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Tuina for spasticity of poststroke: protocol of a systematic review and meta-analysis

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Tuina for spasticity of poststroke: protocol of a systematic review and meta-analysis

Qiongshuai Zhang[1], Gangcheng Ji[2], Fang Cao[3], Yihan Sun[4], Guanyu Hu[1], Shaoqian Sun[5], Yanze Liu[1], Jiazhen Cao[1], Deyu Cong[6], Yufeng Wang[6], Bailin Song[1]

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ABSTRACT

Introduction spasticity is a common complication of post-stroke, tuina is a widely used rehabilitation treatment, although there is a lack of supportive evidence on efficiency and safety for post-stroke spasticity patients. The aim of this systematic review is to assess and synthesis efficacy and safety of tuina for spasticity of post-stroke.

Methods and analysis. A comprehensive electronic search of PubMed, EMBASE, MEDLINE, Cochrane library, Web of Science(WOS), Wiley, Springer, Chinese Science Citation Database(CSCD), China National Knowledge Infrastructure (CNKI), Chinese Biomedical literature Database (CBM), Chinese Scientific and Journal Database (VIP), Wan Fang database(Wanfang), Japanese medical database (CiNii), Korean Robotics Institute Summer Scholars (RISS), and Thailand Thai-Journal Citation Index Centre (TCI) will be conducted to search literatures of randomized controlled trials of tuina for spasticity of post-stroke survivors. There is no language, publication status or date limitations. Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the risk of bias, and the protocol will be conducted according to approach and Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).

Ethics and dissemination ethical approval will not be required, for no primary data of individual patients was collected, We will publish the findings in a peer-reviewed journal.

Strengths and limitations of this study

- To our knowledge this is the first comprehensive systematic review focused on efficiency and safety of tuina for spasticity of post-stroke.
- Only randomized controlled trials (RCTs) will be included in this study.
- The reliability of this systematic review may be limited by the quality of the primary studies included. To solve this problem, authors will assess the quality of the trials included with the Cochrane risk of bias tool.

Stroke has been the first risk factor of death in China[1]. It is also one of the diseases with high mortality and disability rate in the world[2]. Limb spasm is a common complication of post-stroke patients[3] [4]. Recent study show that about 17% - 43% of stroke patients had limb spasticity[5-7], and the medical cost of post-stroke limb spasm patients is about four times as much as post-stroke patients without spasticity[8] [9]. Limb spasm not only severely restricts the activity ability of patients, reduces the quality of life, but also causes psychological impact on patients' rehabilitation, and brings great burden to families and society[10] [11] [12] [13] [14].

Physical therapy, oral or injection drug therapy, and operation therapy are commonly used in western medicine to treat post-stroke spasticity at present. Oral drugs such as baclofen, eperisone, hydrochloride and diazepine have large side effects which hinder the recovery of motor function with long time taking [15]. Botulinum toxin treatment is difficult to achieve long-term results, and it is often injected for moderate or severe cases of post-stroke spasticity [16] [17]. At present, much more of the patients with spasticity after stroke choose external treatment. In China, many external treatment methods of traditional Chinese Medicine (TCM) are applied to the treat this disease.

Tuina, as an external treatment of TCM [18] [19], has been widely used in China for hundreds of years and increasingly practiced in western countries in recent years. Systematic evaluation [20] shows that acupuncture is efficiency and safety in the treatment of limb spasm after stroke. Acupuncture and massage belong to the external treatment of traditional Chinese medicine, and both are based on the same theory of meridians and acupoints. However, it is still unclear whether the effectiveness of acupuncture is also applicable to massage in the treatment of post-stroke spasticity. At present, there is no systematic review of massage in the treatment of post-stroke limb spasticity, so this study will evaluate the efficiency and

safety of massage in the treatment of post-stroke limb spasticity, and provide evidence for clinical decision-making of massage.

Methods

The systematic review will be performed following the guideline of preferred reporting items of systematic reviews a meta-analysis protocol (PRISMA-P) 2015[21].

Inclusion Criteria

Types of studies

We will include randomized controlled trials (RCTs) of tuina for post-stroke spasticity in the treatment groups. RCTs' language of English, Chinese, Japanese, Korean and Thai will be included, there will be no restriction on language.

Types of participants

We will include patients suffering post-stroke spasticity (>18 years old)with no restriction of onset time. Stroke (Cerebral infarction or cerebral hemorrhage)is diagnosed according to WHO criteria [22], participants have the symptoms of limb muscle tension increase, and the modified Ashworth Scale (MAS) score is grade 1-2. Participants of any age, sex, ethnicity will be enrolled(在临床研究中也标明).

Types of interventions

The treatment group using tuina, while the control group receives treatment of oral medication, acupuncture, Chinese herbal medication, physical therapy, surgery, botox injections and so on or even with no treatment will be included.

Types of outcome measures

Primary outcome

The primary outcome measures

Muscle tone will be evaluated by the Modified Ashworth Scale (MAS)

Secondary outcome

Functional rehabilitation was assessed with Fugl-Meyer Assessment scale (FMA) or Simplified Fugl-Meyer Assessment scale

Muscle strength will be defined by surface electromyogram root mean square value (RMS),

Activities of daily living (ADL) will be assessed by the modified Bathel index (MBI),

Quality of life will be measured by stroke specific quality of life scale (SS-QOL) or quality of life 36 item short-form health survey (SF-36)

Limb pain will be assessed by Visual Analogue Scale (VAS)

Search strategy

Electronic searches

The published electronic literature will be searched in PubMed, EMBASE, MEDLINE, Cochrane library, Web of Science(WOS), Wiley, Springer, Chinese Science Citation Database, China National Knowledge Infrastructure (CNKI), Chinese Biomedical literature Database (CBM), Chinese Scientific and Journal Database (VIP), Wan Fang database, Japanese medical database (CiNii), Korean Robotics Institute Summer Scholars (RISS), and Thailand Thai-Journal Citation Index Centre (TCI). We will also cheek reference lists, and the literature will be searched range from the establishment to January 1, 2020.

The search strategy is developed according to published reviews [23] [24]. The detail search strategy of MEDLINE (PubMed) is listed in appendix 1, while the search strategy will be modified according to other different databases.

Data collection and analysis

Selection of literature

Two authors (YZL, JZC) will identify studies according to the inclusion criteria independently. Firstly, they will eliminate duplicate researches by using endnote software (V. x9.0). secondly, screening the title and abstract, if necessary, reading the full article to confirm if it should be included. They also use endnote software to manage the included studies. The screening operation is performed as Figure 1. If there is disagreement during the screening process, discuss with the third experts (GCJ) to make decision.

Data extraction and management

Two authors (SQS and YFW) will extract data from the included studies independently. The general Information, which consists of title, publication year, authors, country, language, journal source; information of participants: gender, age , stroke type, duration of onset, sample size; information of intervention characteristics: type, session, duration, follow-up time; outcome information about primary outcome, second outcome, observation time points, blinding of evaluators and adverse effects.

Assessment of risk of bias in included studies

Two independent authors (QSZ and FC) will evaluate the risk of bias by using the Cochran Collaboration Network Bias Risk Assessment Tool to assess the risk bias of the literature included in the systematic review. The two authors will assess the risk of bias of sequence generation, allocation concealment, blinding of participants personnel and outcome assessment, incomplete outcome data, selective outcome reporting and other bias. The evaluation grades are low, high and unclear risk of bias.

Measures of treatment effect

Two independent authors (YHS and QSZ) will use risk rate (RR) with 95% confidence interval (CI) to analysis the dichotomous data. While,

we will use mean difference(MD) or standard mean difference(SMD) with 95% (CI) for continuous data, the Other binary data will be changed into RR form.

Dealing with missing data

If some information of the included studies missed, we will try to contact the correspondence author through e-mail, phone or other contacts. If failure, we will turn to the following strategies to evaluate the potential influence of missing data [25].

• Worst-case scenario analysis: All participants with missing data counted as failures.

• Extreme worst-case/best-case scenario analysis: Participants with missing outcome data in the exercise arm counted as failures and in the control arm as successes and vice versa.

Assessment of heterogeneity

We will use Q-test and I^2 statistic to assess the heterogeneity of the included studies, as the criteria: I^2<50% indicates low heterogeneity, while I^2>50% indicates high heterogeneity,

Assessment of reporting bias

We will construct a funnel plots to assess asymmetry, only if at least 10 RCTs are included.

Data synthesis

The meta-analysis of intervention and outcome measures methods will be conducted by RevMan 5.3.5 software (the Cochrane Collaboration, Oxford, England). If the statistical heterogeneity is low (P>0.1,or I^2<50%), we will use the fixed-effect model to combine the data, while, if the statistical heterogeneity is high (P<0.1,or I^2>50%), we will use the random-effect model. However, if the heterogeneity level much significant, a descriptive analysis will be performed.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis to assess heterogeneity of the study according to the following factors from the available sufficient data:

Age

Sex

Different types of stroke (Cerebral hemorrhage or cerebral infarction)

Different types of tuina

Different time/course of treatment

Different parts of affected limbs (upper limb or lower limb)

Different types of control group (acupuncture, placebo, oral/Injection drug or no treatment)

Sensitivity analysis

We will perform sensitivity analysis to evaluate the robustness and reliability of the pooled results. If the results are not stable, we

may turn to removing studies of high risk of bias, or cheek up processing method of missing data (Worst-case scenario analysis: All participants with missing data counted as failures; Extreme worst-case/best-case scenario analysis: Participants with missing outcome data)

Grading of evidence quality

We will use the Grading of Recommendations Assessment, Development and Evaluation(GRADE)[26] to access the confidence in cumulative evidence. risk of bias, heterogeneity, indirectness, imprecision and Publication bias wil be assessed, and the results will be divided into three levels: high, moderate, low and very low.

Amendments

We will show all of the amendments with detail description and rationale in the amendments of this study.

Ethics and dissemination

This study needs no ethical approval, because there is nothing of the data, which has relationship with individual patient. We will complete this systematic review according to PRISMA guidelines, the review will provide assessment of effect and safety of tuina for spasticity of post-stroke. We will publish the findings in a peer-reviewed journal.

Discussion

This systematic review will focus on the efficiency and safety of tuina for spasticity of post-stroke. Tuina is a traditional Chinese physical therapy, which is effective for 516 diseases in China [27], of which spasticity is included. clinical reports show tuina is well in treatment of spasticity of post-stroke, however, high quality study still did’ t appear. We conduct this review, aim to provide better evidence and guide for clinical decision making. We plan to publish this review within 1 year since the protocol published, then we will update it every 3 years.

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Contributors QSZ and BLS conceived and designed the protocol, QSZ and YHS registered the protocol review in the Prospero database and drafted the manuscript. YZL and JZC designed the search strategy. QSZ and FC draft the protocol, QSZ, GCJ, FC, YHS, SQS, GYH, YZL, JZC, DYC, YFW and BLS contribute to and approved the final manuscript of the protocol review.

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Competing interests Non declared

Patient consent Not required

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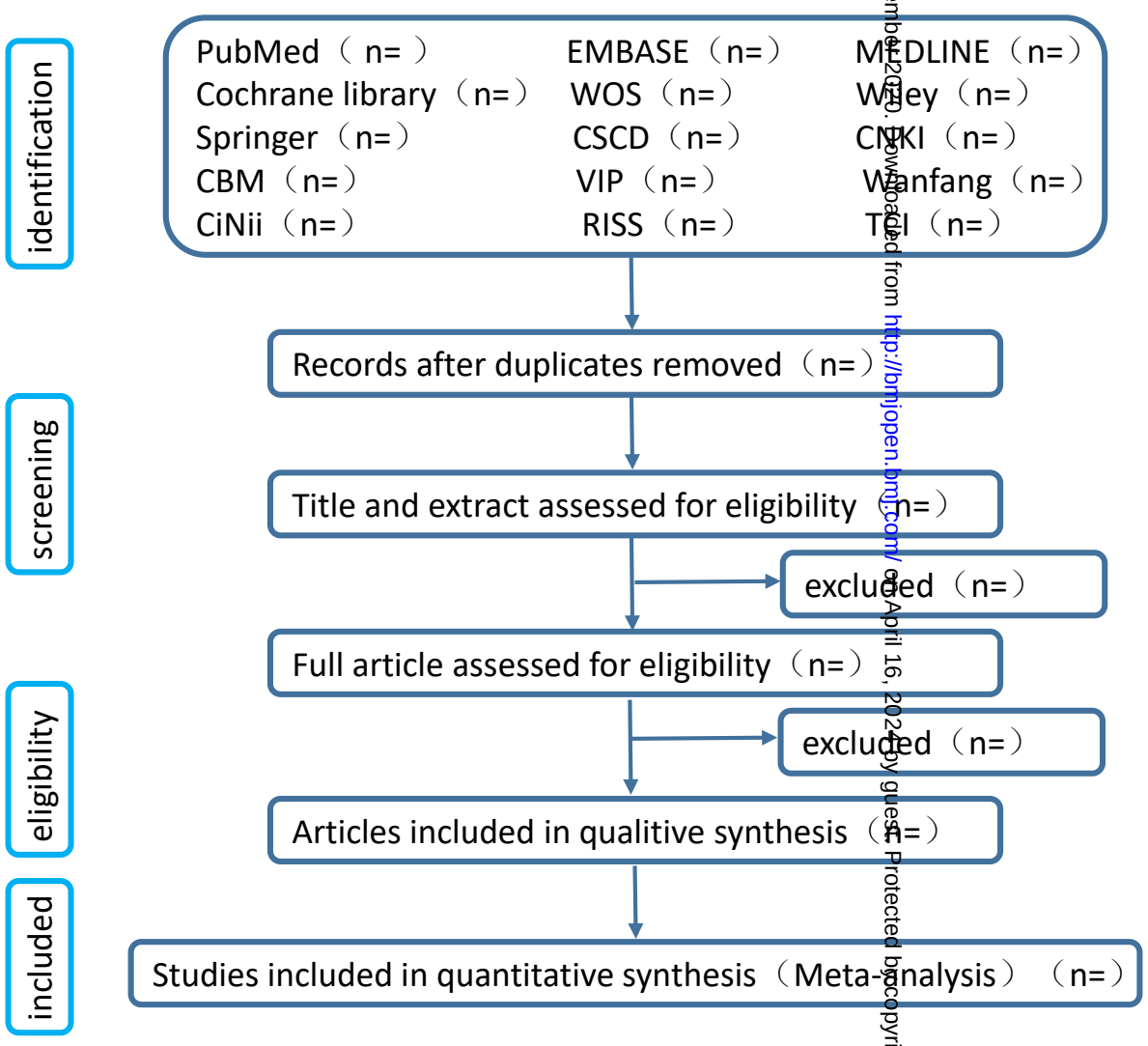

Table1 PubMed search strategy	
Spasticity of post-stroke	#1.Stroke[MeSH] OR Apoplexy [Tiab] OR post-stroke[tiab] OR poststroke[tiab]OR Apoplectic [Tiab] OR Apoplexia [Tiab] OR Cerebral hemorrhage [Tiab] OR Ich [Tiab] OR Cerebrovascular accident [Tiab] OR Cerebrovascular disorders [Tiab] OR Cerebral embolism [Tiab] OR Brain embolism [Tiab] OR Embolic stroke [Tiab] OR Cerebral infarct OR cva*[tiab] #2.spasm[Mesh] OR dystonia[tiab] OR paraparesis,spastic[tiab] OR muscle spasticity*[tiab] OR muscle hypertonia [tiab] OR muscle rigidity*[tiab] OR muscle tonus[tiab] OR spas*[tiab] OR high tone[tiab] #3. #1 AND #2
Tuina	#4.Tuina[tiab] or Massage[tiab] or Acupressure[tiab] or Rub[tiab] or Massageing[tiab] or Massotheraty[tiab] or manipulation[tiab]
Randomised controlled trial	#5. Randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial[tiab] OR groups [tiab]
Final search strategy	6.#3 AND #4 AND #5

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
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	n/a This is a new systematic review

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a Registration is in progress
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1,6,7
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7
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	n/a This is a new systematic review
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	7
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	7
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)	1
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	3
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	3,4
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	3,4, appendix 1
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4,5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers)	4

		through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - 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	4
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	4
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3
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	4
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	3
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	5

Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a all the data will be quantitative synthesised
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	2,5
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

Notes:

- 1b: n/a This is a new systematic review
- 2: n/a Registration in progress
- 4: n/a This is a new systematic review
- 15d: n/a all the data will be quantitative synthesised This checklist was completed on 20. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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ABSTRACT

Introduction spasticity is a common complication of post-stroke, tuina is a widely used rehabilitation treatment, although there is a lack of supportive evidence on efficiency and safety for post-stroke spasticity patients. The aim of this systematic review is to assess and synthesis evidence of efficacy and safety of tuina for spasticity of post-stroke.

Methods and analysis. A comprehensive electronic search of EMBASE, MEDLINE(by Pubmed), Cochrane library, Web of Science(WOS), Wiley, Springer, PEDro, Chinese Science Citation Database(CSCD), China National Knowledge Infrastructure (CNKI), Chinese Biomedical literature Database (CBM), Chinese Scientific and Journal Database (VIP), Wan Fang database(Wanfang), Japanese medical database (CiNii), Korean Robotics Institute Summer Scholars (RISS), and Thailand Thai-Journal Citation Index Centre (TCI) will be conducted to search literatures of randomized controlled trials of tuina for spasticity of post-stroke survivors range from the establishment to January 1, 2020 . There is no time of publicaiton limitations. The primary outcome will be measured with the Modified Ashworth Scale (MAS), and the second outcome will included Fugl-Meyer Assessment scale (FMA), surface electromyogram root mean square value (RMS), the modified Bathel index (MBI), stroke specific quality of life scale (SS-QOL), quality of life 36 item short-form health survey (SF-36), and Visual Analogue Scale (VAS).Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the risk of bias, GRADE will be used to access the confidence in cumulative evidence. The protocol will be conducted according to approach and Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015.

Ethics and dissemination ethical approval will not be required, for no primary data of individual patients was collected, We will publish the findings in a peer-reviewed journal.
PROSPERO registration number CRD42020163384

Strengths and limitations of this study

▸This is the first comprehensive systematic review focused on efficiency and safety of tuina for spasticity of post-stroke.
▸Only randomized controlled trials (not included quasi-RCTs) will be included in this study.
▸We searched databases of English,Chinese, Japanses, Korean and Thailand, whlie other languages may be ignored.

Stroke has been the first risk factor of death in China[1]. It is also one of the diseases with high mortality and disability rate in the world[2]. Limb spasticity is a common complication of post-stroke patients[3 4]. Recent study show that about 17% - 43% of stroke patients had limb spasticity[5-7], and the medical cost of post-stroke limb spasticity patients is about four times as much as post-stroke patients without spasticity[8 9]. Limb spasticity not only severely restricts the ability of patients, reduces the quality of life, but also causes psychological impact on patients' rehabilitation, and brings a great burden to families and society[10 11 12 13 14].
Physical therapy, oral or injection drug therapy, and operation therapy are commonly used in western medicine to treat post-stroke spasticity at present. Oral drugs such as baclofen, eperisone, hydrochloride and diazepine have large side effects which hinder the recovery of motor function with long time taking [15]. Botulinum toxin treatment is difficult to achieve long-term results, and it is often injected for moderate or severe cases of post-stroke spasticity [16 17]. Physical therapy often requires active exercise coordination of patients, however, patients with severe conditions are often unable to cooperate. Surgical treatment is traumatic and a large number of patients often find it difficult to accept. At present, much more of the patients with spasticity after stroke choose external treatment. In China, many external treatment methods of traditional Chinese Medicine (TCM) are applied to the treat this disease.
Tuina is an ancient form of external treatment method, which was based on the meridian and acupoint theory of traditional Chinese medicine , and uses specific operation skill acting on the surface or acupoints of the patient's body to treat diseases. [18 19].Tuinahas been widely used in China for hundreds of years and increasingly practiced in western countries in recent years. Systematic evaluation [20] shows that acupuncture is efficiency and safety in the treatment

of limb spasticity after stroke. Acupuncture and Tuina belong to the external treatment of traditional Chinese medicine, and both are based on the same theory of meridians and acupoints. However, it is still unclear whether the effectiveness of acupuncture is also applicable to Tuina in the treatment of post-stroke spasticity. If tuina therapy for post stroke spasticity is proven to be effective, which has the characteristics of simple operation and low cost. At present, there is no systematic review of Tuina in the treatment of post-stroke limb spasticity, so this study will evaluate the efficiency and safety of Tuina in the treatment of post-stroke limb spasticity, and provide evidence for clinical decision-making of massage.

Methods

The systematic review will be performed following the guideline of Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015[21].

Inclusion Criteria

Types of studies

We will include randomized controlled trials (not included quasi-RCTs) of tuina for post-stroke spasticity in the treatment groups. If muti-arm RCTs comes, we will select the group which used tuina and another without tuina for analysis. We will select the first stage of cross over RCTs, which tuina was firstly used in one group.
RCTs' language of English, Chinese, Japanese, Korean and Thai will be included.

Types of participants

We will include patients suffering post-acute phase of post-stroke spasticity (18 years old). Stroke (Cerebral infarction or cerebral hemorrhage)is diagnosed according to WHO criteria [22], participants have the symptoms of limb muscle tension increase, and the modified Ashworth Scale (MAS) score is grade 1-2. Participants of any age, sex, ethnicity will be enrolled.

Types of interventions

The treatment group using tuina, while the control group receives treatment of oral medication, acupuncture, Chinese herbal medication, physical therapy, surgery, botox injections and so on or even with no treatment will be included.

Types of outcome measures

Primary outcome

The primary outcome measures

Muscle tone will be evaluated by the Modified Ashworth Scale (MAS). MAS is a clinical instrument which is commonly used for measuring spasticity, and some studies have proofed its reliability[23-25].

Secondary outcome

Motor function was assessed with Fugl-Meyer Assessment scale (FMA) or Simplified Fugl-Meyer Assessment scale

Muscle strength will be defined by surface electromyogram root mean square value (RMS),

Activities of daily living (ADL) will be assessed by the modified Bathel index (MBI),

Quality of life will be measured by stroke specific quality of life scale (SS-QOL) or quality of life 36 item short-form health survey (SF-36)

Limb pain will be assessed by Visual Analogue Scale (VAS)

Safety outcome

Aggravation of spasm

Skin abrasions

Exclusion criteria:

•Repeatedly published studies;

•Experiences, letters, systematic reviews, animal experiments;

•Tuina was not only in the experimental group but also in the control group;

•Articles without full text or with data which is missed nor can't be used.

Search strategy

Electronic searches

The published electronic literature will be searched in EMBASE, MEDLINE(by Pubmed), Cochrane library, Web of Science(WOS), Wiley, Springer, PEDro, Chinese Science Citation Database, China National Knowledge Infrastructure (CNKI), Chinese Biomedical literature Database (CBM), Chinese Scientific and Journal Database (VIP), Wan Fang database, Japanese medical database (CiNii), Korean Robotics Institute Summer Scholars (RISS), and Thailand Thai-Journal Citation Index Centre (TCI). We will also cheek reference lists, and the literature will be searched range from the establishment to January 1, 2020.

The search strategy is developed according to published reviews [26] [27]. The detail search strategy of MEDLINE(by Pubmed) is listed in Table 1, while the search strategy will be modified according to other different databases.

Table1 MEDLINE(by Pubmed) search strategy

Spasticity of post-stroke	#1.Stroke[MeSH] OR Apoplexy [Tiab] OR post-stroke[tiab] OR poststroke[tiab]OR Apoplectic [Tiab] OR Apoplexia [Tiab] OR Cerebral hemorrhage [Tiab] OR Ich [Tiab] OR Cerebrovascular accident [Tiab] OR Cerebrovascular disorders [Tiab] OR Cerebral embolism [Tiab] OR Brain

	embolism [Tiab] OR Embolic stroke [Tiab] OR Cerebral infarct OR cva*[tiab] #2.spasm[Mesh] OR dystonia[tiab] OR paraparesis,spastic[tiab] OR muscle spasticity*[tiab] OR muscle hypertonia [tiab] OR muscle rigidity*[tiab] OR muscle tonus[tiab] OR spas*[tiab] OR high tone[tiab] #3. #1 AND #2
Tuina	#4.Tuina[tiab] or Massage[tiab] or Acupressure[tiab] or Rub[tiab] or Massageing[tiab] or Massotheraty[tiab] or manipulation[tiab]
Randomised controlled trial	#5. Randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]
Final search strategy	6.#3 AND #4 AND #5

Data collection and analysis

Selection of literature

Two authors (YZL, JZC) will identify studies according to the inclusion criteria independently. Firstly, they will eliminate duplicate researches by using EndNote software (V. x9.0). Secondly, screening the title and abstract, if necessary, reading the full article to confirm if it should be included. They also use EndNote software to manage the included studies. The screening operation is performed as Figure 1. If there is disagreement during the screening process, discuss with the third experts (GCJ) to make a decision.

Data extraction and management

Two authors (SQS and YFW) will extract data from the included studies independently. The general Information, which consists of title, publication year, authors, country, language, journal source; information of participants: gender, age , stroke type, duration of onset, sample size; information of intervention characteristics: type, session, duration, follow-up time; outcome information about primary outcome, second outcome, observation time points, blinding of evaluators and adverse effects.

Assessment of risk of bias in included studies

Two independent authors (QSZ and FC) will evaluate the risk of bias by using the Cochrane Collaboration bias risk assessment tool to assess the risk bias of the literature included in the systematic review. The two authors will assess the risk of bias of sequence generation, allocation concealment, blinding of participants personnel and outcome assessment, incomplete outcome data, selective outcome reporting and other bias. The evaluation grades are low, high and unclear risk of bias.

Measures of treatment effect

Two independent authors (YHS and QSZ) will use the mean difference(MD) or standard mean difference(SMD) with 95% (CI) for continuous data, the Other binary data will be changed into RR form.

Dealing with missing data

If some information of the included studies missed, we will try to contact the correspondence author through e-mail, phone or other contacts. If failure, we will turn to the following strategies to evaluate the potential influence of missing data [28].

• Worst-case scenario analysis: All participants with missing data counted as failures.

• Extreme worst-case/best-case scenario analysis: Participants with missing outcome data in the exercise arm counted as failures and in the control arm as success and vice versa.

Assessment of heterogeneity

We will use Q-test and I^2 statistic to assess the heterogeneity of the included studies, as the criteria: $I^2<50\%$ indicates low heterogeneity, while $I^2>50\%$ indicates high heterogeneity,

Assessment of reporting bias

We will construct a funnel plots to assess asymmetry, only if at least 10 RCTs are included.

Data synthesis

The meta-analysis of intervention and outcome measures methods will be conducted by RevMan 5.3.5 software (the Cochrane Collaboration, Oxford, England). If the statistical heterogeneity is low ($P>0.1$, or $I^2<50\%$), we will use the fixed-effect model to combine the data, while, if the statistical heterogeneity is high ($P<0.1$, or $I^2>50\%$), we will use the random-effect model. However, if the heterogeneity level much significant, a descriptive analysis will be performed.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis to assess heterogeneity of the study according to the following potential factors from the available sufficient data:

Age

Sex

Different types of stroke (Cerebral hemorrhage or cerebral infarction)

Different types of tuina

Different time/course of treatment

Different parts of affected limbs (upper limb or lower limb)

Different types of control group (acupuncture, placebo, oral/Injection drug or no treatment)

We may make meta-regressions according to age and and the different time/course of treatment if heterogeneity is obvious.

Sensitivity analysis

We will perform the sensitivity analysis to evaluate the robustness and reliability of the pooled results. If the results are not stable, we may turn to removing studies of high risk of bias, or cheek up processing method of missing data (Worst-case scenario analysis: All participants with missing data counted as failures; Extreme worst-case/best-case scenario analysis: Participants with missing outcome data)

Grading of evidence quality

We will use the Grading of Recommendations Assessment, Development and Evaluation(GRADE)[29] to access the confidence in cumulative evidence. Risk of bias, heterogeneity, indirectness, imprecision and Publication bias will be assessed, and the results will be divided into three levels: high, moderate, low and very low.

Amendments

We will show all of the amendments with detail description and rationale in the amendments of this study.

Ethics and dissemination

This study needs no ethical approval, because there is nothing of the data, which have a relationship with an individual patient. We will complete this systematic review according to PRISMA guidelines. The review will provide an assessment of effect and safety of tuina for spasticity of post-stroke. We will publish the findings in a peer-reviewed,open assess journal and the finished systematic review and meta-analysis will be disseminated online, which would be obtained freely for anyone. The results may contribute to improving the therapeutic strategy of patients with post stroke spasticity. This protocol registered on PROSPERO(CRD42020163384).

Patient and public involvement

No patient or public will be involved in our study directly. We only use data that existed in studies published.

Discussion

This systematic review will focus on the efficiency and safety of tuina for spasticity of post-stroke. Tuina is a traditional Chinese physical therapy, which is effective for 516 diseases in China [30], of which spasticity is included. Clinical reports show tuina is well in treatment of spasticity of post-stroke, however, high quality study still did’ t appear. We conduct this review, aim to provide better evidence and guide for clinical decision making. We plan to publish this review within 1 year since the protocol published, then we will update it every 3 years.

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Contributors QSZ and BLS conceived and designed the protocol. QSZ and YHS registered the protocol review in the Prospero database and drafted the manuscript. YZL and JZC designed the search strategy. QSZ and FC draft the protocol, QSZ, GCJ, FC, YHS, SQS, GYH, YZL, JZC, XHX, YFW,XHXand BLS contribute to and approved the final manuscript of the protocol review.
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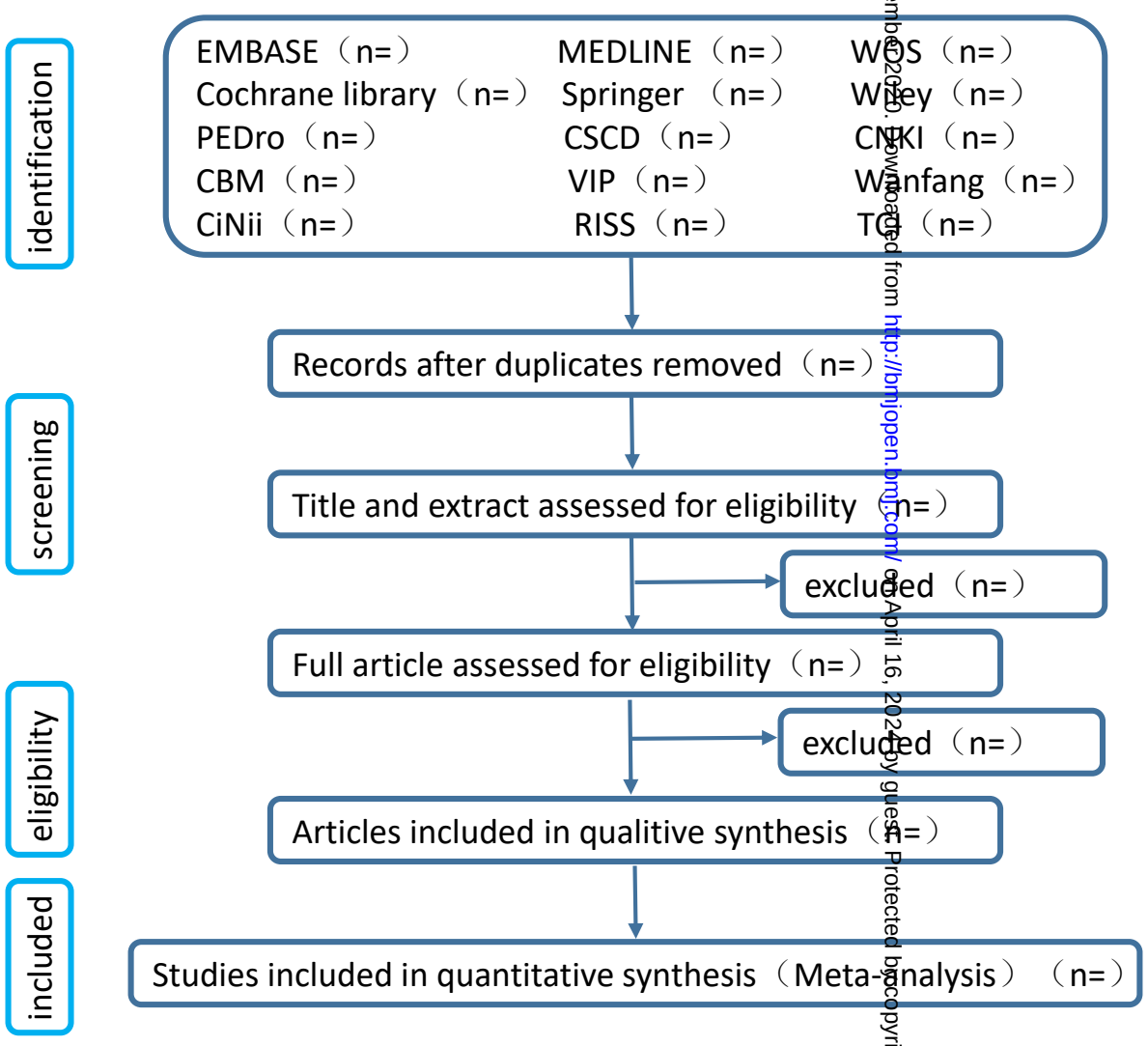
Caption of figure 1: The screening process.



Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
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	n/a This is a new systematic review

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a Registration is in progress
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1,6,7
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7
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	n/a This is a new systematic review
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	7
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	7
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)	1
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	3
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	3,4
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	3,4, appendix 1
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4,5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers)	4

		through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - 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	4
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	4
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3
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	4
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	3
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	5

Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a all the data will be quantitative synthesised
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	2,5
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

Notes:

- 1b: n/a This is a new systematic review
- 2: n/a Registration in progress
- 4: n/a This is a new systematic review
- 15d: n/a all the data will be quantitative synthesised This checklist was completed on 20. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Tuina for spasticity of poststroke: protocol of a systematic review and meta-analysis

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Keywords:	STROKE MEDICINE, Limb reconstruction < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE

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Tuina for spasticity of post stroke: protocol of a systematic review and meta-analysis

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ABSTRACT

Introduction spasticity is a common complication of post-stroke, tuina is a widely used rehabilitation treatment, although there is a lack of supportive evidence on Efficacy and safety for post-stroke spasticity patients. The aim of this systematic review is to assess and synthesis evidence of efficacy and safety of tuina for spasticity of post-stroke.

Methods and analysis. A comprehensive electronic search of EMBASE, MEDLINE, Cochrane library, Web of Science(WOS), Wiley, Springer, PEDro, Chinese Science Citation Database(CSCD), China National Knowledge Infrastructure (CNKI), Chinese Biomedical literature Database (CBM), Chinese Scientific and Journal Database (VIP), Wan Fang database(Wanfang), Japanese medical database (CiNii), Korean Robotics Institute Summer Scholars (RISS), and Thailand Thai-Journal Citation Index Centre (TCI) will be conducted to search literatures of randomized controlled trials of tuina for spasticity of post-stroke survivors range from the establishment to January 1, 2020 There is no time of publication limitations. The primary outcome will be measured with the Modified Ashworth Scale, and the second outcome will included Fugl-Meyer Assessment scale, surface electromyogram root mean square value, the modified Bathel index, stroke specific quality of life scale, quality of life 36 item short-form health survey, and Visual Analogue Scale.Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the risk of bias, GRADE will be used to access the confidence in cumulative evidence. The protocol will be conducted according to approach and Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015.

Ethics and dissemination ethical approval will not be required, for no primary data of individual patients was collected, We will publish the findings in a peer-reviewed journal.
PROSPERO registration number CRD42020163384

Strengths and limitations of this study

▸This is the first comprehensive systematic review focused on Efficacy and safety of tuina for spasticity of post-stroke.
▸Only randomized controlled trials (not included quasi-RCTs) will be included in this study.
▸We searched databases of English, Chinese, Japanses, Korean and Thailand, while other languages may be ignored.

Stroke has been the first risk factor of death in China[1]. It is also one of the diseases with high mortality and disability rate in the world[2]. Limb spasticity is a common complication of post-stroke patients[3 4]. Recent study show that about 17% - 43% of stroke patients had limb spasticity[5-7], and the medical cost of post-stroke limb spasticity patients is about four times as much as post-stroke patients without spasticity[8 9]. Limb spasticity not only severely restricts the ability of patients, reduces the quality of life, but also causes psychological impact on patients' rehabilitation, and brings a great burden to families and society[10 11 12 13 14].
Physical therapy, oral or injection drug therapy, and operation therapy are commonly used in western medicine to treat post-stroke spasticity at present. Oral drugs such as baclofen, eperisone, hydrochloride and diazepine have large side effects which hinder the recovery of motor function with long time taking [15]. Botulinum toxin treatment is difficult to achieve long-term results, and it is often injected for moderate or severe cases of post-stroke spasticity [16 17]. Physical therapy often requires active exercise coordination of patients, however, patients with severe conditions are often unable to cooperate. Surgical treatment is traumatic and a large number of patients often find it difficult to accept. At present, much more of the patients with spasticity after stroke choose external treatment. In China, many external treatment methods of traditional Chinese Medicine (TCM) are applied to the treat this disease.
Tuina is an ancient form of external treatment method, which was based on the meridian and acupoint theory of traditional Chinese medicine , and uses specific operation skill acting on the surface or acupoints of the patient's body to treat diseases. [18 19].Tuina has been widely used in China for hundreds of years and increasingly practiced in western countries in recent years. Systematic evaluation [20] shows that acupuncture is Efficacy and safety in the treatment of

limb spasticity after stroke. Acupuncture and Tuina belong to the external treatment of traditional Chinese medicine, and both are based on the same theory of meridians and acupoints. However, it is still unclear whether the effectiveness of acupuncture is also applicable to Tuina in the treatment of post-stroke spasticity. If tuina therapy for post stroke spasticity is proven to be effective, which has the characteristics of intervention and low cost. At present, there is no systematic review of Tuina in the treatment of post-stroke limb spasticity, so this study will evaluate the Efficacy and safety of Tuina in the treatment of post-stroke limb spasticity, and provide evidence for clinical decision-making of massage.

Methods

The systematic review will be performed following the guideline of Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015[21].

Inclusion Criteria

Types of studies

We will include randomized controlled trials (not included quasi-RCTs) of tuina for post-stroke spasticity in the treatment groups. If muti-arm RCTs comes, we will select the group which used tuina and another without tuina for analysis. We will select the first stage of cross over RCTs, which tuina was firstly used in one group.
RCTs' language of English, Chinese, Japanese, Korean and Thai will be included.

Types of participants

We will include patients suffering post-acute phase of post-stroke spasticity (18 > years old). Stroke (Cerebral infarction or cerebral hemorrhage)is diagnosed according to WHO criteria [22], participants have the symptoms of limb muscle tension increase, and the modified Ashworth Scale (MAS) score is grade 1-2. Participants of any sex, ethnicity will be enrolled.

Types of interventions

The treatment group using tuina, while the control group receives treatment of oral medication, acupuncture, Chinese herbal medication, physical therapy, surgery, botox injections and so on or even with no treatment will be included.

Types of outcome measures

Primary outcome

The primary outcome measures

Muscle tone will be evaluated by the Modified Ashworth Scale (MAS). MAS is a clinical instrument which is commonly used for measuring spasticity, and studies have proofed its reliability[23-25].

Secondary outcome

Motor function was assessed with Fugl-Meyer Assessment scale (FMA) or Simplified Fugl-Meyer Assessment scale

Muscle strength will be defined by surface electromyogram root mean square value (RMS),

Activities of daily living (ADL) will be assessed by the modified Bathel index (MBI),

Quality of life will be measured by stroke specific quality of life scale (SS-QOL) or quality of life 36 item short-form health survey (SF-36)

Limb pain will be assessed by Visual Analogue Scale (VAS)

Safety outcome

Skin abrasions

Exclusion criteria:

•Repeatedly published studies;

•Experiences, letters, systematic reviews, animal experiments;

•Tuina was not only in the experimental group but also in the control group;

•Articles without full text or with data which is missed nor can't be used.

Search strategy

Electronic searches

The published electronic literature will be searched in EMBASE, MEDLINE(by Pubmed), Cochrane library, Web of Science(WOS), Wiley, Springer, PEDro, Chinese Science Citation Database, China National Knowledge Infrastructure (CNKI), Chinese Biomedical literature Database (CBM), Chinese Scientific and Journal Database (VIP), Wan Fang database, Japanese medical database (CiNii), Korean Robotics Institute Summer Scholars (RISS), and Thailand Thai-Journal Citation Index Centre (TCI). We will also cheek reference lists, and the literature will be searched range from the establishment to January 1, 2020.

The search strategy is developed according to published reviews [26] [27]. The detail search strategy of MEDLINE(by Pubmed) is listed in Table 1, while the search strategy will be modified according to other different databases.

Table1 MEDLINE(by Pubmed) search strategy

Spasticity of post-stroke	#1.Stroke[MeSH] OR Apoplexy [Tiab] OR post-stroke[tiab] OR poststroke[tiab]OR Apoplectic [Tiab] OR Apoplexia [Tiab] OR Cerebral hemorrhage [Tiab] OR Ich [Tiab] OR Cerebrovascular accident [Tiab] OR Cerebrovascular disorders [Tiab] OR Cerebral embolism [Tiab] OR Brain embolism [Tiab] OR Embolic stroke [Tiab] OR Cerebral infarct OR cva*[tiab]

	#2.spasm[Mesh] OR dystonia[tiab] OR paraparesis,spastic[tiab] OR muscle spasticity*[tiab] OR muscle hypertonia [tiab] OR muscle rigidity*[tiab] OR muscle tonus[tiab] OR spas*[tiab] OR high tone[tiab] #3. #1 AND #2
Tuina	#4.Tuina[tiab] or Massage[tiab] or Acupressure[tiab] or Rub[tiab] or Massageing[tiab] or Massotheraty[tiab] or manipulation[tiab]
Randomised controlled trial	#5. Randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]
Final search strategy	6.#3 AND #4 AND #5

Data collection and analysis

Selection of literature

Two authors (YZL, JZC) will identify studies according to the inclusion criteria independently. Firstly, they will eliminate duplicate researches by using EndNote software (V. x9.0). Secondly, screening the title and abstract, if necessary, reading the full article to confirm if it should be included. They also use EndNote software to manage the included studies. The screening operation is performed as Figure 1. If there is disagreement during the screening process, discuss with the third experts (GCJ) to make a decision.

Data extraction and management

Two authors (SQS and YFW) will extract data from the included studies independently. In multi-arm RCTs, we will extract data from RCTs of two arms, while we will select one group which contain the treatment of tuina as the treatment group, we will also choose another group the treatment of which without tuina as the control group.The general Information, which consists of title, publication year, authors, country, language, journal source; information of participants: gender, age , stroke type(cerebral infarction or cerebral hemorrhage), duration of onset, sample size; information of intervention characteristics: type, session, duration, follow-up time; outcome information about primary outcome, second outcome, observation time points, and adverse effects.

Assessment of risk of bias in included studies

Two independent authors (QSZ and FC) will evaluate the risk of bias by using the Cochrane Collaboration bias risk assessment tool to assess the risk bias of the literature included in the systematic review. The two authors will assess the risk of bias of sequence generation, allocation concealment, blinding of participants personnel and outcome assessment, incomplete outcome data, selective

outcome reporting and other bias. The evaluation grades are low, high and unclear risk of bias.

Measures of treatment effect

Two independent authors (YHS and QSZ) will use the mean difference(MD) or standard mean difference(SMD) with 95% (CI) for continuous data of final measurements, the Other binary data will be changed into RR form.

Dealing with missing data

If some information of the included studies missed, we will try to contact the correspondence author through e-mail, phone or other contacts. If failure, we will turn to the following strategies to evaluate the potential influence of missing data [28].

• Worst-case scenario analysis: All participants with missing data counted as failures.

• Extreme worst-case/best-case scenario analysis: Participants with missing outcome data in the exercise arm counted as failures and in the control arm as success and vice versa.

Assessment of heterogeneity

We will use Q-test and I^2 statistic to assess the heterogeneity of the included studies, as the criteria: I^2<50% indicates low heterogeneity, while I^2>50% indicates high heterogeneity,

Assessment of reporting bias

We will construct a funnel plots to assess asymmetry, only if at least 10 RCTs are included.

Data synthesis

The meta-analysis of intervention and outcome measures methods will be conducted by RevMan 5.3.5 software (the Cochrane Collaboration, Oxford, England). If the statistical heterogeneity is low (P>0.1,or I^2<50%), we will use the fixed-effect model to combine the data, while, if the statistical heterogeneity is high (P<0.1,or I^2>50%), we will use the random-effect model. However, if the heterogeneity level much significant, a descriptive analysis will be performed.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analysis to assess heterogeneity of the study according to the following potential factors from the available sufficient data:

Age

Sex

Different types of stroke (Cerebral hemorrhage or cerebral infarction)

Different types of tuina

Different time/course of treatment

Different parts of affected limbs (upper limb or lower limb)

Different types of control group (acupuncture, placebo, oral/Injection drug or no treatment)

We may make meta-regressions according to age and and the different time/course of treatment if heterogeneity is obvious.

Sensitivity analysis

We will perform the sensitivity analysis to evaluate the robustness and reliability of the pooled results. If the results are not stable, we may turn to removing studies of high risk of bias, or cheek up processing method of missing data (Worst-case scenario analysis: All participants with missing data counted as failures; Extreme worst-case/best-case scenario analysis: Participants with missing outcome data)

Grading of evidence quality

We will use the Grading of Recommendations Assessment, Development and Evaluation(GRADE)[29] to access the confidence in cumulative evidence. Risk of bias, heterogeneity, indirectness, imprecision and Publication bias will be assessed, and the results will be divided into three levels: high, moderate, low and very low.

Amendments

We will show all of the amendments with detail description and rationale in the amendments of this study.

Ethics and dissemination

This study needs no ethical approval, because there is nothing of the data, which have a relationship with an individual patient. We will complete this systematic review according to PRISMA guidelines. The review will provide an assessment of effect and safety of tuina for spasticity of post-stroke. We will publish the findings in a peer-reviewed,open assess journal and the finished systematic review and meta-analysis will be disseminated online, which would be obtained freely for anyone. The results may contribute to improving the therapeutic strategy of patients with post stroke spasticity. This protocol registered on PROSPERO(CRD42020163384).

Patient and public involvement

No patient or public will be involved in our study directly. We only use data that existed in studies published.

Discussion

This systematic review will focus on the Efficacy and safety of tuina for spasticity of post-stroke. Tuina is a traditional Chinese physical therapy, which is effective for 516 diseases in China [30], of which spasticity is included. Clinical reports show tuina is well in treatment of spasticity of post-stroke, however, high quality study still did’ t appear. We conduct this review, aim to provide better evidence and guide for clinical decision making. We plan to publish

this review within 1 year since the protocol published, then we will update it every 3 years.

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Contributors QSZ and BLS conceived and designed the protocol. QSZ and YHS registered the protocol review in the Prospero database and drafted the manuscript. YZL and JZC designed the search strategy. QSZ and FC draft the protocol, QSZ, GCJ, FC, YHS, SQS, GYH, YZL, JZC, XHX, YFW,XHXand BLS contribute to and approved the final manuscript of the protocol review.
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Competing interests Non declared
Patient consent Not required
Provenance and peer review not commissioned; externally peer reviewed

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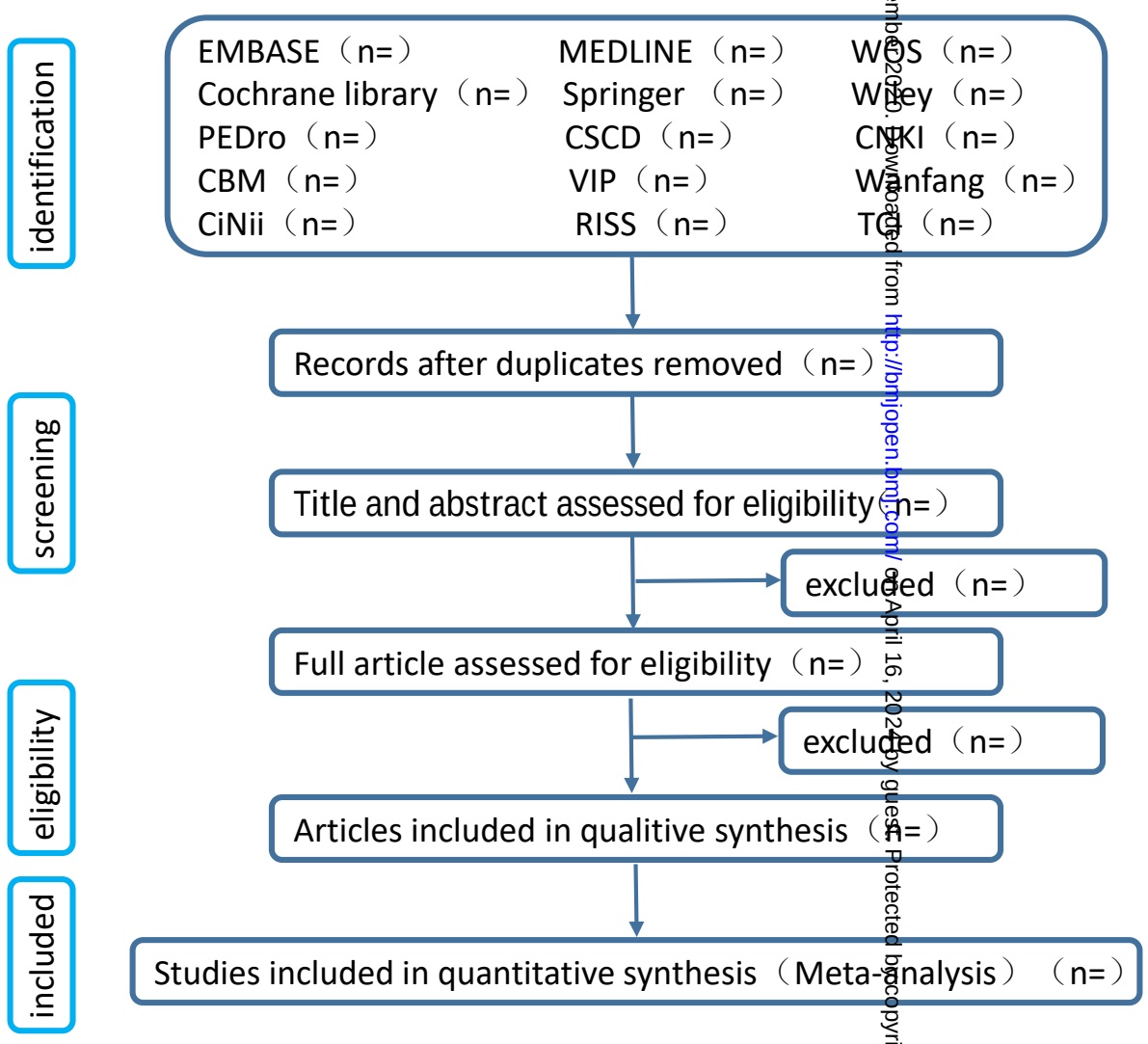
Caption of figure 1: The screening process.



Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
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	n/a This is a new systematic review

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a Registration is in progress
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1,6,7
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	7
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	n/a This is a new systematic review
Support			
Sources	#5a	Indicate sources of financial or other support for the review	7
Sponsor	#5b	Provide name for the review funder and / or sponsor	7
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	7
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)	1
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	3
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	3,4
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	3,4, appendix 1
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4,5
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers)	4

		through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - 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	4
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	4
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	3
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	4
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	3
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	5

Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a all the data will be quantitative synthesised
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	2,5
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

Notes:

- 1b: n/a This is a new systematic review
- 2: n/a Registration in progress
- 4: n/a This is a new systematic review
- 15d: n/a all the data will be quantitative synthesised This checklist was completed on 20. March 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai