessment of heterogeneity

I^2 value will be applied to calculate statistical heterogeneity among these studies. If heterogeneity is little(I^2 50%), then the fixed-effect model will be selected. Instead, the random-effects model will be selected. Heterogeneity will always be present regardless of the sample size of the study, so we will switch our focus from examining the presence of heterogeneity to assessing the impact of heterogeneity on the meta-analysis. Our researchers will explore the sources of heterogeneity in four dimensions: population, intervention, outcome, study design and implementation, and will explain heterogeneity through subgroup analysis, meta-regression or sensitivity analysis.

Data synthesis

Based on some preliminary research, for the data synthesis section we will use the random-effects model. The input clinical data will be processed by the Review Manager software (RevMan) and the forest plot can be generated by this software to make the presentation of the study results more intuitive. The results of the study will be presented in tabular form, including key information on the quality of the evidence, the effect sizes of the interventions studied and the sum of the available data for all important outcomes for a given comparison.

Subgroup analysis and investigation of heterogeneity

Our researchers will explore the sources of heterogeneity in four dimensions: population, intervention, outcome, study design and implementation, and will explain heterogeneity through subgroup analysis, meta-regression or sensitivity analysis. Subgroup analysis will be used to interpret heterogeneity according to the type of acupuncture (manual acupuncture, electro-acupuncture, needle warming moxibustion and needle pricking) and the type of control (sham acupuncture, varicocelectomy, conventional drugs, Chinese herbal medicine).

Sensitivity analysis

Sensitivity analysis will be applied to assess the robustness of the study results. The specific implementation method will base on the "change model analysis" and the "exclusion of literature on a case-by-case basis". When heterogeneity is high ($I^2 > 50\%$) the random-effects model will be applied, otherwise, the fixed-effect model will be applied. When using the literature-by-exclusion method, any change in heterogeneity will be observed after the exclusion of each literature and the change in the value of the combined effect, WMD, RR need to be recorded at the same time. If heterogeneity changes after the exclusion of a piece of literature, then that piece of literature may be the source of the heterogeneity.

Assessment of reporting biases

If the number of studies is more than 10, our researchers will use funnel plots to detect reporting bias; if not, the reporting biases is not necessary. Our study will try to avoid reporting bias as much as possible by conducting a comprehensive search for studies that meet the inclusion criteria, integrating unpublished studies and searching the trial registries.

Summary of evidence

Our researchers will use the Grading of Recommendation Assessment, Development and Evaluation (GRADE system) to assess the quality of the evidence for the results reported in systematic reviews. The system requires an assessment of the quality of evidence for each individual outcome. The assessment includes limitations

in the design and implementation of available studies suggesting high likelihood of bias, unexplained heterogeneity or inconsistency of results, indirectness of evidence, imprecision of results and high probability of publication bias.

Patient and public involvement

As mentioned, this study is a secondary study based on clinical studies so it does not involve any patient and public.

DISCUSSION

Varicocele is one of the most common causes of male infertility. The exact mechanism by which VC may affect spermatogenesis remains obscure, [3] but some recent literature can conclude that VC can affect fertility by affecting testicular histology, sperm function, semen quality and reproductive hormones[5 6]. As all surgical methods have some potential for recurrence and complications. Non-surgical treatments have attracted the interest of clinicians and acupuncture is increasingly being used to relieve VC. This systematic evaluation will assess evidence from randomized controlled trials to demonstrate the effectiveness and safety of acupuncture in the treatment of VC. The aim is to provide more effective and safe treatment options for clinical practice. The potential limitations of this study may have some impact on the results. The non-inclusion of studies published in languages other than English and Chinese may result in limitations related to publication bias. Multiple types of acupuncture therapies may have the potential to increase the risk of heterogeneity.

Contributors

WSJ and TZA participated in the research design. DJ and WCY conducted a literature search and screened data extraction. SMM and CJN did some statistical analysis. WSJ conceived the review protocol and drafted the manuscript. Several studies from different opinions were determined by TZA. SHS, RJJ and ZGM participated in the correction of the manuscript. All authors reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests None declared.

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

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed. this is a protocol without data.

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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	Reported on 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	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	10
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	2-3
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2
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 characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
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	5
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	5-6

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6-7
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)	7-9
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	7
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	7-8
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 I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9-10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9-10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9-10

*** 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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Safety and Efficacy of Acupuncture for Varicocele-Induced Male Infertility: A systematic review protocol

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Safety and Efficacy of Acupuncture for Varicocele-Induced Male Infertility: A systematic review protocol

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ABSTRACT

Introduction

Varicocele (VC) is a common clinical disease in andrology. Among a number of ways for VC treatment, surgery is the most common one, but the measurable benefit of surgical repair was slight. A growing exploration of complementary therapies has been conducted in clinical research on acupuncture for VC, but there is no relevant systematic review and meta-analysis to assess the efficacy and safety of acupuncture for VC.

Methods and analysis

All relevant publications published from database inception through August 2022 will be searched in three English-language databases (Embase, CENTRAL, MEDLINE) and four Chinese-language databases (China National Knowledge Infrastructure, China Science and Technology Journal Database, Chinese Biomedical Literature Database and Wanfang Data). Randomized controlled trials (RCTs) in English and Chinese concerned with acupuncture for patients with varicocele will be included. The input clinical data will be processed by the Review Manager software (RevMan). The literature will be appraised with the Cochrane Collaboration risk of bias tool. The Grading of Recommendations Assessment, Development and Evaluation system (GRADE system) will be used to evaluate the quality of evidence.

Ethics and dissemination

This study is a secondary study based on clinical studies so it does not relate to any individual patient information or infringe the rights of participants. Hence no ethical approval is required. The results will be reported in peer-reviewed journals or disseminated at relevant conferences.

Registration number

PROSPERO registration number: CRD42022316005.

Strengths and limitations of this study

►The data extraction and management, assessment of risk of bias sections will be carried out by two or more researchers independently.

►Multiple types of acupuncture therapies may increase the risk of heterogeneity, this will be further explored in the subgroup analysis.

►The exclusion of studies published in languages other than English and Chinese may result in limitations related to publication bias.

INTRODUCTION

Varicocele (VC) is regarded as the abnormal dilation of the internal testicular vein and pampiniform venus plexus within the spermatic cord, which is one of the most common causes of male infertility. It accounts for 35% of patients with primary infertility and up to 81% with secondary infertility.[1 2]

In addition to affecting fertility, VC may also cause symptoms such as enlargement of the scrotum, swelling, dull aching pain and cramping in the lower abdomen, which can be exacerbated by prolonged standing, walking or heavy physical work. Several theories explain the role of varicocele in terms of pathophysiology, including altered testicular blood flow, increased temperature, oxidative stress, development of anti-sperm antibodies, reflux of adrenal and gonadal hormone metabolites and alterations in the hypothalamic-pituitary-gonadal axis.[3] The precise mechanism by which VC potentially affects spermatogenesis remains unclear,[4 5] but some recent documents allows for the conclusion that VC can injure fertility by affecting testicular histology, sperm function, semen quality and reproductive hormones.[5-7] Currently surgery remains the main treatment option for VC, which includes surgical treatment and interventional treatment. Surgical treatments for VC include the traditional inguinal or high retroperitoneal ligation, laparoscopic repair and microsurgical repair via an inguinal or subinguinal incision and embolization.[8-10] However there is some possibility of recurrence and complications with different surgical techniques (Table 1); besides, the measurable benefit of surgical repair was slight according to the Cochrane review[11]. The recurrence rate varies depending on the technique of varicocele repair, ranging from 0% to 35% and the incidence of post-operative hydrocele formation varies from 0% to 29%.[12 13] For patients with mild symptoms, conventional medications such as clomiphene citrate and levocarnitine are often used. These drugs mainly work by promoting sperm maturation, improving semen quality and dilating blood vessels. However, it cannot fundamentally address the

anatomical basis of the disease, so the overall outcome is often unsatisfactory.[14-17]

Therefore, there is an urgent need to develop complementary therapies. Known as a safe therapy with low side effects, acupuncture has already been widely used in the treatment of VC. The incidence of adverse reactions to acupuncture is significantly lower than other drugs or other conventional medical procedures under the same conditions, which is one of the significant advantages of acupuncture.[18] Specific acupuncture methods that have been used clinically include manual acupuncture, electro-acupuncture, needle warming moxibustion and needle pricking, etc. Acupuncture treatment for VC may have a therapeutic effect on VC by lowering the scrotal skin temperature of patients,[19] and inhibiting patient's oxidative stress process,[20 21] and adjust patients' serum testosterone (T) and follicle stimulating hormone (FSH) by stimulating the sympathetic trunk and regulating endocrine and gonadal axis function.[22-25] Also, it can increase the blood flow and vasodilatory elasticity of spermatic veins in patients with VC infertility improve the blood circulation and relieve VC by lowering the viscosity of blood flow[25] and mitigate muscle tissue spasm and ischaemia by regulating pathologically tight muscles. It may touch on the anatomical basis of the disease, more specific and deeper mechanisms of action need to be explored in further studies.

At present, there are a certain number of documents on acupuncture treatment of VC. These experimental and theoretical studies on the improvement of treating VC by acupuncture can provide preliminary evidence that acupuncture is effective in treating varicocele-induced male infertility, but there still lacks a systematic review is still lacking. Therefore, this paper is to evaluate the safety and efficacy of acupuncture in the treatment of VC.

Table 1 Postoperative spontaneous pregnancy rates, recurrence rates, hydrocele formation rates among the techniques

Technique	Spontaneous pregnancy rate	Recurrence rate	Hydrocele formation rate	Advantages	Disadvantages
Palomo[26-29]	37.69%	14.97%	8.24%	Good for pain relief , shorter surgery time.	Highest recurrence rate and hydrocele formation rate.
Laparoscopic varicocelectomy[26 28-30]	30.07%	4.3%	2.84%	Suitable for bilateral varicocele and recurrent varicocele. Less invasive surgery, faster recovery and fewer complications.	May cause damage to intestines and blood vessels. Requires high level of surgical skills, anaesthesia and is more expensive.
Radiologic embolization[26 29 31 32]	33.2%	12.7%	0%-12%	Less damage and faster recovery. No accidental injury to the internal	Potential risks of radiation exposure, misplaced embolism and displacement of embolic agents.

				spermatic artery.	
Mcroscopic inguinal (Ivanissevich) [26 33-35]	36%	2.63%	7.3%	More effective in improving sperm concentration.	Increased chance of arterial and lymphatic vessel damage, requiring more surgical skill.
Microsurgical varicocelectomy[10 26 30 36 37]	41.97%	1.05%-2.60%	0.44%	Relatively good efficacy and low recurrence and complication rates. Better control of post-operative pain.	Less than 40% of infertile couples achieve spontaneous pregnancy after microsurgical varicocelectomy, and most of them still require additional interventions such as advanced assisted reproductive technologies (ARTS).
Subinguinal microsurgical varicocclectomy[1 32 35]	42.8%,	0.8%,	0.6%。	The "gold standard" for the treatment of varicocele.	Most patients still need the help of advanced ARTS, such as the costly intracytoplasmic sperm injection (ICSI).

METHODS AND ANALYSIS

Study registration

The protocol was registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), and the registration number is: CRD42022316005.

Criteria for included studies in this review

Type of studies

Inclusion criteria are as follows: (a) Randomized controlled trials; (b) Articles published in the English or Chinese will be included.

Exclusion criteria are as follows: (a) Case reports, animal studies; (b) Meta-analysis and systematic review, narrative review, overviews and conference abstract; (c) Studies in which the required data were unavailable.

Types of participants

Taking into account the fact that the childbearing age of men varies in different countries and regions, we have adjusted the age limit appropriately. In addition , unilateral varicocele is more common in clinical practice, but there are also a small number of patients with bilateral varicocele, both with similar pathogenesis. To fully demonstrate the efficacy and safety of acupuncture as a complementary alternative therapy in improving the condition of patients with VC, RCTs containing a

small number of patients with bilateral varicocele will also be included. To ensure the practicability of the study, we allow for deviations within reasonable limits. If an included RCT partially deviates from the criteria below, we will decide whether to include the RCT after panel discussion.

Inclusion criteria are as follows: (a) Male participants diagnosed with varicocele infertility, regardless of restriction on racial origin. (b) Male participants aged 18-55 years old. (c) The couple in question having at least 12 months of infertility.

Exclusion criteria are as follow: (a) Patients who had received acupuncture treatment or had taken Chinese herbal medicine in the previous three months; (b) Bleeding disorders, genetic abnormalities, chronic inflammatory diseases and severe chronic diseases including cancer; (c) Female partner documented with infertility (including ovulatory, uterine, cervical dysfunction and pathological changes). (d) The presence of other causes of infertility in male patients.

Types of interventions

Acupuncture therapy includes body acupuncture (manual/electric acupuncture), warm acupuncture, auricular acupuncture, acupoint catgut embedding, needle picking and other acupuncture techniques, where needles are used to penetrate acupoints, pain points or trigger points, etc. However, non-penetrating forms of stimulation of acupuncture points, such as moxibustion, acupressure or transcutaneous electrical nerve stimulation, will be excluded. Acupuncture combined with other positive treatments will also be included. There is no restriction on the frequency of treatment.

The included comparators or control groups will be considered as follows:

1. Acupuncture versus sham acupuncture.
2. Acupuncture versus surgical control.
3. Acupuncture versus conventional medication/herbal medicine.
4. Acupuncture plus positive treatment versus positive treatment alone.

Studies aiming to compare different acupuncture points, different methods of acupoint stimulation, and different frequencies and durations of treatment were excluded.

Types of outcome measures

Primary outcome

A routine semen analysis (semen volume, sperm density, sperm viability, sperm deformity rate, sperm DNA fragmentation index)

Secondary outcomes

1. The pregnancy rates.
2. The maximum internal diameter of spermatic vein (D_R) during calm breathing under color Doppler ultrasound.
3. The reproductive endocrine hormone level (FSH, LH, PRL, et al.).

4. Adverse events such as local haematomas, haematuria and syncope induced by acupuncture interventions.

Search strategy

All relevant publications published from database inception through August 2022 will be searched in three English-language databases: Embase, CENTRAL (The Cochrane Central Register of Controlled Trials), MEDLINE and four Chinese-language databases: China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP Database), Chinese Biomedical Literature Database (SinoMed) and Wanfang Data. We will search the above databases using a combination of MeSH terms and free words, using the following terms: (1) Varicocele. (2) Acupuncture therapy, acupuncture, electro-acupuncture, manual acupuncture, auricular acupuncture, needle picking, warm acupuncture and acupoint. (3) Randomized controlled trial, RCT, randomized controlled, clinical trial. Languages are limited to English and Chinese. The researchers will then screen these literatures with EndNote software. The same Chinese search strategy, properly tuned where needed, will also be used for searches in Chinese databases. For small registries or registries with limited search tools, searches in the registry will be based on disease terms only. The recommended full search strategy for MEDLINE is shown in Table 2. Full search strategies for all databases, registers and websites are shown in supplementary file.

Table 2 Medline (via Ovid) search strategy

PI(CO)S	#	Search
Population	#1	exp Varicocele/
	#2	exp Infertility, Male/
	#3	((male* or men) adj7 (infertil* or subfertil*)).tw.
	#4	(Varicocele* or Varicocoele*).tw.
	#5	(varicocele or varicocoele or varicoceles or spermatic vein varicosity or varicose spermatic veins or pampinocele or spermophlebectasia or cirsocele or varicole or ramex).tw.
	#6	or/1-5
Intervention	#7	exp Acupuncture/
	#8	exp Acupuncture Therapy/ or exp Electroacupuncture/ or acupuncture needle.mp.
	#9	exp Acupressure/

	#10	acupoint.mp. or exp Acupuncture Points/
	#11	needle pricking.mp.
	#12	warming needle moxibustion.mp.
	#13	(acupunctur* or acupressur*).tw.
	#14	(electrostimulat* or electroacupunctur*).tw.
	#15	(acupoint* or acupotom*).tw.
	#16	(auriculotherap* or auriculoacupunct*).tw.
	#17	(needl* or needl* prick*).tw.
	#18	body needl*.tw.
	#19	dry needl*.tw.
	#20	warm* needle moxibustion.mp. or warm* acupuncture.tw. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	#21	meridian*.tw.
	#22	qi.tw.
	#23	or/7-22
Study design	#24	randomized controlled trial.pt.
	#25	controlled clinical trial.pt.
	#26	randomized.ab.
	#27	placebo.ab.
	#28	drug therapy.fs.
	#29	clinical trials as topic.sh.
	#39	randomly.ab.

	#31	trial.ti.
	#32	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
	#33	exp animals/ not humans.sh.
	#34	32 not 33
	#35	6 and 23 and 34

Searching other resources

The unpublished or ongoing randomized clinical trials will be searched on the International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, PROSEPERO and Chinese Clinical Registry (CHICTR). In addition, relevant references will also be searched.

Data collection and analysis

Literature screening and data extraction

First, in accordance with the search strategy, two independent researchers imported the acquired articles into Endnote and read through the titles and abstracts to identify articles that met the filtering criteria. Then the included literature will be read in full by two researchers for a further screening. In case of a discrepancy of opinion between the two researchers, a group discussion will be held and an experienced researcher and corresponding author will be invited to arbitrate the final decision. Articles that have been excluded will be marked with the reason of their exclusion. The flow chart and selection process is shown in Figure 1.

The following data will be extracted separately by the two researchers, including: Title, first author, year of publication, country, participants (number, age), random method, blinding, treatment group, control group, follow-up, outcome, results, and adverse events, etc. If there is any missing detail or unclear aspect of the presentation, the researchers will contact the corresponding author to make the supplementation or clarification accordingly.

Figure 1 Flow diagram of the trial selection process.

Assessment of risk of bias

Two researchers will independently assess the risk of bias for this study using the latest version of the Cochrane risk-of-bias tool 2 (ROB 2)[38] and will assess bias from five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results). The risk of bias will be judged (low/high/some concerns) and the overall risk of bias of the assessment results will be predicated. The differences between the two

researchers will be eventually resolved by the corresponding author. If a RCT was judged to have "some concerns" about the risk of bias in three or more domains, it was excluded from the systematic review due to the high risk of bias.

Measures of treatment effect

Data will be entered into RevMan software (RevMan V.5.4) for synthesis and statistical analysis. 95% CI for relative risk will be used for analysis of dichotomous variables (e.g. adverse events for acupuncture interventions). Continuous variables (e.g. semen analysis results, reproductive endocrine hormone level) will be analyzed using the 95% CI for weighted mean difference (WMD) or standard mean difference (SMD).

The issue concerning the unit of analysis

As for the issue concerning the unit of analysis[39], if the included RCTs have more than two intervention groups that are relevant to the systematic review/ particular meta-analysis, then the multiple groups qualified for experimental or comparator interventions will be combined to form a single pair-wise comparison to overcome the unit of analysis error. For dichotomous results, both the sample size and the number of people who had an adverse event can be summed across groups. For continuous results, means and standard deviations can be combined using the method described.

Dealing with missing data

As noted above, if there is any essential data missing, our researcher will contact the corresponding author to fill in the blanks. If the missing data is not recoverable, then sensitivity analysis will be conducted to address the issue of missing data. This will be elaborated in the discussion section.

Heterogeneity assessment

Heterogeneity assessment of all studies will be performed by RevMan. Statistical heterogeneity between studies will be calculated using I^2 values. To explore potential sources of heterogeneity, sensitivity analysis or subgroup analysis will be used for assessment.

Data synthesis

Based on some preliminary research, we will use the random-effects model for the data synthesis section. The input clinical data will be processed by the RevMan and the forest plot can be generated by this software to make the presentation of the study results more understandable. The results of the study will be presented in tabular form, including key information on the quality of the evidence, the effect sizes of the interventions and the sum of the available data for all important

outcomes for a given comparison.

Subgroup analysis and investigation of heterogeneity

A random effects model will be used since individual RCTs were conducted in different locations and there will be certainly discrepancy across different experimental protocols, and among different groups of patients. Heterogeneity will always be present regardless of the sample size of the study, so we will switch our focus from examining the presence of heterogeneity to assessing the impact of heterogeneity on the meta-analysis. Our researchers will explore the sources of heterogeneity in four dimensions: Population, intervention, outcome, study design and implementation, and will explain heterogeneity through subgroup analysis, meta-regression or sensitivity analysis. If sufficient studies are identified, subgroup analyses can be performed among different types of acupuncture methods, as well as different follow-up times, types of controls or intensity of treatment.

Sensitivity analysis

Sensitivity analysis will be applied to assess the robustness of the study results. The specific implementation method will be based on the "change model analysis" and the "exclusion of literature on a case-by-case basis". When using the literature-by-exclusion method, any change in heterogeneity will be observed after the exclusion of each literature, and the change in the value of the combined effect, WMD, RR need to be recorded at the same time. If heterogeneity changes after the exclusion of a piece of literature, then that piece of literature may be the source of the heterogeneity.

Assessment of reporting biases

If the number of studies is more than 10, our researchers will use funnel plots to detect reporting bias; if not, the reporting bias detection is not necessary. Our study will try to avoid reporting bias as much as possible by conducting a comprehensive search for studies that meet the inclusion criteria by incorporating unpublished studies and searching the trial registries.

Summary of evidence

Our researchers will use the Grading of Recommendation Assessment, Development and Evaluation (GRADE system) to assess the quality of the evidence for the results reported in systematic reviews. The system requires an assessment of the quality of evidence for each individual outcome. The assessment includes limitations in the design and implementation of available studies, suggesting that there is high likelihood of bias, unexplained heterogeneity or inconsistency of results, indirectness of evidence, imprecision of results and high probability of publication biases.

Patient and public involvement

As mentioned, this study is a secondary study based on clinical studies so it does not involve any patient or the public.

DISCUSSION

Varicocele is one of the most common causes of male infertility although it can occur without causing infertility. In mild cases, there may be no obvious clinical symptoms; however, in severe cases, there may be a sensation of swelling or dull pain in the scrotum, which worsens after prolonged standing and exertion and mitigates or disappears after lying down or resting. Considering that some patients with varicocele may not seek medical help because they have no need for fertility or their discomfort has little impact on their daily lives, our study was limited to recruiting patients with varicocele-induced infertility. The exact mechanism by which VC may affect spermatogenesis remains obscure, [4] but some recent literature can conclude that VC can affect fertility by influencing testicular histology, sperm function, semen quality and reproductive hormones[6 7]. As all surgical methods have some potential risks of recurrence and complications,non-surgical treatments have attracted the interest of clinicians and acupuncture is increasingly being used to relieve VC. This systematic evaluation will assess evidence from randomized controlled trials to demonstrate the effectiveness and safety of acupuncture in the treatment of VC. The aim is to provide more effective and safe treatment options for clinical practice. The potential limitations of this study may have some impact on the results. The exclusion of studies published in languages other than English and Chinese may result in publication bias, and the adoption of multiple types of acupuncture therapies may have the potential to increase the risk of heterogeneity.

Amendments to protocol

To ensure transparency, any change from this protocol will be amended on the PROSPERO database.

Ethics and dissemination

This study is a secondary study based on clinical studies, and thus it is unnecessary to obtain ethical approval. The results will be reported in peer-reviewed journals or disseminated at relevant conferences.

Contributors

WSJ, TZA and ZGM participated in the research design. LRC, RJJ and CJN developed the search strategies. LRC, WCY and LQ implemented the search strategies and screened data extraction. LRC, SMM and DJ did some statistical analysis. WSJ conceived the review protocol and drafted the manuscript. Several studies from

different opinions were determined by TZA. WSJ, LRC and SHS participated in the correction of the manuscript. All authors reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed. This is a protocol without data.

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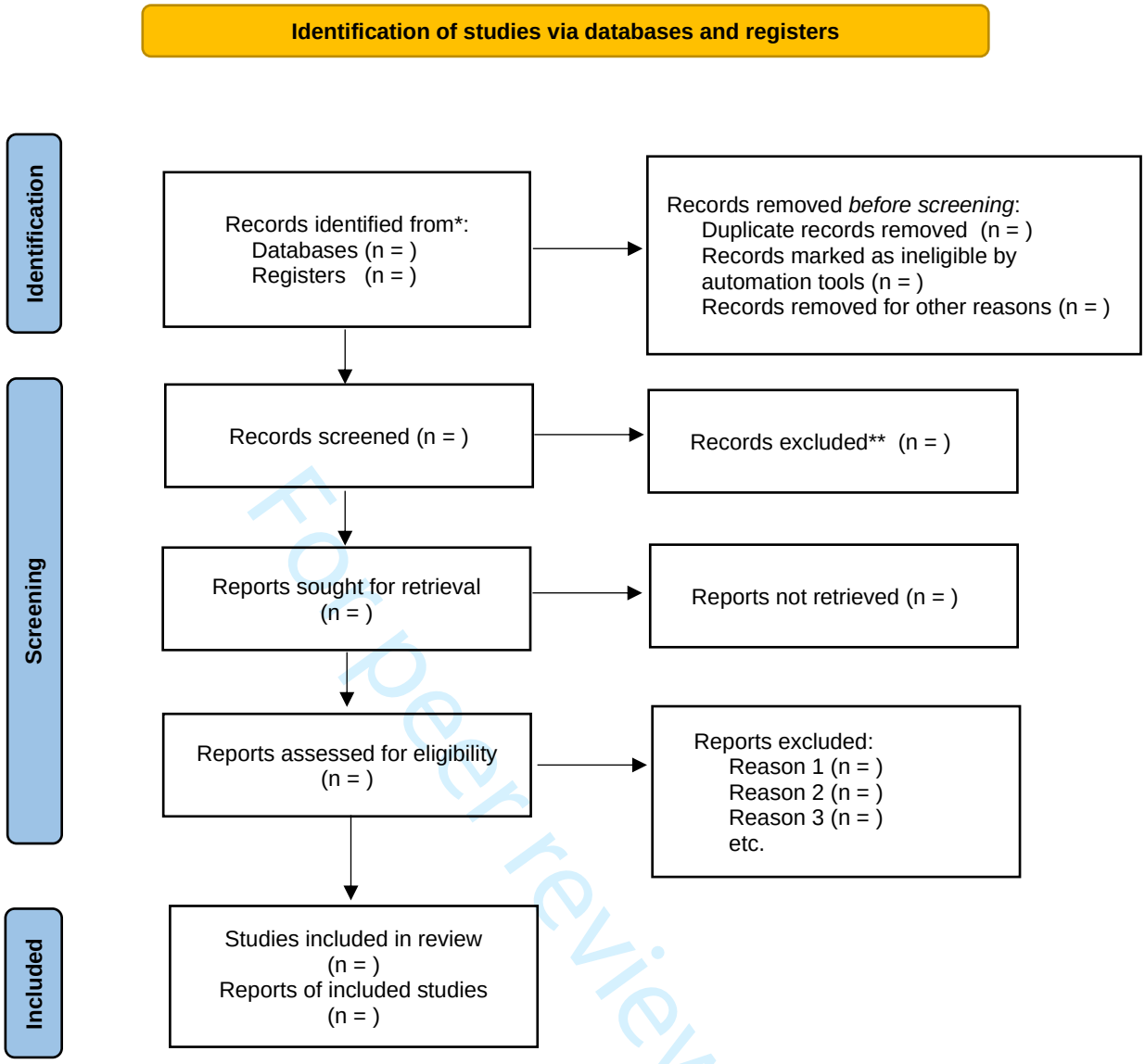

MEDLINE via Ovid

PI(CO)S	#	Search
Population	#1	exp Varicocele/
	#2	exp Infertility, Male/
	#3	((male* or men) adj7 (infertil* or subfertil*)).tw.
	#4	(Varicocele* or Varicocoele*).tw.
	#5	(varicocele or varicocoele or varicoceles or spermatic vein varicosity or varicose spermatic veins or pampinocele or spermophlebectasia or cirsocele or varicole or ramex).tw.
	#6	or/1-5
Intervention	#7	exp Acupuncture/
	#8	exp Acupuncture Therapy/ or exp Electroacupuncture/ or acupuncture needle.mp.
	#9	exp Acupressure/
	#10	acupoint.mp. or exp Acupuncture Points/
	#11	needle pricking.mp.
	#12	warming needle moxibustion.mp.
	#13	(acupunctur* or acupressur*).tw.
	#14	(electrostimulat* or electroacupunctur*).tw.
	#15	(acupoint* or acupotom*).tw.
	#16	(auriculotherap* or auriculoacupunct*).tw.
	#17	(needl* or needl* prick*).tw.
	#18	body needl*.tw.
	#19	dry needl*.tw.
	#20	warm* needle moxibustion.mp. or warm* acupuncture.tw. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	#21	meridian*.tw.
	#22	qi.tw.
	#23	or/7-22
Study design	#24	randomized controlled trial.pt.
	#25	controlled clinical trial.pt.
	#26	randomized.ab.
	#27	placebo.ab.
	#28	drug therapy.fs.
	#29	clinical trials as topic.sh.
	#39	randomly.ab.
	#31	trial.ti.
	#32	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
	#33	exp animals/ not humans.sh.

	#34	32 not 33
	#35	6 and 23 and 34

EMBASE

PI(CO)S	#	Search
Population	#1	'varicocele'/exp
	#2	'male infertility'/exp
	#3	varicocele*:ab,ti OR varicocoele*:ab,ti
	#4	('male* infertil*'):ab,ti OR (('men infertil*'):ab,ti) OR (('male* subfertil*'):ab,ti) OR (('men subfertil*'):ab,ti)
	#5	(Varicocele):ab,ti OR ((varicocoele):ab,ti) OR ((varicoceles):ab,ti) OR (('spermatic vein varicosity'):ab,ti) OR ((varicose):ab,ti) OR (('spermatic vein*'):ab,ti) OR ((pampinocele):ab,ti) OR ((spermophlebectasia):ab,ti) OR ((cirsocele):ab,ti) OR ((varicole):ab,ti) OR ((ramex):ab,ti)
	#6	#1 OR # OR #2 OR #3 OR #4 OR #5
Intervention	#7	'acupuncture'/exp
	#8	'acupuncture needle'/exp
	#9	'acupressure'/exp
	#10	'acupoint'/exp
	#11	'needle pricking'/exp
	#12	'warming needle moxibustion'/exp
	#13	acupunctur*:ab,ti OR acupressur*:ab,ti
	#14	(electro* NEAR/1 (stimulat* OR acupunctur*)):ab,ti
	#15	electrostimulat*:ab,ti OR electroacupunctur*:ab,ti
	#16	acupoint*:ab,ti OR acupotom*:ab,ti
	#17	auriculotherap*:ab,ti OR auriculoacupunct*:ab,ti
	#18	needl*:ab,ti
	#19	('needl* prick*'):ab,ti
	#20	(body NEXT/1 needl*):ab,ti
	#21	(dry NEXT/1 needl*):ab,ti
	#22	('warm* needle moxibustion'):ab,ti OR ('warm* acupuncture'):ab,ti
	#23	meridian*:ab,ti
	#24	qi:ab,ti
	#25	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
Study design	#26	'randomized controlled trial'/de
	#27	'controlled clinical trial'/de
	#28	random*:ti,ab,tt
	#29	randomization'/de

	#30	'intermethod comparison'/de
	#31	placebo:ti,ab,tt
	#32	(compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)
	#33	((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
	#34	(open NEXT/1 label):ti,ab,tt
	#35	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
	#36	'double blind procedure'/de
	#37	(parallel NEXT/1 group*):ti,ab,tt
	#38	(crossover:ti,ab,tt OR 'cross over':ti,ab,tt)
	#39	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt
	#40	(assigned:ti,ab,tt OR allocated:ti,ab,tt)
	#41	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt
	#42	(volunteer:ti,ab,tt OR volunteers:ti,ab,tt)
	#43	'human experiment'/de
	#44	trial:ti,tt
	#45	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44
	#46	(((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))
	#47	('cross - sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))
	#48	('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))
	#49	('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt))
	#50	(nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)
	#51	'random field*':ti,ab,tt
	#52	('random cluster' NEAR/4 sampl*):ti,ab,tt
	#53	(review:ab AND review:it) NOT trial:ti,tt

	#54	('we searched':ab AND (review:ti,tt OR review:it))
	#55	'update review':ab
	#56	(databases NEAR/5 searched):ab
	#57	((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)
	#58	('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
	#59	34 #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58
	#60	#45 NOT #59
	#61	#6 AND #25 AND #60

Central Register of Controlled Trials (CENTRAL) via Cochrane Library

PI(CO)S	#	Search
Population	#1	MeSH descriptor: [varicocele] explode all trees
	#2	MeSH descriptor: [Infertility, Male] explode all trees
	#3	(varicocele*):ti,ab,kw OR (varicocoele*):ti,ab,kw
	#4	(male* infertil*):ti,ab,kw OR (men infertil*):ti,ab,kw OR (men subfertil*):ti,ab,kw OR (male* subfertil):ti,ab,kw
	#5	(varicocele):ti,ab,kw OR (varicocoele):ti,ab,kw OR (varicoceles):ti,ab,kw OR (spermatic vein varicosity):ti,ab,kw OR (varicose spermatic veins):ti,ab,kw
	#6	(pampinocele):ti,ab,kw OR (spermophlebectasia):ti,ab,kw OR (cirsocele):ti,ab,kw OR (varicole):ti,ab,kw OR (ramex):ti,ab,kw
	#7	#1 OR # OR #2 OR #3 OR #4 OR #5 OR #6
Intervention	#8	MeSH descriptor: [Acupuncture] explode all trees
	#9	MeSH descriptor: [Acupressure] explode all trees
	#10	MeSH descriptor: [Acupuncture Points] explode all trees
	#11	(acupressur*):ti,ab,kw OR (acupunctur*):ti,ab,kw
	#12	(electro* NEAR/1 stimulat*):ti,ab,kw OR (electro* NEAR/1 acupunctur*):ti,ab,kw
	#13	(electrostimulat*):ti,ab,kw OR (electroacupunctur*):ti,ab,kw
	#14	(acupoint*):ti,ab,kw OR (acupotom*):ti,ab,kw
	#15	(auriculotherap*):ti,ab,kw OR (auriculoacupunct*):ti,ab,kw
	#16	(needl*):ti,ab,kw
	#17	(needl* prick*):ti,ab,kw
	#18	(body NEXT/1 needl*):ti,ab,kw

	#19	(dry NEXT/1 needl*):ti,ab,kw
	#20	(warm* needle moxibustion):ti,ab,kw OR (warm* acupuncture):ti,ab,kw
	#21	(meridian*):ti,ab,kw
	#22	(qi):ti,ab,kw
	#23	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
Study design	#24	MeSH descriptor: [randomized controlled trial] explode all trees
	#25	MeSH descriptor: [controlled clinical trial] explode all trees
	#26	MeSH descriptor: [clinical trial] explode all trees
	#27	random*:ti,ab,kw
	#28	placebo:ti,ab,kw
	#29	trial:ti,ab,kw
	#30	#24 OR #25 OR #26 OR #27 OR #28 OR #29
	#31	MeSH descriptor: [animal] explode all trees
	#32	#30 NOT #31
	#33	#7 AND #23 AND #32

China National Knowledge Infrastructure(CNKI)

(TKA='针灸' OR TKA='针刺' OR TKA='温针' OR TKA='电针' OR TKA='针挑') AND (TKA='精索静脉曲张') AND TKA='随机'

Filter by: synonym expansion

China Science and Technology Journal Database (VIP Database)

(M=针灸 OR 针刺 OR 温针 OR 电针 OR 针挑) AND (M=精索静脉曲张) AND (R=随机)

Chinese Biomedical Literature Database (SinoMed)

("随机"[常用字段:智能]) AND ("精索静脉曲张"[常用字段:智能]) AND ("针灸"[常用字段:智能] OR "针刺"[常用字段:智能] OR "温针"[常用字段:智能] OR "电针"[常用字段:智能] OR "针挑"[常用字段:智能])

Wanfang Data

(((摘要=随机)) AND (题名或关键词=精索静脉曲张)) AND ((((((题名或关键词=针刺) OR 题名或关键词=针灸) OR 题名或关键词=温针) OR 题名或关键词=电针) OR 题名或关键词=针挑))

International Clinical Trials Registry Platform (ICTRP)

Condition: varicocele* OR varicocoele OR spermatic vein varicosity OR varicose spermatic vein* OR varicole

Intervention: acupuncture OR acupoint OR needl* prick* OR electroacupunctur* OR warm* needl* moxibustion

ClinicalTrials.gov

Condition or disease: "varicocele" OR "varicocoele" OR "spermatic vein varicosity" OR "varicose spermatic veins" OR "varicole"

Other terms: "acupuncture" OR "acupoint OR "needle pricking" OR "electroacupuncture" OR "warming needle moxibustion"

Chinese Clinical Registry (CHICTR)

Target disease: varicocele

PROSEPERO

Search bar: varicocele

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	Reported on 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	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	11-12
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	11
Support:			
Sources	5a	Indicate sources of financial or other support for the review	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	11-12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2-3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2
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	4-5
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	6-8
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	6-7

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	5
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
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	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	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)	9
	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)	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.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Safety and Efficacy of Acupuncture for Varicocele-Induced Male Infertility: A systematic review protocol

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Reproductive medicine, Urology, Complementary medicine
Keywords:	COMPLEMENTARY MEDICINE, GENITOURINARY MEDICINE, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Safety and Efficacy of Acupuncture for Varicocele-Induced Male Infertility: A systematic review protocol

Sijia Wang[1△], Rongchen Lu[2△], Hongshuo Shi[2], Jiangnan Chen[1], Miaomiao Sun[1], Jing Ding[1], Qiang Lv [1], Chenyao Wang[1], Jianjun Ren[1], Guangming Zhou[1*], Zhian Tang[1*].

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*These authors have contributed equally to this work.

ABSTRACT

Introduction

Varicocele (VC) is a common clinical disease in andrology. Among a number of ways for VC treatment, surgery is the most common one, but the measurable benefit of surgical repair was slight. A growing exploration of complementary therapies has been conducted in clinical research on acupuncture for VC, but there is no relevant systematic review and meta-analysis to assess the efficacy and safety of acupuncture for VC.

Methods and analysis

All relevant publications published from database inception through August 2022 will be searched in three English-language databases (Embase, CENTRAL, MEDLINE) and four Chinese-language databases (China National Knowledge Infrastructure, China Science and Technology Journal Database, Chinese Biomedical Literature Database and Wanfang Data). Randomized controlled trials (RCTs) in English and Chinese concerned with acupuncture for patients with varicocele will be included. The input clinical data will be processed by the Review Manager software (RevMan). The literature will be appraised with the Cochrane Collaboration risk of bias tool. The Grading of Recommendations Assessment, Development and Evaluation system (GRADE system) will be used to evaluate the quality of evidence.

Ethics and dissemination

This study is a secondary study based on clinical studies so it does not relate to any individual patient information or infringe the rights of participants. Hence no ethical approval is required. The results will be reported in peer-reviewed journals or disseminated at relevant conferences.

Registration number

PROSPERO registration number: CRD42022316005.

Strengths and limitations of this study

►The data extraction and management, assessment of risk of bias sections will be carried out by two or more researchers independently.

►Multiple types of acupuncture therapies may increase the risk of heterogeneity, this will be further explored in the subgroup analysis.

►The exclusion of studies published in languages other than English and Chinese may result in limitations related to publication bias.

INTRODUCTION

Varicocele (VC) is regarded as the abnormal dilation of the internal testicular vein and pampiniform venus plexus within the spermatic cord, which is one of the most common causes of male infertility. It accounts for 35% of patients with primary infertility and up to 81% with secondary infertility.[1 2]

In addition to affecting fertility, VC may also cause symptoms such as enlargement of the scrotum, swelling, dull aching pain and cramping in the lower abdomen, which can be exacerbated by prolonged standing, walking or heavy physical work. Several theories explain the role of varicocele in terms of pathophysiology, including altered testicular blood flow, increased temperature, oxidative stress, development of anti-sperm antibodies, reflux of adrenal and gonadal hormone metabolites and alterations in the hypothalamic-pituitary-gonadal axis.[3] The precise mechanism by which VC potentially affects spermatogenesis remains unclear,[4 5] but some recent documents allows for the conclusion that VC can injure fertility by affecting testicular histology, sperm function, semen quality and reproductive hormones.[5-7] Currently surgery remains the main treatment option for VC, which includes surgical treatment and interventional treatment. Surgical treatments for VC include the traditional inguinal or high retroperitoneal ligation, laparoscopic repair and microsurgical repair via an inguinal or subinguinal incision and embolization.[8-10] However there is some possibility of recurrence and complications with different surgical techniques (Table 1); besides, the measurable benefit of surgical repair was slight according to the Cochrane review[11]. The recurrence rate varies depending on the technique of varicocele repair, ranging from 0% to 35% and the incidence of post-operative hydrocele formation varies from 0% to 29%.[12 13] For patients with mild symptoms, conventional medications such as clomiphene citrate and levocarnitine are often used. These drugs mainly work by promoting sperm maturation, improving semen quality and dilating blood vessels. However, it cannot fundamentally address the

anatomical basis of the disease, so the overall outcome is often unsatisfactory.[14-17]

Therefore, there is an urgent need to develop complementary therapies. Known as a safe therapy with low side effects, acupuncture has already been widely used in the treatment of VC. The incidence of adverse reactions to acupuncture is significantly lower than other drugs or other conventional medical procedures under the same conditions, which is one of the significant advantages of acupuncture.[18] Specific acupuncture methods that have been used clinically include manual acupuncture, electro-acupuncture, needle warming moxibustion and needle pricking, etc. Acupuncture treatment for VC may have a therapeutic effect on VC by lowering the scrotal skin temperature of patients,[19] and inhibiting patient's oxidative stress process,[20 21] and adjust patients' serum testosterone (T) and follicle stimulating hormone (FSH) by stimulating the sympathetic trunk and regulating endocrine and gonadal axis function.[22-25] Also, it can increase the blood flow and vasodilatory elasticity of spermatic veins in patients with VC infertility improve the blood circulation and relieve VC by lowering the viscosity of blood flow[25] and mitigate muscle tissue spasm and ischaemia by regulating pathologically tight muscles. It may touch on the anatomical basis of the disease, more specific and deeper mechanisms of action need to be explored in further studies.

At present, there are a certain number of documents on acupuncture treatment of VC. These experimental and theoretical studies on the improvement of treating VC by acupuncture can provide preliminary evidence that acupuncture is effective in treating varicocele-induced male infertility, but there still lacks a systematic review. Therefore, this paper is to evaluate the safety and efficacy of acupuncture in the treatment of VC.

Table 1 Postoperative spontaneous pregnancy rates, recurrence rates, hydrocele formation rates among the techniques

Technique	Spontaneous pregnancy rate	Recurrence rate	Hydrocele formation rate	Advantages	Disadvantages
Palomo[26-29]	37.69%	14.97%	8.24%	Good for pain relief , shorter surgery time.	Highest recurrence rate and hydrocele formation rate.
Laparoscopic varicocelectomy[26 28-30]	30.07%	4.3%	2.84%	Suitable for bilateral varicocele and recurrent varicocele. Less invasive surgery, faster recovery and fewer complications.	May cause damage to intestines and blood vessels. Requires high level of surgical skills, anaesthesia and is more expensive.
Radiologic embolization[26 29 31 32]	33.2%	12.7%	0%-12%	Less damage and faster recovery. No accidental injury to the internal	Potential risks of radiation exposure, misplaced embolism and displacement of embolic agents.

				spermatic artery.	
Mcroscopic inguinal (Ivanissevich) [26 33-35]	36%	2.63%	7.3%	More effective in improving sperm concentration.	Increased chance of arterial and lymphatic vessel damage, requiring more surgical skill.
Microsurgical varicocelectomy[10 26 30 36 37]	41.97%	1.05%-2.60%	0.44%	Relatively good efficacy and low recurrence and complication rates. Better control of post-operative pain.	Less than 40% of infertile couples achieve spontaneous pregnancy after microsurgical varicocelectomy, and most of them still require additional interventions such as advanced assisted reproductive technologies (ARTS).
Subinguinal microsurgical varicocclectomy[1 32 35]	42.8%,	0.8%,	0.6%。	The "gold standard" for the treatment of varicocele.	Most patients still need the help of advanced ARTS, such as the costly intracytoplasmic sperm injection (ICSI).

METHODS AND ANALYSIS

Study registration

The protocol was registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), and the registration number is: CRD42022316005.

Criteria for included studies in this review

Type of studies

Inclusion criteria are as follows: (a) Randomized controlled trials; (b) Articles published in the English or Chinese will be included.

Exclusion criteria are as follows: (a) Case reports, animal studies; (b) Meta-analysis and systematic review, narrative review, overviews and conference abstract; (c) Studies in which the required data were unavailable.

Types of participants

Taking into account the fact that the childbearing age of men varies in different countries and regions, we have adjusted the age limit appropriately. In addition , unilateral varicocele is more common in clinical practice, but there are also a small number of patients with bilateral varicocele, both with similar pathogenesis. To fully demonstrate the efficacy and safety of acupuncture as a complementary alternative therapy in improving the condition of patients with VC, RCTs containing a

small number of patients with bilateral varicocele will also be included. To ensure the practicability of the study, we allow for deviations within reasonable limits. If an included RCT partially deviates from the criteria below, we will decide whether to include the RCT after panel discussion.

Inclusion criteria are as follows: (a) Male participants diagnosed with varicocele infertility, regardless of restriction on racial origin. (b) Male participants aged 18-55 years old. (c) The couple in question having at least 12 months of infertility.

Exclusion criteria are as follow: (a) Patients who had received acupuncture treatment or had taken Chinese herbal medicine in the previous three months; (b) Bleeding disorders, genetic abnormalities, chronic inflammatory diseases and severe chronic diseases including cancer; (c) Female partner documented with infertility (including ovulatory, uterine, cervical dysfunction and pathological changes). (d) The presence of other causes of infertility in male patients.

Types of interventions

Acupuncture therapy includes body acupuncture (manual/electric acupuncture), warm acupuncture, auricular acupuncture, acupoint catgut embedding, needle picking and other acupuncture techniques, where needles are used to penetrate acupoints, pain points or trigger points, etc. However, non-penetrating forms of stimulation of acupuncture points, such as moxibustion, acupressure or transcutaneous electrical nerve stimulation, will be excluded. Acupuncture combined with other positive treatments will also be included. There is no restriction on the frequency of treatment.

The included comparators or control groups will be considered as follows:

1. Acupuncture versus sham acupuncture.
2. Acupuncture versus surgical control.
3. Acupuncture versus conventional medication/herbal medicine.
4. Acupuncture plus positive treatment versus positive treatment alone.

Studies aiming to compare different acupuncture points, different methods of acupoint stimulation, and different frequencies and durations of treatment were excluded.

Types of outcome measures

Primary outcome

A routine semen analysis (semen volume, sperm density, sperm viability, sperm deformity rate, sperm DNA fragmentation index)

Secondary outcomes

1. The pregnancy rates.
2. The maximum internal diameter of spermatic vein (D_R) during calm breathing under color Doppler ultrasound.
3. The reproductive endocrine hormone level (FSH, LH, PRL, et al.).

4. Adverse events such as local haematomas, haematuria and syncope induced by acupuncture interventions.

Search strategy

All relevant publications published from database inception through August 2022 will be searched in three English-language databases: Embase, CENTRAL (The Cochrane Central Register of Controlled Trials), MEDLINE and four Chinese-language databases: China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP Database), Chinese Biomedical Literature Database (SinoMed) and Wanfang Data. We will search the above databases using a combination of MeSH terms and free words, using the following terms: (1) Varicocele. (2) Acupuncture therapy, acupuncture, electro-acupuncture, manual acupuncture, auricular acupuncture, needle picking, warm acupuncture and acupoint. (3) Randomized controlled trial, RCT, randomized controlled, clinical trial. Languages are limited to English and Chinese. The researchers will then screen these literatures with EndNote software. The same Chinese search strategy, properly tuned where needed, will also be used for searches in Chinese databases. For small registries or registries with limited search tools, searches in the registry will be based on disease terms only. The recommended full search strategy for MEDLINE is shown in Table 2. Full search strategies for all databases, registers and websites are shown in supplementary file.

Table 2 Medline (via Ovid) search strategy

PI(CO)S	#	Search
Population	#1	exp Varicocele/
	#2	exp Infertility, Male/
	#3	((male* or men) adj7 (infertil* or subfertil*)).tw.
	#4	(Varicocele* or Varicocoele*).tw.
	#5	(varicocele or varicocoele or varicoceles or spermatic vein varicosity or varicose spermatic veins or pampinocele or spermophlebectasia or cirsocele or varicole or ramex).tw.
	#6	or/1-5
Intervention	#7	exp Acupuncture/
	#8	exp Acupuncture Therapy/ or exp Electroacupuncture/ or acupuncture needle.mp.
	#9	exp Acupressure/

	#10	acupoint.mp. or exp Acupuncture Points/
	#11	needle pricking.mp.
	#12	warming needle moxibustion.mp.
	#13	(acupunctur* or acupressur*).tw.
	#14	(electrostimulat* or electroacupunctur*).tw.
	#15	(acupoint* or acupotom*).tw.
	#16	(auriculotherap* or auriculoacupunct*).tw.
	#17	(needl* or needl* prick*).tw.
	#18	body needl*.tw.
	#19	dry needl*.tw.
	#20	warm* needle moxibustion.mp. or warm* acupuncture.tw. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	#21	meridian*.tw.
	#22	qi.tw.
	#23	or/7-22
Study design	#24	randomized controlled trial.pt.
	#25	controlled clinical trial.pt.
	#26	randomized.ab.
	#27	placebo.ab.
	#28	drug therapy.fs.
	#29	clinical trials as topic.sh.
	#39	randomly.ab.

	#31	trial.ti.
	#32	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
	#33	exp animals/ not humans.sh.
	#34	32 not 33
	#35	6 and 23 and 34

Searching other resources

The unpublished or ongoing randomized clinical trials will be searched on the International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, PROSPERO and Chinese Clinical Registry (CHICTR). In addition, relevant references will also be searched.

Data collection and analysis

Literature screening and data extraction

First, in accordance with the search strategy, two independent researchers will import the acquired articles into Endnote and read through the titles and abstracts to identify articles that will meet the filtering criteria. Then the included literature will be read in full by two researchers for a further screening. In case of a discrepancy of opinion between the two researchers, a group discussion will be held and an experienced researcher and corresponding author will be invited to arbitrate the final decision. Articles that have been excluded will be marked with the reason of their exclusion. The flow chart and selection process is shown in Figure 1.

The following data will be extracted separately by the two researchers, including: Title, first author, year of publication, country, participants (number, age), random method, blinding, treatment group, control group, follow-up, outcome, results, and adverse events, etc. If there is any missing detail or unclear aspect of the presentation, the researchers will contact the corresponding author to make the supplementation or clarification accordingly.

Figure 1 Flow diagram of the trial selection process.

Assessment of risk of bias

Two researchers will independently assess the risk of bias for this study using the latest version of the Cochrane risk-of-bias tool 2 (ROB 2)[38] and will assess bias from five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results). The risk of bias will be judged (low/high/some concerns) and the overall risk of bias of the assessment results will be predicated. The differences between the two

researchers will be eventually resolved by the corresponding author. If a RCT was judged to have "some concerns" about the risk of bias in three or more domains, it will be excluded from the systematic review due to the high risk of bias.

Measures of treatment effect

Data will be entered into RevMan software (RevMan V.5.4) for synthesis and statistical analysis. 95% CI for relative risk will be used for analysis of dichotomous variables (e.g. adverse events for acupuncture interventions). Continuous variables (e.g. semen analysis results, reproductive endocrine hormone level) will be analyzed using the 95% CI for weighted mean difference (WMD) or standard mean difference (SMD).

The issue concerning the unit of analysis

As for the issue concerning the unit of analysis[39], if the included RCTs have more than two intervention groups that are relevant to the systematic review/ particular meta-analysis, then the multiple groups qualified for experimental or comparator interventions will be combined to form a single pair-wise comparison to overcome the unit of analysis error. For dichotomous results, both the sample size and the number of people who had an adverse event can be summed across groups. For continuous results, means and standard deviations can be combined using the method described.

Dealing with missing data

As noted above, if there is any essential data missing, our researcher will contact the corresponding author to fill in the blanks. If the missing data is not recoverable, then sensitivity analysis will be conducted to address the issue of missing data. This will be elaborated in the discussion section.

Heterogeneity assessment

Heterogeneity assessment of all studies will be performed by RevMan. Statistical heterogeneity between studies will be calculated using I^2 values. To explore potential sources of heterogeneity, sensitivity analysis or subgroup analysis will be used for assessment.

Data synthesis

Based on some preliminary research, we will use the random-effects model for the data synthesis section. The input clinical data will be processed by the RevMan and the forest plot can be generated by this software to make the presentation of the study results more understandable. The results of the study will be presented in tabular form, including key information on the quality of the evidence, the effect sizes of the interventions and the sum of the available data for all important

outcomes for a given comparison.

Subgroup analysis and investigation of heterogeneity

A random effects model will be used since individual RCTs were conducted in different locations and there will be certainly discrepancy across different experimental protocols, and among different groups of patients. Heterogeneity will always be present regardless of the sample size of the study, so we will switch our focus from examining the presence of heterogeneity to assessing the impact of heterogeneity on the meta-analysis. Our researchers will explore the sources of heterogeneity in four dimensions: Population, intervention, outcome, study design and implementation, and will explain heterogeneity through subgroup analysis, meta-regression or sensitivity analysis. If sufficient studies are identified, subgroup analyses can be performed among different types of acupuncture methods, as well as different follow-up times, types of controls or intensity of treatment.

Sensitivity analysis

Sensitivity analysis will be applied to assess the robustness of the study results. The specific implementation method will be based on the "change model analysis" and the "exclusion of literature on a case-by-case basis". When using the literature-by-exclusion method, any change in heterogeneity will be observed after the exclusion of each literature, and the change in the value of the combined effect, WMD, RR need to be recorded at the same time. If heterogeneity changes after the exclusion of a piece of literature, then that piece of literature may be the source of the heterogeneity.

Assessment of reporting biases

If the number of studies is more than 10, our researchers will use funnel plots to detect reporting bias; if not, the detection of the reporting bias is infeasible. Our study will try to avoid reporting bias as much as possible by conducting a comprehensive search for studies that meet the inclusion criteria by incorporating unpublished studies and searching the trial registries.

Summary of evidence

Our researchers will use the Grading of Recommendation Assessment, Development and Evaluation (GRADE system) to assess the quality of the evidence for the results reported in systematic reviews. The system requires an assessment of the quality of evidence for each individual outcome. The assessment includes limitations in the design and implementation of available studies, suggesting that there is high likelihood of bias, unexplained heterogeneity or inconsistency of results, indirectness of evidence, imprecision of results and high probability of publication biases.

Patient and public involvement

As mentioned, this study is a secondary study based on clinical studies so it does not involve any patient or the public.

DISCUSSION

Varicocele is one of the most common causes of male infertility although it can occur without causing infertility. In mild cases, there may be no obvious clinical symptoms; however, in severe cases, there may be a sensation of swelling or dull pain in the scrotum, which worsens after prolonged standing and exertion and mitigates or disappears after lying down or resting. Considering that some patients with varicocele may not seek medical help because they have no need for fertility or their discomfort has little impact on their daily lives, our study was limited to recruiting patients with varicocele-induced infertility. The exact mechanism by which VC may affect spermatogenesis remains obscure, [4] but some recent literature can conclude that VC can affect fertility by influencing testicular histology, sperm function, semen quality and reproductive hormones[6 7]. As all surgical methods have some potential risks of recurrence and complications, non-surgical treatments have attracted the interest of clinicians and acupuncture is increasingly being used to relieve VC. This systematic evaluation will assess evidence from randomized controlled trials to demonstrate the effectiveness and safety of acupuncture in the treatment of VC. The aim is to provide more effective and safe treatment options for clinical practice. The potential limitations of this study may have some impact on the results. The exclusion of studies published in languages other than English and Chinese may result in publication bias, and the adoption of multiple types of acupuncture therapies may have the potential to increase the risk of heterogeneity.

Amendments to protocol

To ensure transparency, any change from this protocol will be amended on the PROSPERO database.

Ethics and dissemination

This study is a secondary study based on clinical studies, and thus it is unnecessary to obtain ethical approval. The results will be reported in peer-reviewed journals or disseminated at relevant conferences.

Contributors

WSJ, TZA and ZGM participated in the research design. LRC, RJJ and CJN developed the search strategies. LRC, WCY and LQ implemented the search strategies and screened data extraction. LRC, SMM and DJ did some statistical analysis. WSJ conceived the review protocol and drafted the manuscript. Several studies from

different opinions were determined by TZA. WSJ, LRC and SHS participated in the correction of the manuscript. All authors reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed. This is a protocol without data.

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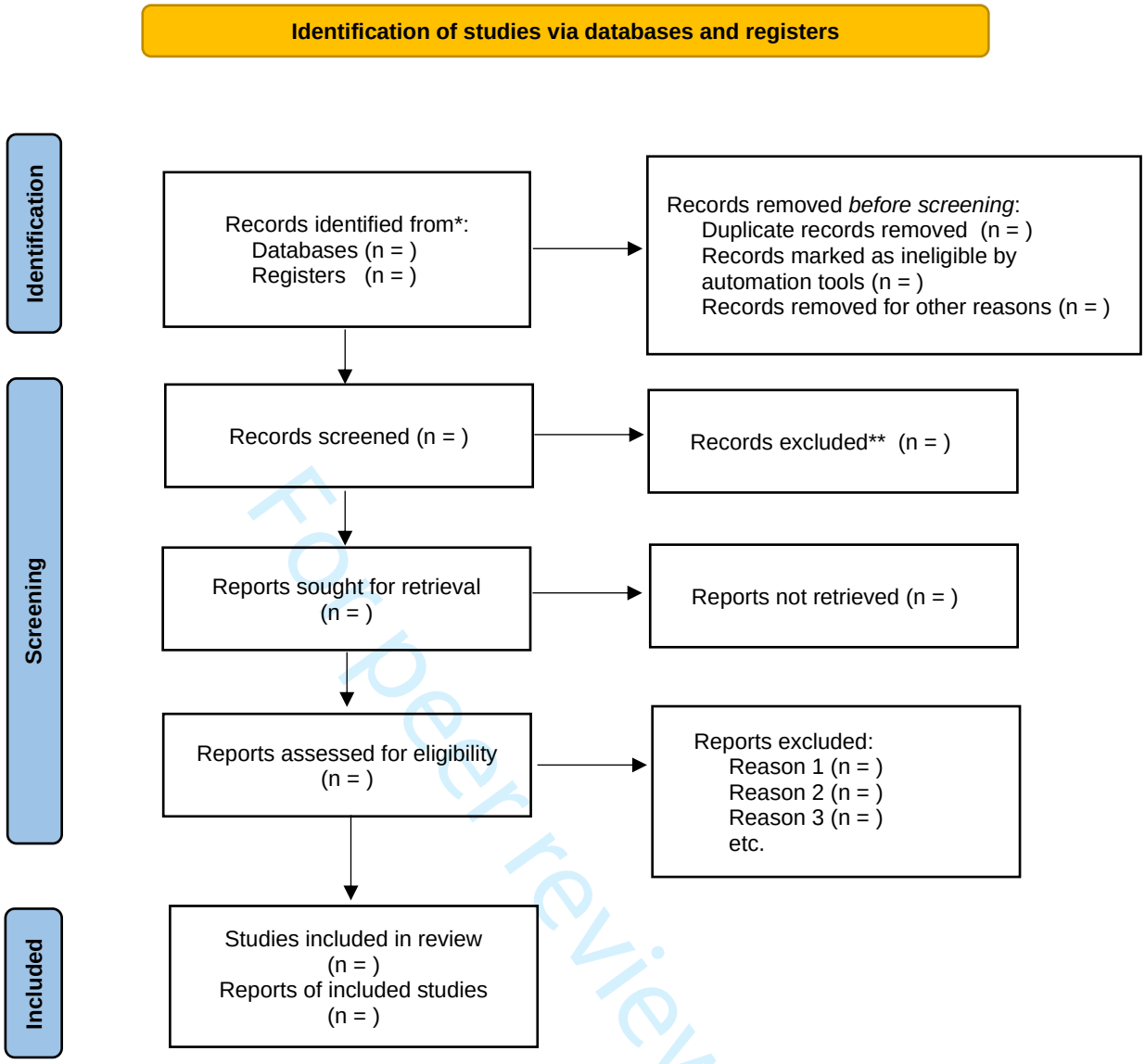

MEDLINE via Ovid

PI(CO)S	#	Search
Population	#1	exp Varicocele/
	#2	exp Infertility, Male/
	#3	((male* or men) adj7 (infertil* or subfertil*)).tw.
	#4	(Varicocele* or Varicocoele*).tw.
	#5	(varicocele or varicocoele or varicoceles or spermatic vein varicosity or varicose spermatic veins or pampinocele or spermophlebectasia or cirsocele or varicole or ramex).tw.
	#6	or/1-5
Intervention	#7	exp Acupuncture/
	#8	exp Acupuncture Therapy/ or exp Electroacupuncture/ or acupuncture needle.mp.
	#9	exp Acupressure/
	#10	acupoint.mp. or exp Acupuncture Points/
	#11	needle pricking.mp.
	#12	warming needle moxibustion.mp.
	#13	(acupunctur* or acupressur*).tw.
	#14	(electrostimulat* or electroacupunctur*).tw.
	#15	(acupoint* or acupotom*).tw.
	#16	(auriculotherap* or auriculoacupunct*).tw.
	#17	(needl* or needl* prick*).tw.
	#18	body needl*.tw.
	#19	dry needl*.tw.
	#20	warm* needle moxibustion.mp. or warm* acupuncture.tw. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
	#21	meridian*.tw.
	#22	qi.tw.
	#23	or/7-22
Study design	#24	randomized controlled trial.pt.
	#25	controlled clinical trial.pt.
	#26	randomized.ab.
	#27	placebo.ab.
	#28	drug therapy.fs.
	#29	clinical trials as topic.sh.
	#39	randomly.ab.
	#31	trial.ti.
	#32	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
	#33	exp animals/ not humans.sh.

	#34	32 not 33
	#35	6 and 23 and 34

EMBASE

PI(CO)S	#	Search
Population	#1	'varicocele'/exp
	#2	'male infertility'/exp
	#3	varicocele*:ab,ti OR varicocoele*:ab,ti
	#4	('male* infertil*'):ab,ti OR (('men infertil*'):ab,ti) OR (('male* subfertil*'):ab,ti) OR (('men subfertil*'):ab,ti)
	#5	(Varicocele):ab,ti OR ((varicocoele):ab,ti) OR ((varicoceles):ab,ti) OR (('spermatic vein varicosity'):ab,ti) OR ((varicose):ab,ti) OR (('spermatic vein*'):ab,ti) OR ((pampinocele):ab,ti) OR ((spermophlebectasia):ab,ti) OR ((cirsocele):ab,ti) OR ((varicole):ab,ti) OR ((ramex):ab,ti)
	#6	#1 OR # OR #2 OR #3 OR #4 OR #5
Intervention	#7	'acupuncture'/exp
	#8	'acupuncture needle'/exp
	#9	'acupressure'/exp
	#10	'acupoint'/exp
	#11	'needle pricking'/exp
	#12	'warming needle moxibustion'/exp
	#13	acupunctur*:ab,ti OR acupressur*:ab,ti
	#14	(electro* NEAR/1 (stimulat* OR acupunctur*)):ab,ti
	#15	electrostimulat*:ab,ti OR electroacupunctur*:ab,ti
	#16	acupoint*:ab,ti OR acupotom*:ab,ti
	#17	auriculotherap*:ab,ti OR auriculoacupunct*:ab,ti
	#18	needl*:ab,ti
	#19	('needl* prick*'):ab,ti
	#20	(body NEXT/1 needl*):ab,ti
	#21	(dry NEXT/1 needl*):ab,ti
	#22	('warm* needle moxibustion'):ab,ti OR ('warm* acupuncture'):ab,ti
	#23	meridian*:ab,ti
	#24	qi:ab,ti
	#25	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
Study design	#26	'randomized controlled trial'/de
	#27	'controlled clinical trial'/de
	#28	random*:ti,ab,tt
	#29	randomization'/de

	#30	'intermethod comparison'/de
	#31	placebo:ti,ab,tt
	#32	(compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)
	#33	((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))
	#34	(open NEXT/1 label):ti,ab,tt
	#35	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt
	#36	'double blind procedure'/de
	#37	(parallel NEXT/1 group*):ti,ab,tt
	#38	(crossover:ti,ab,tt OR 'cross over':ti,ab,tt)
	#39	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt
	#40	(assigned:ti,ab,tt OR allocated:ti,ab,tt)
	#41	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt
	#42	(volunteer:ti,ab,tt OR volunteers:ti,ab,tt)
	#43	'human experiment'/de
	#44	trial:ti,tt
	#45	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44
	#46	(((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))
	#47	('cross - sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))
	#48	('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))
	#49	('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt))
	#50	(nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)
	#51	'random field*':ti,ab,tt
	#52	('random cluster' NEAR/4 sampl*):ti,ab,tt
	#53	(review:ab AND review:it) NOT trial:ti,tt

	#54	('we searched':ab AND (review:ti,tt OR review:it))
	#55	'update review':ab
	#56	(databases NEAR/5 searched):ab
	#57	((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)
	#58	('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
	#59	34 #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58
	#60	#45 NOT #59
	#61	#6 AND #25 AND #60

Central Register of Controlled Trials (CENTRAL) via Cochrane Library

PI(CO)S	#	Search
Population	#1	MeSH descriptor: [varicocele] explode all trees
	#2	MeSH descriptor: [Infertility, Male] explode all trees
	#3	(varicocele*):ti,ab,kw OR (varicocoele*):ti,ab,kw
	#4	(male* infertil*):ti,ab,kw OR (men infertil*):ti,ab,kw OR (men subfertil*):ti,ab,kw OR (male* subfertil):ti,ab,kw
	#5	(varicocele):ti,ab,kw OR (varicocoele):ti,ab,kw OR (varicoceles):ti,ab,kw OR (spermatic vein varicosity):ti,ab,kw OR (varicose spermatic veins):ti,ab,kw
	#6	(pampinocele):ti,ab,kw OR (spermophlebectasia):ti,ab,kw OR (cirsocele):ti,ab,kw OR (varicole):ti,ab,kw OR (ramex):ti,ab,kw
	#7	#1 OR # OR #2 OR #3 OR #4 OR #5 OR #6
Intervention	#8	MeSH descriptor: [Acupuncture] explode all trees
	#9	MeSH descriptor: [Acupressure] explode all trees
	#10	MeSH descriptor: [Acupuncture Points] explode all trees
	#11	(acupressur*):ti,ab,kw OR (acupunctur*):ti,ab,kw
	#12	(electro* NEAR/1 stimulat*):ti,ab,kw OR (electro* NEAR/1 acupunctur*):ti,ab,kw
	#13	(electrostimulat*):ti,ab,kw OR (electroacupunctur*):ti,ab,kw
	#14	(acupoint*):ti,ab,kw OR (acupotom*):ti,ab,kw
	#15	(auriculotherap*):ti,ab,kw OR (auriculoacupunct*):ti,ab,kw
	#16	(needl*):ti,ab,kw
	#17	(needl* prick*):ti,ab,kw
	#18	(body NEXT/1 needl*):ti,ab,kw

	#19	(dry NEXT/1 needl*):ti,ab,kw
	#20	(warm* needle moxibustion):ti,ab,kw OR (warm* acupuncture):ti,ab,kw
	#21	(meridian*):ti,ab,kw
	#22	(qi):ti,ab,kw
	#23	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
Study design	#24	MeSH descriptor: [randomized controlled trial] explode all trees
	#25	MeSH descriptor: [controlled clinical trial] explode all trees
	#26	MeSH descriptor: [clinical trial] explode all trees
	#27	random*:ti,ab,kw
	#28	placebo:ti,ab,kw
	#29	trial:ti,ab,kw
	#30	#24 OR #25 OR #26 OR #27 OR #28 OR #29
	#31	MeSH descriptor: [animal] explode all trees
	#32	#30 NOT #31
	#33	#7 AND #23 AND #32

China National Knowledge Infrastructure(CNKI)

(TKA='针灸' OR TKA='针刺' OR TKA='温针' OR TKA='电针' OR TKA='针挑') AND (TKA='精索静脉曲张') AND TKA='随机'

Filter by: synonym expansion

China Science and Technology Journal Database (VIP Database)

(M=针灸 OR 针刺 OR 温针 OR 电针 OR 针挑) AND (M=精索静脉曲张) AND (R=随机)

Chinese Biomedical Literature Database (SinoMed)

("随机"[常用字段:智能]) AND ("精索静脉曲张"[常用字段:智能]) AND ("针灸"[常用字段:智能] OR "针刺"[常用字段:智能] OR "温针"[常用字段:智能] OR "电针"[常用字段:智能] OR "针挑"[常用字段:智能])

Wanfang Data

(((摘要=随机)) AND (题名或关键词=精索静脉曲张)) AND ((((((题名或关键词=针刺) OR 题名或关键词=针灸) OR 题名或关键词=温针) OR 题名或关键词=电针) OR 题名或关键词=针挑))

International Clinical Trials Registry Platform (ICTRP)

Condition: varicocele* OR varicocoele OR spermatic vein varicosity OR varicose spermatic vein* OR varicole

Intervention: acupuncture OR acupoint OR needl* prick* OR electroacupunctur* OR warm* needl* moxibustion

ClinicalTrials.gov

Condition or disease: "varicocele" OR "varicocoele" OR "spermatic vein varicosity" OR "varicose spermatic veins" OR "varicole"

Other terms: "acupuncture" OR "acupoint OR "needle pricking" OR "electroacupuncture" OR "warming needle moxibustion"

Chinese Clinical Registry (CHICTR)

Target disease: varicocele

PROSPERO

Search bar: varicocele

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	Reported on 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	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	11-12
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	11
Support:			
Sources	5a	Indicate sources of financial or other support for the review	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	11-12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2-3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2
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	4-5
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	6-8
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	6-7

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	5
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
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	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	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)	9
	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)	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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