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Management of haemorrhoids: protocol of an umbrella review of systematic reviews and meta-analyses

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Complete List of Authors:	Chen, Min; Hospital of Chengdu University of Traditional Chinese Medicine Tang, Tai-Chun; Hospital of Chengdu University of Traditional Chinese Medicine He, Tao-Hong; Hospital of Chengdu University of Traditional Chinese Medicine Du, Yong-Jun; Hospital of Chengdu University of Traditional Chinese Medicine Qin, Di; Chengdu University of Traditional Chinese Medicine Zheng, Hui ; Chengdu University of Traditional Chinese Medicine,
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Management of haemorrhoids: protocol of an umbrella review of systematic reviews and meta-analyses

Running title: Management of haemorrhoids: an umbrella review

Authors: Min Chen[1], Tai-Chun Tang[1], Tao-Hong He[1], Yong-Jun Du[1], Di Qin[2], Hui Zheng[2]

Affiliations:

1 Department of anorectal diseases, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China (Min Chen, Tai-Chun Tang, Tao-Hong He, Yong-Jun Du)

2 The third Hospital/Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, China (Di Qin, Hui Zheng)

Corresponding author:

Hui Zheng, 37 Shi-er-qiao Road, Chengdu, Sichuan, China, 610075. Email: zhenghui@cdutcm.edu.cn. TEL/FAX: 86-28-87689918

Email address of all authors:

Min Chen: cm@cdutcm.edu.cn

Tai-Chun Tang: tangtaichun@cdutcm.edu.cn

Tao-Hong He: 569524159@qq.com

Yong-Jun Du: 357087610@qq.com

Di Qin: qindi@stu.cdutcm.edu.cn

Hui Zheng: zhenghui@cdutcm.edu.cn

Article summary

Strength and limitations

- This will be the first umbrella review trying to summarise current evidence on conservative and surgical treatments for haemorrhoids.
- This will be the first systematic review to evaluate the overall credibility and strength of published systematic reviews and meta-analyses assessing treatments for haemorrhoids and classify them into convincing, highly suggestive, suggestive, and weak evidence.
- Plentiful treatment options are available or haemorrhoidal management, so it may be impossible to include all available treatments.

ABSTRACT

Introduction: The prevalence of haemorrhoid was high in general population, and many treatment modalities are proposed for the management of haemorrhoids. The treatments include conservative and surgical interventions; the credibility and strength of current evidence of their effectiveness was not comprehensively evaluated. We aim to evaluate the credibility of systematic reviews and meta-analyses assessing treatments for haemorrhoid through an umbrella review.

Methods and analysis: We will search OVID Medline, Embase, and Cochrane library from inception to August 2019 without any language restriction. We will include meta-analyses examining the effectiveness of a treatment in the management of haemorrhoids. Two reviewers will independently screen the titles and abstracts of retrieved articles, and they will extract data from the included meta-analyses. For each meta-analysis we will estimate the effect size of a treatment through random-effects model and fixed-effects model, and we will evaluate between-study heterogeneity (Cochrane's Q and I2 statistics) and small-study effect (Egger's test); we will also estimate the evidence of excess significance bias. Evidence of each treatment will be graded according to prespecified criteria. Methodological quality of each meta-analysis will be evaluated by using AMSTAR2.

Ethics and dissemination: We will present results of the umbrella review at conferences and publish the final report. The umbrella review does not require ethical approval.

Registration number: PROSPERO CRD42019140702

INTRODUCTION

Haemorrhoids are swellings veins at the top of the anal canal. Symptoms related to haemorrhoids include bleeding during or after defecation, pain or discomfort, peri-anal itch or irritation. According a national health survey, an estimated 23 million adults were diagnosed with haemorrhoids in the US, accounting for 13% of the US population. Another study from Australian showed that 38.93% of its general population suffered from haemorrhoids[1]. Haemorrhoids have substantial socioeconomic impact. There were 306,000 hospital dischargers for haemorrhoids in the year 2004 in the US, and the demand for haemorrhoid therapy is predicted to increase[2]. Although there are no published figures about the total costs for medications being used to treat haemorrhoid, one of the popular medications for haemorrhoid, Preparation H, was sold for a total cost of $136 million in 2017[3].

Many treatment options are proposed for the management of haemorrhoids. For lower grade of haemorrhoids (grade I-II by a classification system proposed by Sir Goligher[4]), conservative treatments like dietary interventions, life-style modification, and medication treatment are usually adopted[4,5]. A meta-analysis showed that fibre supplementation could reduce the risk of bleeding after defecation[6]. Another meta-analysis showed that fibre supplementation provided consistent beneficial effect on peri-anal pain and itching[7]. Constipation is a known risk factor for the development of haemorrhoids[8], and prebiotics and probiotics improve defecation of soft and hydrated stools[9] and therefore are helpful as supplements for managing haemorrhoids[10]. For medication treatment, clinical experience indicates that topical glucocorticoids, vasoconstrictors like phenylephrine-based suppositories, or

analgesics may be beneficial for temporarily relieving haemorrhoidal symptoms[5]. Herbal remedies are also prepared as suppositories or topical agents for controlling haemorrhoidal symptoms[11]. Although options of conservative medication treatments are plentiful in clinical practice, many of them are not evidence-based and the long-term effectiveness of them have not been verified in randomized controlled trials[5].

For higher grade of haemorrhoids (grade III-IV), surgical interventions are suggested; these interventions include rubber band ligation (RBL), stapled haemorrhoidopexy, haemorrhoidectomy, and transanal haemorrhoidal dearterialization (THD). The most commonly used surgical interventions are traditionally excisional haemorrhoidectomy including open (Milligan-Morgan procedure) and closed (Ferguson procedure) haemorrhoidectomy. The most important disadvantage of haemorrhoidectomy is believed to be postoperative complications like postoperative pain and urinary retention. For the consideration of this disadvantage, new surgical procedures like RBL and stapled haemorrhoidopexy are developed to lower the incidence of postoperative complications. However, these new procedures are criticized for high recurrence rate after surgery and high healthcare expenditure, although they reduce the rate of the postoperative complications.

Several meta-analyses comparing the effectiveness of different surgical interventions have been published[12–18]. The quality of these meta-analyses varied across studies. There is not a systematic review of these meta-analyses to provide an evidence map for the management of haemorrhoids. Umbrella review is a new systematic review

method that quantitatively summarise up-to-date evidence on a specific clinical question[19]. It provides overview of current evidence and finds out uncertainty to guide future research[20]. For the large amount of evidence on conservative and surgical treatments for haemorrhoid management, we aim to conduct an umbrella systematic review to summarise the findings of meta-analyses on conservative and surgical treatments for haemorrhoid management and evaluate the strength and credibility of the findings.

METHODS AND ANALYSIS

Protocol registration and reporting of findings

We design the protocol of the review according to the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)[21]. The protocol has been registered in PROSPERO (no. CRD42019140702). The results of the review will be reported according to the recommendation of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)[22]. Any amendments to the protocol will be recorded and reported in an article with final results. Figure 1 shows the study process.

Inclusion and exclusion criteria

We will include meta-analyses examining the effectiveness of any types of treatment (versus placebo, sham procedures, usual care, or active control) for haemorrhoids, since the primary aim of this umbrella review is to quantitatively evaluate the credibility of current evidence. Meta-analyses of combined treatments (eg, adding a topical bioactive gel to surgical intervention) will also be evaluated. We will consider all main outcomes as reported in the meta-analyses. Outcomes of interest are classified as: hemorrhoidal symptoms (rectal bleeding, defecation pain, and peri-anal itching with a sense of swelling), surgical related conditions (surgical time, postoperative pain, postoperative bleeding, and urinary retention), recurrence of haemorrhoidal symptoms (< 1 year and >1 year), patient's satisfaction (quality of life, time needed for return to usual activities, and hospital stay). We will set no restrictions to the age of participants, study settings (eg, only inpatient or outpatient setting), or

the language of publications. When multiple meta-analyses on the same topic (with the same treatment and the same outcomes) were retrieved, we will include the most recent one. We will consider inclusion of ongoing meta-analyses under the condition that primary analyses of these meta-analyses have been finished. We will exclude meta-analyses reporting only a summary estimate of effect size (ES) without further data (eg, mean, standard deviation, and the number of events) on the primary studies. We will exclude narrative reviews since they provide no quantitative data for analysis, and we will exclude meta-analyses published in the format of letters-to-the-editor since they usually contain little valuable information.

Study source and selection process

We will electronically search OVID Medline, Embase, and the Cochrane Library for potentially eligible candidates. The search strategy will be developed in consultation with an experienced librarian. The following keywords, Mesh terms, and text words will be searched in combination: haemorrhoid, haemorrhoidal, systematic reviews, and meta-analyses. Additional search will be performed by reading the reference lists of the retrieved articles and searching ongoing meta-analysis registered in PROSPERO or the Cochrane Library. Table 1 shows the strategy developed for searching in OVID Medline. Two reviewers will independently screen titles and abstracts of retrieved articles according to the inclusion criteria. Full-text copies will be accessed when the reviewers cannot determine inclusion of a study through title or abstract screening. The excluded studies will be recorded along with the reason for exclusion at each screening stage. We will contact the corresponding authors of the published articles

for additional information if necessary. When disagreement between reviewers on the inclusion of a study was occurred, we will solve the problem through group discussion.

Data collection and verification

Standardised abstraction forms will be used for data collection. Two reviewers (Tai-Chun Tang and Min Chen) will use the forms to collect the following information: characteristics of included meta-analyses (name of first author, publication year, name of intervention, the number of studies included in each meta-analysis, total sample size, and the number of meta-analyses), disease conditions (the grading of haemorrhoid[23]), intervention and control (name of intervention or control, sample size of each treatment cohort, and details of treatment), and outcomes (name and definition of outcome, summary ES and its related 95% confidence interval [95%CI], and the number of participants included in the outcome assessment). When the data are only provided through plots, we will use Ycasd[29] to determine the ES and its 95%CI; when necessary data were not provided in the article, we will contact the corresponding authors to ask for data. All data will be entered into Epi Info™ (version 7.2) for data analysis. A third reviewer (Yong-Jun Du) will check the completeness and correctness of the extracted data.

Assessment of methodological quality

Methodological quality of the included meta-analyses will be assessed by using the Assessment of Multiple Systematic Reviews 2 (AMSTAR2, an updated version of AMSTAR) tool[24]. AMSTAR2 has 16 domains; 7 were critical domains upon which the quality rating of individual systematic reviews depends. Two reviewers (Tao-Hong He

and Di Qin) will rate the quality of each meta-analysis as high, moderate, low, and critically low based on the overall score of the AMSTAR2.

Data analysis

We will use standardised methods adopted by previous umbrella reviews[25–27], and state-of-the-art approaches will be used to set criteria to evaluate the credibility of the findings[20,27]. We will first estimate the summary ES and its related 95%CI using both random-effects and fixed-effects models. Second, we will estimate the 95% prediction interval (95%PI) for the summary estimate based on the random-effects model. The 95%PI specifies the uncertainty for the effect that will be expected in a future study examining the same clinical question. Third, we will evaluate heterogeneity of each meta-analysis by using Cochrane's Q test (considered significant heterogeneity when $p<0.1$), and we will classified the degree of heterogeneity into low ($I^2<25\%$), moderate ($25\% \leq I^2<50\%$), large ($50\% \leq I^2<75\%$), or very large ($I^2 \geq 75\%$) through I^2 statistics.

Fourth, we will use Egger's test to evaluate publication bias and small-study effect, and a p-value <0.1 in the test confirms the bias and small-study effect. Fifth, we will perform an analysis that examines whether the observed number of original studies with positive findings in each meta-analysis is larger than their expected number to detect excess significance bias[28]. The expected number is calculated as the sum of the statistical power estimates for each original study in a meta-analysis. The power of each study will be calculated through an algorithm using noncentral-t distribution[29,30]; the power calculation depends on the value of true ES. Since the

true ES for any meta-analysis is impossible to acquire, we will use the ES from the largest study in a meta-analysis to substitute[25]. We will calculate the ratio of observed number over expected number to evaluate the extent of excess significance bias, and we will claim existence of the bias when a chi-squared test arrives at a level of $p<0.1$[31].

Criteria for evaluating credibility of evidence

We will use the following criteria to evaluate the credibility of current meta-analysis[25,26,32]: (1) having $p<10^{-6}$ on the basis of random-effects model; (2) having >1000 participants in a single meta-analysis; (3) having low or moderate heterogeneity (I^2 <50%); (4) having 95%PI that excludes the null value; (5) having no evidence of small-study effect; (6) having no evidence of excess significance bias. Meta-analysis that meets criteria (1) to (6) will be classified as convincing evidence (not suggestive of bias; class I evidence); meta-analysis that meets criteria (1) to (4) will be classified as highly suggestive evidence (class II evidence); meta-analysis that meets criteria (2) and has $p<0.001$ will be classified as suggestive evidence (class III evidence); meta-analysis that has only $p<0.05$ will be classified as weak evidence (class IV evidence).

DISCUSSION

Regarding the high prevalence of haemorrhoids in the general population and its heavy socioeconomic impact, we believe that it is important to provide an evidence map with all available treatments on it for clinical practitioners and patients, especially when plenty of systematic reviews and meta-analyses assessing various treatments

for haemorrhoidal management are available.

To the best of our knowledge, the review will be the first to adopt the method of umbrella review, which provides overview of the credibility of the evidence for all the treatments. The umbrella review is initially designed for confirmation of risk factors in the development of a specific disease condition[19], and it is used for evaluating the effectiveness of multiple treatments for a disease in the recent 5 years[25–27]. We therefore assume that it is essential to use this method to screen and find out treatments that are with convincing evidence for haemorrhoidal management.

The biggest challenge in the conducting the review is how to determine all treatments for haemorrhoids, and one of the study limitations is that we may miss some of the treatments. We will cope with the challenge by asking specialists to help develop search strategy, building a team with colorectal specialists, asking patients to involve in the study design, and register the study protocol at PROSPERO.

The result of this review will be published in a peer-reviewed journal, and we believe that the result will benefit clinical practitioners, patients, and policy makers.

Acknowledgement

The authors thank Dr. Ling Yue and Dr. An-Mei Zhang from Chengdu University of Traditional Chinese Medicine for their suggestions in the search strategy development and data extraction protocol.

Authors' contributions

Min Chen and Hui Zheng designed the study. Di Qin developed the search strategy.

Min Chen and Tai-Chun Tang will perform literature search and screen the eligibility of the retrieved articles. Tao-Hong He and Di Qin will evaluate the quality of the retrieved meta-analyses. Yong-Jun Du and Tao-Hong He will extract information from the eligible studies and prepare the information for data analysis. Min Chen and Hui Zheng will perform data analysis. Min Chen wrote the first draft of the protocol, and all authors read the article and approve it for publication.

Funding statement

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Conflict of interest statement

The authors report no competing interests in this study.

Patient and Public Involvement statement

The study is a systematic review focusing on the management of haemorrhoids. Patients from the inpatient setting of the colorectal department at Chengdu University of Traditional Chinese Medicine participated in the design of outcome assessments.

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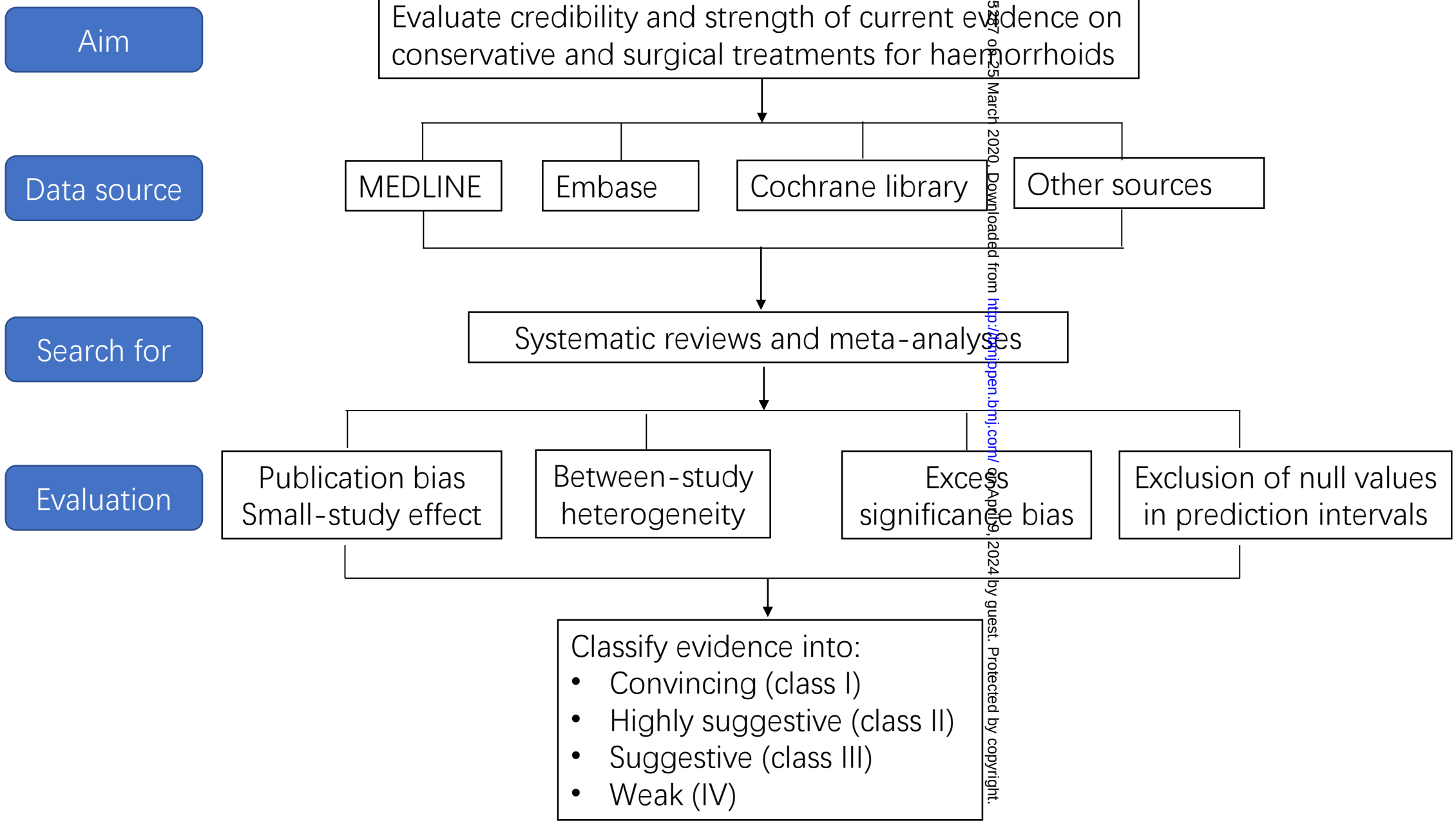
Table 1. Search strategy (via OVID Medline)

No.	Search items
1	hemorrhoid/
2	(hemorrhoid* or haemorrhoid*).ti,ab,kw,tw.
3	1 or 2
4	systematic review/ or meta-analysis/ or systematic review as topic/ or meta-analysis as topic/ or network meta-analysis/
5	(systematic review or meta-analys$).ti,ab,kw,tw.
6	4 or 5
7	3 and 6

Figure legend

Figure 1. Study flowchart



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

Section and topic	Item No	Checklist item	Page no.
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	Not an update
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12-13
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	No
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12-13
Sponsor	5b	Provide name for the review funder and/or sponsor	12-13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7-8
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	8-9
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	Table 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
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)	8-9
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	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
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	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10-11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10-11

*** 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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Complete List of Authors:	Chen, Min; Hospital of Chengdu University of Traditional Chinese Medicine Tang, Tai-Chun; Hospital of Chengdu University of Traditional Chinese Medicine He, Tao-Hong; Hospital of Chengdu University of Traditional Chinese Medicine Du, Yong-Jun; Hospital of Chengdu University of Traditional Chinese Medicine Qin, Di; Chengdu University of Traditional Chinese Medicine Zheng, Hui ; Chengdu University of Traditional Chinese Medicine,
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Management of haemorrhoids: protocol of an umbrella review of systematic reviews and meta-analyses

Running title: Management of haemorrhoids: an umbrella review

Authors: Min Chen[1], Tai-Chun Tang[1], Tao-Hong He[1], Yong-Jun Du[1], Di Qin[2], Hui Zheng[2]

Affiliations:

1 Department of anorectal diseases, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China (Min Chen, Tai-Chun Tang, Tao-Hong He, Yong-Jun Du)

2 The third Hospital/Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, China (Di Qin, Hui Zheng)

Corresponding author:

Hui Zheng, 37 Shi-er-qiao Road, Chengdu, Sichuan, China, 610075. Email: zhenghui@cdutcm.edu.cn. TEL/FAX: 86-28-87689918

Email address of all authors:

Min Chen: cm@cdutcm.edu.cn

Tai-Chun Tang: tangtaichun@cdutcm.edu.cn

Tao-Hong He: 569524159@qq.com

Yong-Jun Du: 357087610@qq.com

Di Qin: qindi@stu.cdutcm.edu.cn

Hui Zheng: zhenghui@cdutcm.edu.cn

ABSTRACT

Introduction: The prevalence of haemorrhoidal diseases was high in general population, and many treatments are proposed for the management of haemorrhoids. The treatments include conservative and surgical interventions; the credibility and strength of current evidence of their effectiveness are not comprehensively evaluated. We aim to evaluate the credibility of systematic reviews and meta-analyses that assess the effectiveness of the treatments for haemorrhoidal diseases through an umbrella review.

Methods and analysis: We will search OVID Medline, Embase, and Cochrane library from inception to March 2020 without any language restriction. We will include meta-analyses that examine the effectiveness of treatments in the management of haemorrhoids. Two reviewers will independently screen the titles and abstracts of retrieved articles, and they will extract data from the included meta-analyses. For each meta-analysis we will estimate the effect size of a treatment through random-effects model and fixed-effects model, and we will evaluate between-study heterogeneity (Cochrane's Q and I^2 statistics) and small-study effect (Egger's test); we will also estimate the evidence of excess significance bias. Evidence of each treatment will be graded according to prespecified criteria. Methodological quality of each meta-analysis will be evaluated by using AMSTAR2. The Corrected Cover Area (CCA) method will be used to assess the impact of overlap in reviews on the findings of the umbrella review.

Ethics and dissemination: We will present the results of the umbrella review at conferences and publish the final report in a peer-reviewed journal. The umbrella

review does not require ethical approval.

Registration number: PROSPERO CRD42019140702

Article summary

Strength and limitations

- This will be the first umbrella review that summarises current evidence of using conservative and surgical treatments to treat haemorrhoids.
- The umbrella review will evaluate the overall credibility and strength of the published systematic reviews and meta-analyses that assess treatments for haemorrhoids and classify them into convincing, highly suggestive, suggestive, and weak evidence.
- Plentiful treatment options are available or the management of haemorrhoidal diseases, so we might not include all treatments in the umbrella review.

INTRODUCTION

Haemorrhoidal disease is one of the most common anorectal conditions encountered in daily practice by general practitioners[1]. Symptoms related to haemorrhoids include bleeding during or after defecation, pain or discomfort, and peri-anal itch or irritation. According a national health survey, an estimated 23 million adults were diagnosed with haemorrhoids in the US, accounting for 13% of the US population. Another study from Australian showed that 38.93% of its general population suffered from haemorrhoidal diseases[1]. There were 306,000 hospital dischargers and at least 2.2-million outpatient evaluations for haemorrhoids in the US[2,3], and the demand for haemorrhoidal therapy is predicted to increase[2]. Although the total annual costs for medications being used to treat haemorrhoid is unclear, one of the popular medications for haemorrhoid, *Preparation H*, was sold for a total cost of $136 million in 2017[4].

Many treatment options are proposed for the management of haemorrhoids. For lower grade of haemorrhoids (grade I-II by a classification system proposed by Sir Goligher[5]), conservative treatments like dietary interventions, lifestyle modification, and medication treatment are usually adopted[5,6]. A meta-analysis showed that fibre supplementation could reduce the risk of bleeding after defecation[7]. Another meta-analysis showed that fibre supplementation provided consistent beneficial effect on peri-anal pain and itching[8]. Constipation is a known risk factor for the development of haemorrhoids[9], and prebiotics and probiotics improve the symptoms of constipation[10] and therefore are helpful as supplements for managing haemorrhoids[11]. For medication treatment, topical glucocorticoids,

vasoconstrictors like phenylephrine-based suppositories, or analgesics may be beneficial for temporarily relieving haemorrhoidal symptoms[6]. Herbal remedies are also prepared as suppositories or topical agents for alleviating haemorrhoidal symptoms[12]. Although plentiful options of conservative treatments are available in clinical practice, many of them are not evidence-based and the long-term effectiveness of them have not been verified in randomized controlled trials[6].

For higher grade of haemorrhoids (grade III-IV), surgical interventions are normally suggested; these interventions include rubber band ligation (RBL), stapled haemorrhoidopexy, haemorrhoidectomy, and haemorrhoidal artery ligation (HAL). The most commonly used surgical interventions are traditionally excisional haemorrhoidectomy including open (Milligan-Morgan procedure) and closed (Ferguson procedure) haemorrhoidectomy. The most important disadvantage of haemorrhoidectomy is believed to be postoperative complications like postoperative pain and urinary retention. For the consideration of this disadvantage, new surgical procedures like HAL and stapled haemorrhoidopexy are developed to lower the incidence of postoperative complications. However, these new procedures are criticized for high recurrence rate after surgery and high healthcare expenditure, although they reduce the rate of the postoperative complications.

Several meta-analyses comparing the effectiveness of different surgical interventions have been published[13–19]. The quality of these meta-analyses varied across studies. No systematic review of these meta-analyses has been performed to provide an evidence map for the management of haemorrhoids. Umbrella review is a new

systematic review method that quantitatively summarise up-to-date evidence of a specific clinical scenario[20]. It provides overview of current evidence and finds out the uncertainty to guide future research[21]. For the large amount of evidence on conservative and surgical treatments for the management of haemorrhoidal diseases, we aim to conduct an umbrella review to summarise the findings of meta-analyses on conservative and surgical treatments for the management of haemorrhoids and evaluate the strength and credibility of the findings.

METHODS AND ANALYSIS

Protocol registration and reporting of findings

We design the protocol of the review according to the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)[22]. The protocol has been registered in PROSPERO (no. CRD42019140702). The results of the review will be reported according to the recommendation of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)[23]. Any amendments to the protocol will be recorded and reported in an article with final results. Figure 1 shows the study process.

Patient and Public Involvement statement

The study is an umbrella review focusing on the management of haemorrhoids. Patients from the inpatient setting of the colorectal department at Hospital of Chengdu University of Traditional Chinese Medicine participated in the design of outcome assessments.

Inclusion and exclusion criteria

We will include meta-analyses that examine the effectiveness of lifestyle modification, conservative pharmacological treatments, and surgical interventions (versus placebo, sham procedures, usual care, or active control) in the management of haemorrhoids. Conservative pharmacological treatments will include oral supplements (insoluble fibres, hydrophilic bulk-forming colloids, prebiotics, probiotics, and synbiotics), topical agents (glucocorticoids, vasoconstrictors, and analgesics), and phlebotonic drugs comprising flavonoids. We will assess the efficacy and safety of lifestyle modification and conservative pharmacological treatments in the management of grade I-II

haemorrhoids. Surgical interventions will include RBL, HAL, sclerotherapy, infrared coagulation, stapled haemorrhoidopexy, and haemorrhoidectomy. Meta-analyses of combined treatments (eg, adding a topical bioactive gel to a surgical intervention) will also be evaluated. Outcomes of interest are classified as: symptoms related to haemorrhoids (rectal bleeding, defecation pain, and peri-anal itching with a sense of swelling), surgical related conditions (surgical time, postoperative pain, postoperative bleeding, and urinary retention), recurrence of haemorrhoidal symptoms (< 1 year and >1 year), patient's satisfaction (quality of life, time needed for return to usual activities, and hospital stay). We will set no restrictions to the age of participants, study settings (eg, only inpatient or outpatient setting), or the language of publications. When multiple meta-analyses on the same topic (with the same treatment and the same outcomes) were retrieved, we will include the most recent one. We will consider inclusion of ongoing meta-analyses under the condition that primary analyses of these meta-analyses have been finished, and we will contact the authors to ask for related data when possible. We will exclude meta-analyses that report only a summary estimate of effect size (ES) without any further data (eg, mean, standard deviation, and the number of events) of the primary studies. We will exclude narrative reviews since they provide no quantitative data (eg, means, standard deviations, or event rate) for analysis. We will exclude meta-analyses published in the format of letters-to-the-editor since they usually contain little valuable information.

Outcome assessments

We will assess the following outcomes: improvement of haemorrhoidal symptoms,

surgical related outcomes, and patient's satisfaction. The improvement of haemorrhoidal symptoms will be assessed in conservative treatments. The haemorrhoidal symptoms will include rectal bleeding, defecation pain, and peri-anal itching with a sense of swelling. We will adopt the criteria for justification of improvement of haemorrhoidal symptoms as reported in each included systematic review. The surgical related outcomes will be assessed in surgical treatments. These outcomes will include surgical time, postoperative pain, postoperative bleeding, urinary retention, and recurrence of haemorrhoidal symptoms (< 1 year and >1 year). The surgical time refers to the duration needed for surgical procedure in managing haemorrhoids, which will be assessed as defined in each systematic review. Postoperative pain will be defined as acute pain at day 1-3 after surgical intervention, including pain during or after defecation, pain during body movement, or rest pain at rest. The assessment of the patient's satisfaction includes quality of life, time needed for return to usual activities, and hospital stay; it will be assessed in surgical treatments, and it will be assessed at 1 month, 6 months, and 12 months after treatment.

Study source and selection process

We will electronically search OVID Medline, Embase, the Cochrane Library, and Web of Science from inception to March 2020 without any language restriction for potentially eligible candidates. The search strategy will be developed in consultation with an experienced librarian (Yu-Lan Ren from Chengdu University of Traditional Chinese Medicine). In developing the search strategy, four specialists (Min Chen, Tai-

Chun Tang, Tao-Hong He, and Yong-Jun Du) from colorectal department in Hospital of Chengdu University of Traditional Chinese Medicine will decide keywords, Mesh terms, and text words, which will be searched in combination: haemorrhoid, haemorrhoidal, systematic reviews, and meta-analyses (Table 1 and the supplements). Additional search will be performed by manual search of the reference lists of the retrieved articles and the search for ongoing meta-analyses registered in PROSPERO or the Cochrane Library. Table 1 shows the strategy developed for searching in OVID Medline, and the search strategy for Embase and the Cochrane library is showed in the supplements. Retrieved articles will be imported into Zotero (version 5.0.82) for screening. Two reviewers will independently screen titles and abstracts of retrieved articles according to the inclusion criteria. Full-text copies will be accessed when the reviewers cannot decide the inclusion of a study through title or abstract screening. The excluded studies will be recorded along with the reason for exclusion at each screening stage. We will contact the corresponding authors of the published articles for additional information if necessary. When disagreement between reviewers on the inclusion of a study was occurred, we will solve the problem through group discussion.

Data collection and verification

Standardised abstraction forms will be used for data collection. Two reviewers (Tai-Chun Tang and Min Chen) will use the forms to collect the following information: characteristics of included meta-analyses (name of first author, publication year, name of intervention, the number of studies included in each meta-analysis, total sample size, and the number of meta-analyses), disease conditions (the grading of

haemorrhoid[24]), intervention and control (name of intervention or control, sample size of each treatment cohort, and details of treatment), and outcomes (name and definition of outcome, summary ES and its related 95% confidence interval [95%CI], and the number of participants included in the outcome assessment). When the data are only provided through plots, we will use Ycasd[25] to determine the ES and its 95%CI; when necessary data were not provided in the article, we will contact the corresponding authors to ask for data. All data will be entered into Epi Info™ (version 7.2) for data analysis. A third reviewer (Yong-Jun Du) will check the completeness and correctness of the extracted data.

Assessment of methodological quality

Methodological quality of the included meta-analyses will be assessed by using the Assessment of Multiple Systematic Reviews 2 (AMSTAR2, an updated version of AMSTAR) tool[26]. AMSTAR2 has 16 domains; 7 were critical domains, upon which the quality rating of an individual systematic review depends. Two reviewers (Tao-Hong He and Di Qin) will rate the quality of each meta-analysis as high, moderate, low, and critically low based on the overall score of the AMSTAR2.

Data analysis

We will use standardised methods adopted by previous umbrella reviews[27–29], and state-of-the-art approaches will be used to set criteria to evaluate the credibility of the findings[21,29]. We will first estimate the summary ES and its related 95%CI using both random-effects and fixed-effects models. Second, we will estimate the 95% prediction interval (95%PI) for the summary estimate based on the random-effects

model. The 95%PI specifies the uncertainty for the effect that will be expected in a future study examining the same clinical question. Third, we will evaluate heterogeneity of each meta-analysis by using Cochrane's Q test (considered significant heterogeneity when $p<0.1$), and we will classify the degree of heterogeneity into low ($I^2<25\%$), moderate ($25\% \leq I^2<50\%$), large ($50\% \leq I^2<75\%$), or very large ($I^2 \geq 75\%$) through I^2 statistics.

Fourth, we will use Egger's test to evaluate publication bias and small-study effect, and a p-value <0.1 in the test confirms the bias and small-study effect. Fifth, we will perform an analysis that examines whether the observed number of original studies with positive findings in each meta-analysis is larger than their expected number to detect excess significance bias[30]. The expected number is calculated as the sum of the statistical power estimates for each original study in a meta-analysis. The power of each study will be calculated through an algorithm using noncentral-t distribution[31,32]; the power calculation depends on the value of true ES. Since the true ES for any meta-analysis is impossible to acquire, we will use the ES from the largest study in a meta-analysis to substitute[27]. We will calculate the ratio of observed number over expected number to evaluate the extent of excess significance bias, and we will claim existence of the bias when a chi-squared test arrives at a level of $p<0.1$[33].

Many systematic reviews and meta-analyses focusing on a similar topic include a different number of primary studies, the overall results and conclusions of an umbrella review might therefore be biased. To assess the potential impact of the overlap in the

inclusion of the same primary studies, the degree of overlap within and between reviews was measured using the validated Corrected Cover Area (CCA) method[34]. A CCA score of 0–5 indicates slight overlap, 6–10 moderate, 11–15 high, and >15 very high[34].

Criteria for evaluating credibility of evidence

We will use the following criteria to evaluate the credibility of the included meta-analyses[27,28,35]: (1) having $p<10^{-6}$ on the basis of random-effects model; (2) having >1000 participants in a single meta-analysis; (3) having low or moderate heterogeneity (I^2 <50%); (4) having 95%PI that excludes the null value; (5) having no evidence of small-study effect; (6) having no evidence of excess significance bias. Meta-analysis that meets criteria (1) to (6) will be classified as convincing evidence (not suggestive of bias; class I evidence); meta-analysis that meets criteria (1) to (4) will be classified as highly suggestive evidence (class II evidence); meta-analysis that meets criteria (2) and has p<0.001 will be classified as suggestive evidence (class III evidence); meta-analysis that has only p<0.05 will be classified as weak evidence (class IV evidence).

DISCUSSION

Regarding the high prevalence of haemorrhoids in the general population and its heavy socioeconomic impact, we believe that it is important to provide an evidence map of treatments for haemorrhoids for clinical practitioners and patients, especially when plentiful systematic reviews and meta-analyses are available.

Haemorrhoidal disease is one of the most common clinical condition in practice. Multiple treatments including conservative and surgical treatments are available for the management of different grades of haemorrhoids. Conservative treatments are usually prescribed for grade I-II haemorrhoids, and surgical treatments are for grade II-IV haemorrhoids[3,36–39]. Numerous clinical studies have been performed to study the effect of conservative and surgical treatments on haemorrhoids[5,6], and many systematic reviews and meta-analyses were conducted to evaluate and confirm the effectiveness of these treatments. However, an overview of the systematic reviews and meta-analyses is still lacking. An evidence map of treatments for the management of haemorrhoids is necessary, to facilitate the decision making of clinical practitioners and participants. Current guidelines usually focus on the evidence of surgical treatments but neglect the evidence of conservative treatments[40], which also warrants an overview of current evidence.

Umbrella review is a review of systematic reviews and meta-analyses, which is viewed as one of the four next-generation meta-analysis[20]. An umbrella review is able to quantitatively synthesise information from all systematic reviews and meta-analyses on a given topic. Being different from narrative reviews of systematic reviews, the umbrella review recalculates the effect size of a treatment, evaluates the credibility of the evidence by estimating excess significance bias and small-study effect, and further classifies the confidence of the evidence into 4 levels[29,41]. Our review will adopt the method of umbrella review, to re-evaluate the credibility of the evidence of treatments for haemorrhoidal diseases, especially the conservative

treatments. To the best of our knowledge, the review will be the first to adopt the method of umbrella review in assessing the credibility of current evidence of haemorrhoidal management. The umbrella review is initially designed for confirmation of risk factors in the development of a specific disease condition[20], and it is used for evaluating the effectiveness of multiple treatments for a disease in the recent 5 years[27–29]. We therefore assume that it is essential to use this method to screen and find out treatments that are with convincing evidence for haemorrhoidal management.

The result of this review will be published in a peer-reviewed journal, and we believe that the result will benefit clinical practitioners, patients, and policy makers.

Ethics and dissemination

The study is an umbrella review, which requires no ethical approval. We will present the results of the umbrella review at conferences and publish the final report in a peer-reviewed journal.

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Authors' contributions

Min Chen and Hui Zheng designed the study. Di Qin developed the search strategy. Min Chen and Tai-Chun Tang will perform literature search and screen the eligibility of the retrieved articles. Tao-Hong He and Di Qin will evaluate the quality of the

retrieved meta-analyses. Yong-Jun Du and Tao-Hong He will extract information from the eligible studies and prepare the information for data analysis. Min Chen and Hui Zheng will perform data analysis. Min Chen wrote the first draft of the protocol, and all authors read the article and approve it for publication.

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Conflict of interest statement

The authors report no competing interests in this study.

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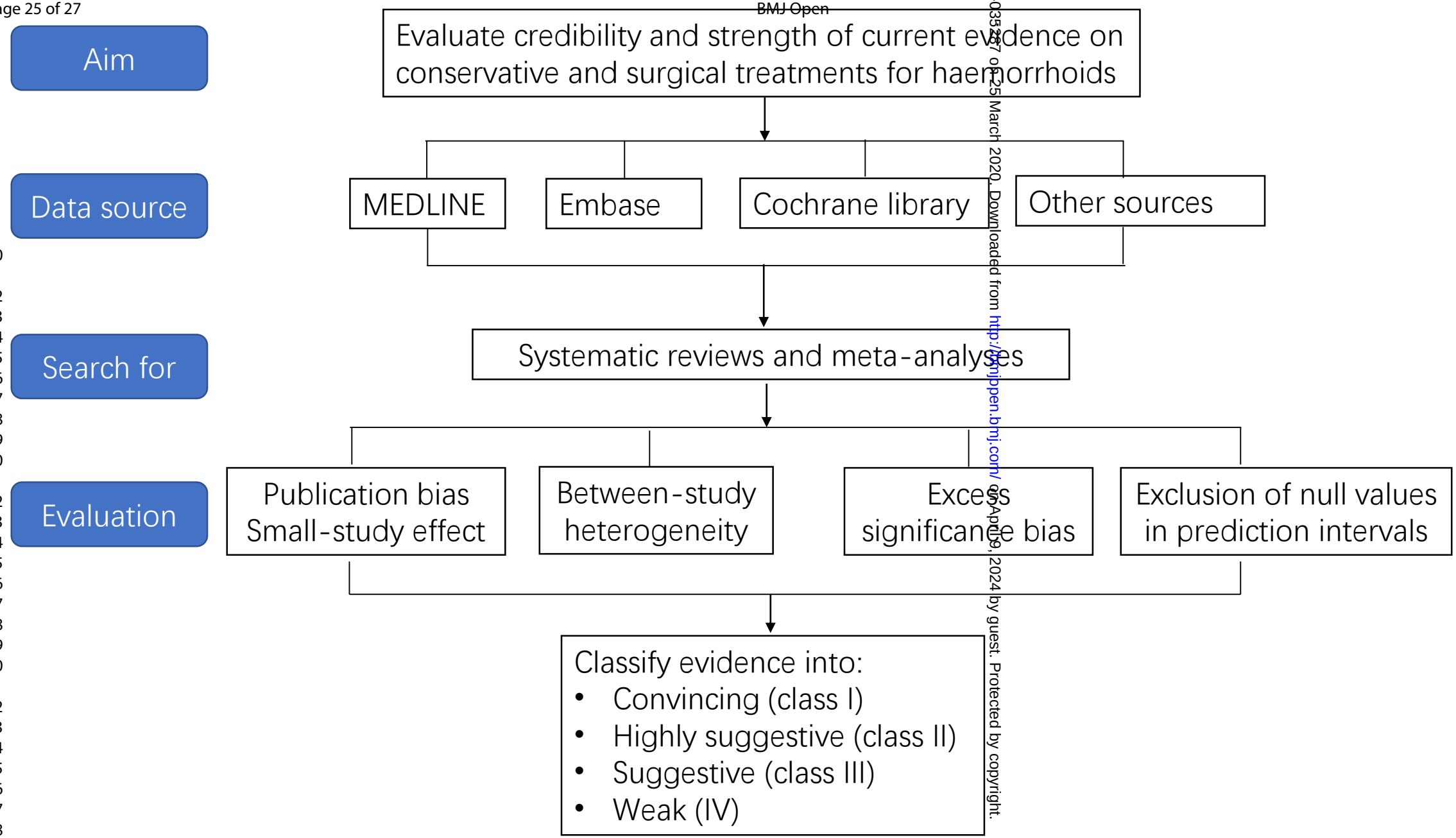
Table 1. Search strategy (via OVID Medline)

No.	Search items
1	hemorrhoid/
2	(hemorrhoid* or haemorrhoid*).ti,ab,kw,tw.
3	1 or 2
4	systematic review/ or meta-analysis/ or systematic review as topic/ or meta-analysis as topic/ or network meta-analysis/
5	(systematic review or meta-analys$).ti,ab,kw,tw.
6	4 or 5
7	3 and 6

Figure legend

Figure 1. Study flowchart



Search strategy

EMBASE

No.	Search terms
1	'hemorrhoid'/exp
2	hemorrhoid* :ab,ti,kw OR haemorrhoid*:ab,ti,kw
3	1 OR 2
4	'systematic review'/exp OR 'meta-analysis'/exp
5	'systematic review':ti,ab,kw OR 'meta analys*:ti,ab,kw
6	4 OR 5
7	3 AND 6

Cochrane library

No.	Search terms
1	hemorrhoid
2	hemorrhoid*
3	haemorrhoid*
4	1 or 2 or 3
5	systematic review
6	meta-analysis
7	meta-analys*
8	5 or 6 or 7
9	4 and 8

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

Section and topic	Item No	Checklist item	Page no.
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	Not an update
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12-13
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	No
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12-13
Sponsor	5b	Provide name for the review funder and/or sponsor	12-13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7-8
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	8-9
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	Table 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
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)	8-9
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	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
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	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10-11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10-11

*** 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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Management of haemorrhoids: protocol of an umbrella review of systematic reviews and meta-analyses

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Management of haemorrhoids: protocol of an umbrella review of systematic reviews and meta-analyses

Running title: Management of haemorrhoids: an umbrella review

Authors: Min Chen[1], Tai-Chun Tang[1], Tao-Hong He[1], Yong-Jun Du[1], Di Qin[2], Hui Zheng[2]

Affiliations:

1 Department of anorectal diseases, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China (Min Chen, Tai-Chun Tang, Tao-Hong He, Yong-Jun Du)

2 The third Hospital/Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, China (Di Qin, Hui Zheng)

Corresponding author:

Hui Zheng, 37 Shi-er-qiao Road, Chengdu, Sichuan, China, 610075. Email: zhenghui@cdutcm.edu.cn. TEL/FAX: 86-28-87689918

Email address of all authors:

Min Chen: cm@cdutcm.edu.cn

Tai-Chun Tang: tangtaichun@cdutcm.edu.cn

Tao-Hong He: 569524159@qq.com

Yong-Jun Du: 357087610@qq.com

Di Qin: qindi@stu.cdutcm.edu.cn

Hui Zheng: zhenghui@cdutcm.edu.cn

ABSTRACT

Introduction: The prevalence of haemorrhoidal diseases was high in general population, and many treatments are proposed for the management of haemorrhoids. The treatments include conservative and surgical interventions; the credibility and strength of current evidence of their effectiveness are not comprehensively evaluated. We aim to evaluate the credibility of systematic reviews and meta-analyses that assess the effectiveness of the treatments for haemorrhoidal diseases through an umbrella review.

Methods and analysis: We will search OVID Medline, Embase, Cochrane library, and Web of Science from inception to March 2020 without any language restriction. We will include meta-analyses that examine the effectiveness of treatments in the management of haemorrhoids. Two reviewers will independently screen the titles and abstracts of retrieved articles, and they will extract data from the included meta-analyses. For each meta-analysis we will estimate the effect size of a treatment through random-effects model and fixed-effects model, and we will evaluate between-study heterogeneity (Cochrane's Q and I^2 statistics) and small-study effect (Egger's test); we will also estimate the evidence of excess significance bias. Evidence of each treatment will be graded according to prespecified criteria. Methodological quality of each meta-analysis will be evaluated by using AMSTAR2. The Corrected Cover Area (CCA) method will be used to assess the impact of overlap in reviews on the findings of the umbrella review.

Ethics and dissemination: We will present the results of the umbrella review at conferences and publish the final report in a peer-reviewed journal. The umbrella

review does not require ethical approval.

Registration number: PROSPERO CRD42019140702

Article summary

Strength and limitations

- This will be the first umbrella review that summarises current evidence of using conservative and surgical treatments to treat haemorrhoids.
- The umbrella review will evaluate the overall credibility and strength of the published systematic reviews and meta-analyses that assess treatments for haemorrhoids and classify them into convincing, highly suggestive, suggestive, and weak evidence.
- Plentiful treatment options are available or the management of haemorrhoidal diseases, so we might not include all treatments in the umbrella review.

INTRODUCTION

Haemorrhoidal disease is one of the most common anorectal conditions encountered in daily practice by general practitioners[1]. Symptoms related to haemorrhoids include bleeding during or after defecation, pain or discomfort, and peri-anal itch or irritation. According a national health survey, an estimated 23 million adults were diagnosed with haemorrhoids in the US, accounting for 13% of the US population. Another study from Australian showed that 38.93% of its general population suffered from haemorrhoidal diseases[1]. There were 306,000 hospital dischargers and at least 2.2-million outpatient evaluations for haemorrhoids in the US[2,3], and the demand for haemorrhoidal therapy is predicted to increase[2]. Although the total annual costs for medications being used to treat haemorrhoid is unclear, one of the popular medications for haemorrhoid, *Preparation H*, was sold for a total cost of $136 million in 2017[4].

Many treatment options are proposed for the management of haemorrhoids. For lower grade of haemorrhoids (grade I-II by a classification system proposed by Sir Goligher[5]), conservative treatments like dietary interventions, lifestyle modification, and medication treatment are usually adopted[5,6]. A meta-analysis showed that fibre supplementation could reduce the risk of bleeding after defecation[7]. Another meta-analysis showed that fibre supplementation provided consistent beneficial effect on peri-anal pain and itching[8]. Constipation is a known risk factor for the development of haemorrhoids[9], and prebiotics and probiotics improve the symptoms of constipation[10] and therefore are helpful as supplements for managing haemorrhoids[11]. For medication treatment, topical glucocorticoids,

vasoconstrictors like phenylephrine-based suppositories, or analgesics may be beneficial for temporarily relieving haemorrhoidal symptoms[6]. Herbal remedies are also prepared as suppositories or topical agents for alleviating haemorrhoidal symptoms[12]. Although plentiful options of conservative treatments are available in clinical practice, many of them are not evidence-based and the long-term effectiveness of them have not been verified in randomized controlled trials[6].

For higher grade of haemorrhoids (grade III-IV), surgical interventions are normally suggested; these interventions include rubber band ligation (RBL), stapled haemorrhoidopexy, haemorrhoidectomy, and haemorrhoidal artery ligation (HAL). The most commonly used surgical interventions are traditionally excisional haemorrhoidectomy including open (Milligan-Morgan procedure) and closed (Ferguson procedure) haemorrhoidectomy. The most important disadvantage of haemorrhoidectomy is believed to be postoperative complications like postoperative pain and urinary retention. For the consideration of this disadvantage, new surgical procedures like HAL and stapled haemorrhoidopexy are developed to lower the incidence of postoperative complications. However, these new procedures are criticized for high recurrence rate after surgery and high healthcare expenditure, although they reduce the rate of the postoperative complications.

Several meta-analyses comparing the effectiveness of different surgical interventions have been published[13–19]. The quality of these meta-analyses varied across studies. No systematic review of these meta-analyses has been performed to provide an evidence map for the management of haemorrhoids. Umbrella review is a new

systematic review method that quantitatively summarise up-to-date evidence of a specific clinical scenario[20]. It provides overview of current evidence and finds out the uncertainty to guide future research[21]. For the large amount of evidence on conservative and surgical treatments for the management of haemorrhoidal diseases, we aim to conduct an umbrella review to summarise the findings of meta-analyses on conservative and surgical treatments for the management of haemorrhoids and evaluate the strength and credibility of the findings.

METHODS AND ANALYSIS

Protocol registration and reporting of findings

We design the protocol of the review according to the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)[22]. The protocol has been registered in PROSPERO (no. CRD42019140702). The results of the review will be reported according to the recommendation of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)[23]. Any amendments to the protocol will be recorded and reported in an article with final results. Figure 1 shows the study process.

Patient and Public Involvement statement

The study is an umbrella review focusing on the management of haemorrhoids. Patients from the inpatient setting of the colorectal department at Hospital of Chengdu University of Traditional Chinese Medicine participated in the design of outcome assessments.

Inclusion and exclusion criteria

We will include meta-analyses that examine the effectiveness of lifestyle modification, conservative pharmacological treatments, and surgical interventions (versus placebo, sham procedures, usual care, or active control) in the management of haemorrhoids. Conservative pharmacological treatments will include oral supplements (insoluble fibres, hydrophilic bulk-forming colloids, prebiotics, probiotics, and synbiotics), topical agents (glucocorticoids, vasoconstrictors, and analgesics), and phlebotonic drugs comprising flavonoids. We will assess the efficacy and safety of lifestyle modification and conservative pharmacological treatments in the management of grade I-II

haemorrhoids. Surgical interventions will include RBL, HAL, sclerotherapy, infrared coagulation, stapled haemorrhoidopexy, and haemorrhoidectomy. Meta-analyses of combined treatments (eg, adding a topical bioactive gel to a surgical intervention) will also be evaluated. Outcomes of interest are classified as: symptoms related to haemorrhoids (rectal bleeding, defecation pain, and peri-anal itching with a sense of swelling), surgical related conditions (surgical time, postoperative pain, postoperative bleeding, and urinary retention), recurrence of haemorrhoidal symptoms (< 1 year and >1 year), patient's satisfaction (quality of life, time needed for return to usual activities, and hospital stay). We will set no restrictions to the age of participants, study settings (eg, only inpatient or outpatient setting), or the language of publications. When multiple meta-analyses on the same topic (with the same treatment and the same outcomes) were retrieved, we will include the most recent one. We will consider inclusion of ongoing meta-analyses under the condition that primary analyses of these meta-analyses have been finished, and we will contact the authors to ask for related data when possible. We will exclude meta-analyses that report only a summary estimate of effect size (ES) without any further data (eg, mean, standard deviation, and the number of events) of the primary studies. We will exclude narrative reviews since they provide no quantitative data (eg, means, standard deviations, or event rate) for analysis. We will exclude meta-analyses published in the format of letters-to-the-editor since they usually contain little valuable information.

Outcome assessments

We will assess the following outcomes: improvement of haemorrhoidal symptoms,

surgical related outcomes, and patient's satisfaction. The improvement of haemorrhoidal symptoms will be assessed in conservative treatments. The haemorrhoidal symptoms will include rectal bleeding, defecation pain, and peri-anal itching with a sense of swelling. We will adopt the criteria for justification of improvement of haemorrhoidal symptoms as reported in each included systematic review. The surgical related outcomes will be assessed in surgical treatments. These outcomes will include surgical time, postoperative pain, postoperative bleeding, urinary retention, and recurrence of haemorrhoidal symptoms (< 1 year and >1 year). The surgical time refers to the duration needed for surgical procedure in managing haemorrhoids, which will be assessed as defined in each systematic review. Postoperative pain will be defined as acute pain at day 1-3 after surgical intervention, including pain during or after defecation, pain during body movement, or rest pain at rest. The assessment of the patient's satisfaction includes quality of life, time needed for return to usual activities, and hospital stay; it will be assessed in surgical treatments, and it will be assessed at 1 month, 6 months, and 12 months after treatment.

Study source and selection process

We will electronically search OVID Medline, Embase, the Cochrane Library, and Web of Science from inception to March 2020 without any language restriction for potentially eligible candidates. The search strategy will be developed in consultation with an experienced librarian (Yu-Lan Ren from Chengdu University of Traditional Chinese Medicine). In developing the search strategy, four specialists (Min Chen, Tai-

Chun Tang, Tao-Hong He, and Yong-Jun Du) from colorectal department in Hospital of Chengdu University of Traditional Chinese Medicine will decide keywords, Mesh terms, and text words, which will be searched in combination: haemorrhoid, haemorrhoidal, systematic reviews, and meta-analyses (Table 1 and the supplements). Additional search will be performed by manual search of the reference lists of the retrieved articles and the search for ongoing meta-analyses registered in PROSPERO or the Cochrane Library. Table 1 shows the strategy developed for searching in OVID Medline, and the search strategy for Embase and the Cochrane library is showed in the supplements. Retrieved articles will be imported into Zotero (version 5.0.82) for screening. Two reviewers will independently screen titles and abstracts of retrieved articles according to the inclusion criteria. Full-text copies will be accessed when the reviewers cannot decide the inclusion of a study through title or abstract screening. The excluded studies will be recorded along with the reason for exclusion at each screening stage. We will contact the corresponding authors of the published articles for additional information if necessary. When disagreement between reviewers on the inclusion of a study was occurred, we will solve the problem through group discussion.

Data collection and verification

Standardised abstraction forms will be used for data collection. Two reviewers (Tai-Chun Tang and Min Chen) will use the forms to collect the following information: characteristics of included meta-analyses (name of first author, publication year, name of intervention, the number of studies included in each meta-analysis, total sample size, and the number of meta-analyses), disease conditions (the grading of

haemorrhoid[24]), intervention and control (name of intervention or control, sample size of each treatment cohort, and details of treatment), and outcomes (name and definition of outcome, summary ES and its related 95% confidence interval [95%CI], and the number of participants included in the outcome assessment). When the data are only provided through plots, we will use Ycasd[25] to determine the ES and its 95%CI; when necessary data were not provided in the article, we will contact the corresponding authors to ask for data. All data will be entered into Epi Info™ (version 7.2) for data analysis. A third reviewer (Yong-Jun Du) will check the completeness and correctness of the extracted data.

Assessment of methodological quality

Methodological quality of the included meta-analyses will be assessed by using the Assessment of Multiple Systematic Reviews 2 (AMSTAR2, an updated version of AMSTAR) tool[26]. AMSTAR2 has 16 domains; 7 were critical domains, upon which the quality rating of an individual systematic review depends. Two reviewers (Tao-Hong He and Di Qin) will rate the quality of each meta-analysis as high, moderate, low, and critically low based on the overall score of the AMSTAR2.

Data analysis

We will use standardised methods adopted by previous umbrella reviews[27–29], and state-of-the-art approaches will be used to set criteria to evaluate the credibility of the findings[21,29]. We will first estimate the summary ES and its related 95%CI using both random-effects and fixed-effects models. Second, we will estimate the 95% prediction interval (95%PI) for the summary estimate based on the random-effects

model. The 95%PI specifies the uncertainty for the effect that will be expected in a future study examining the same clinical question. Third, we will evaluate heterogeneity of each meta-analysis by using Cochrane's Q test (considered significant heterogeneity when $p<0.1$), and we will classify the degree of heterogeneity into low ($I^2<25\%$), moderate ($25\% \leq I^2<50\%$), large ($50\% \leq I^2<75\%$), or very large ($I^2 \geq 75\%$) through I^2 statistics.

Fourth, we will use Egger's test to evaluate publication bias and small-study effect, and a p-value <0.1 in the test confirms the bias and small-study effect. Fifth, we will perform an analysis that examines whether the observed number of original studies with positive findings in each meta-analysis is larger than their expected number to detect excess significance bias[30]. The expected number is calculated as the sum of the statistical power estimates for each original study in a meta-analysis. The power of each study will be calculated through an algorithm using noncentral-t distribution[31,32]; the power calculation depends on the value of true ES. Since the true ES for any meta-analysis is impossible to acquire, we will use the ES from the largest study in a meta-analysis to substitute[27]. We will calculate the ratio of observed number over expected number to evaluate the extent of excess significance bias, and we will claim existence of the bias when a chi-squared test arrives at a level of $p<0.1$[33].

Many systematic reviews and meta-analyses focusing on a similar topic include a different number of primary studies, the overall results and conclusions of an umbrella review might therefore be biased. To assess the potential impact of the overlap in the

inclusion of the same primary studies, the degree of overlap within and between reviews was measured using the validated Corrected Cover Area (CCA) method[34]. A CCA score of 0–5 indicates slight overlap, 6–10 moderate, 11–15 high, and >15 very high[34].

Criteria for evaluating credibility of evidence

We will use the following criteria to evaluate the credibility of the included meta-analyses[27,28,35]: (1) having $p<10^{-6}$ on the basis of random-effects model; (2) having >1000 participants in a single meta-analysis; (3) having low or moderate heterogeneity (I^2 <50%); (4) having 95%PI that excludes the null value; (5) having no evidence of small-study effect; (6) having no evidence of excess significance bias. Meta-analysis that meets criteria (1) to (6) will be classified as convincing evidence (not suggestive of bias; class I evidence); meta-analysis that meets criteria (1) to (4) will be classified as highly suggestive evidence (class II evidence); meta-analysis that meets criteria (2) and has p<0.001 will be classified as suggestive evidence (class III evidence); meta-analysis that has only p<0.05 will be classified as weak evidence (class IV evidence).

DISCUSSION

Regarding the high prevalence of haemorrhoids in the general population and its heavy socioeconomic impact, we believe that it is important to provide an evidence map of treatments for haemorrhoids for clinical practitioners and patients, especially when plentiful systematic reviews and meta-analyses are available.

Haemorrhoidal disease is one of the most common clinical condition in practice. Multiple treatments including conservative and surgical treatments are available for the management of different grades of haemorrhoids. Conservative treatments are usually prescribed for grade I-II haemorrhoids, and surgical treatments are for grade II-IV haemorrhoids[3,36–39]. Numerous clinical studies have been performed to study the effect of conservative and surgical treatments on haemorrhoids[5,6], and many systematic reviews and meta-analyses were conducted to evaluate and confirm the effectiveness of these treatments. However, an overview of the systematic reviews and meta-analyses is still lacking. An evidence map of treatments for the management of haemorrhoids is necessary, to facilitate the decision making of clinical practitioners and participants. Current guidelines usually focus on the evidence of surgical treatments but neglect the evidence of conservative treatments[40], which also warrants an overview of current evidence.

Umbrella review is a review of systematic reviews and meta-analyses, which is viewed as one of the four next-generation meta-analysis[20]. An umbrella review is able to quantitatively synthesise information from all systematic reviews and meta-analyses on a given topic. Being different from narrative reviews of systematic reviews, the umbrella review recalculates the effect size of a treatment, evaluates the credibility of the evidence by estimating excess significance bias and small-study effect, and further classifies the confidence of the evidence into 4 levels[29,41]. Our review will adopt the method of umbrella review, to re-evaluate the credibility of the evidence of treatments for haemorrhoidal diseases, especially the conservative

treatments. To the best of our knowledge, the review will be the first to adopt the method of umbrella review in assessing the credibility of current evidence of haemorrhoidal management. The umbrella review is initially designed for confirmation of risk factors in the development of a specific disease condition[20], and it is used for evaluating the effectiveness of multiple treatments for a disease in the recent 5 years[27–29]. We therefore assume that it is essential to use this method to screen and find out treatments that are with convincing evidence for haemorrhoidal management.

The result of this review will be published in a peer-reviewed journal, and we believe that the result will benefit clinical practitioners, patients, and policy makers.

Ethics and dissemination

The study is an umbrella review, which requires no ethical approval. We will present the results of the umbrella review at conferences and publish the final report in a peer-reviewed journal.

Acknowledgement

The authors thank Dr. Yu-Lan Ren, Dr. Ling Yue, and Dr. An-Mei Zhang from Chengdu University of Traditional Chinese Medicine for their suggestions in the search strategy development and data extraction protocol.

Authors' contributions

Min Chen and Hui Zheng designed the study. Di Qin developed the search strategy. Min Chen and Tai-Chun Tang will perform literature search and screen the eligibility of the retrieved articles. Tao-Hong He and Di Qin will evaluate the quality of the

retrieved meta-analyses. Yong-Jun Du and Tao-Hong He will extract information from the eligible studies and prepare the information for data analysis. Min Chen and Hui Zheng will perform data analysis. Min Chen wrote the first draft of the protocol, and all authors read the article and approve it for publication.

Funding statement

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Conflict of interest statement

The authors report no competing interests in this study.

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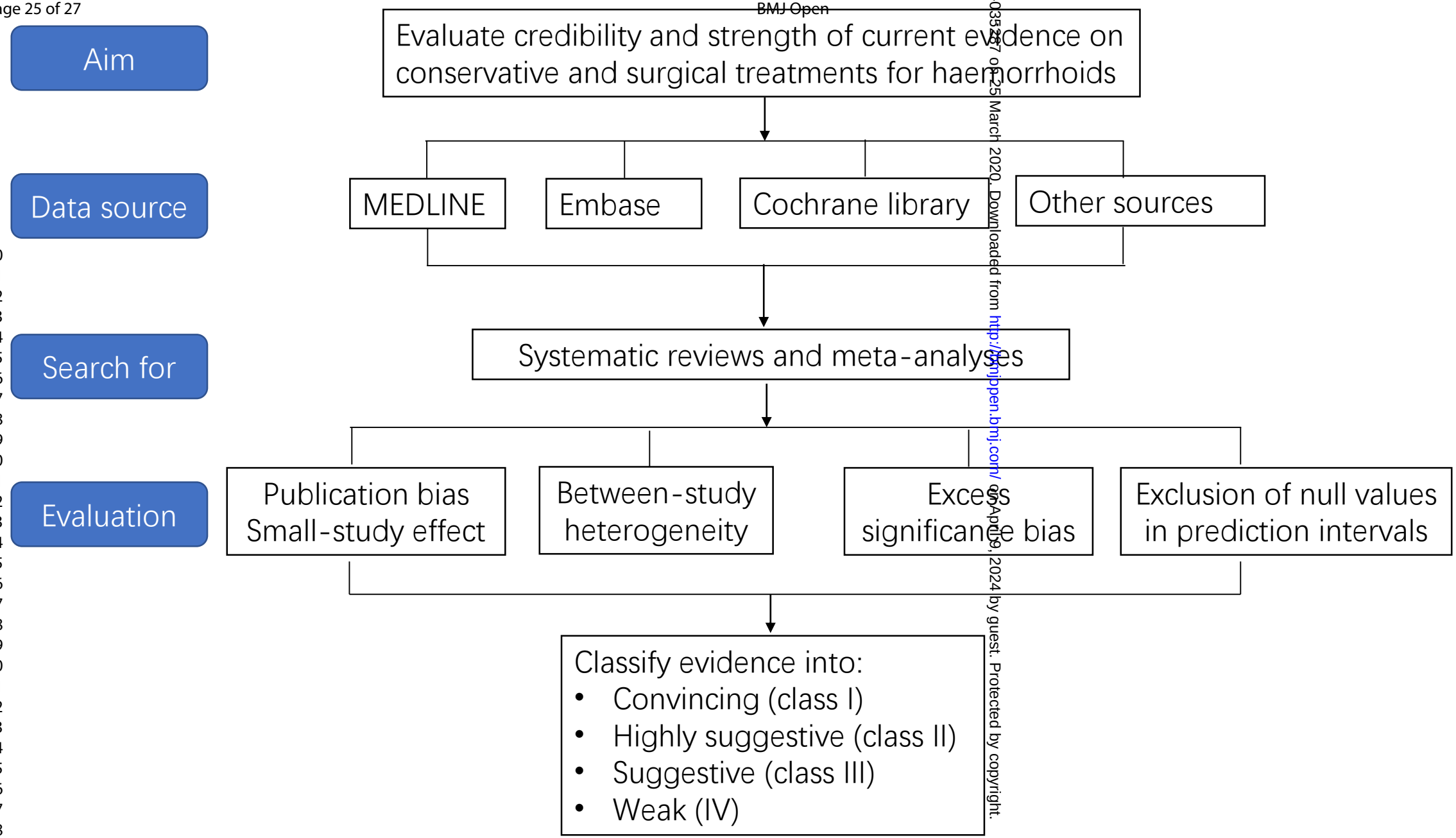
Table 1. Search strategy (via OVID Medline)

No.	Search items
1	hemorrhoid/
2	(hemorrhoid* or haemorrhoid*).ti,ab,kw,tw.
3	1 or 2
4	systematic review/ or meta-analysis/ or systematic review as topic/ or meta-analysis as topic/ or network meta-analysis/
5	(systematic review or meta-analys$).ti,ab,kw,tw.
6	4 or 5
7	3 and 6

Figure legend

Figure 1. Study flowchart



Search strategy

EMBASE

No.	Search terms
1	'hemorrhoid'/exp
2	hemorrhoid* :ab,ti,kw OR haemorrhoid*:ab,ti,kw
3	1 OR 2
4	'systematic review'/exp OR 'meta-analysis'/exp
5	'systematic review':ti,ab,kw OR 'meta analys*:ti,ab,kw
6	4 OR 5
7	3 AND 6

Cochrane library

No.	Search terms
1	hemorrhoid
2	hemorrhoid*
3	haemorrhoid*
4	1 or 2 or 3
5	systematic review
6	meta-analysis
7	meta-analys*
8	5 or 6 or 7
9	4 and 8

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

Section and topic	Item No	Checklist item	Page no.
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	Not an update
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12-13
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	No
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12-13
Sponsor	5b	Provide name for the review funder and/or sponsor	12-13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	7-8
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	8-9
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	Table 1

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
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)	8-9
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	9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9
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	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10-11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10-11

*** 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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