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Endovenous ablation and surgery in great saphenous vein reflux. A systematic review and network meta-analysis of randomized controlled trials protocol

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Keywords:	endovenous, saphenous vein reflux, stripping, saphenofemoral ligation, sclerotherapy

Endovenous ablation and surgery in great saphenous vein reflux. A systematic review and network meta-analysis of randomized controlled trials protocol.

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Abstract

Introduction. Endovenous ablations are the new standard procedures for treatment of great saphenous vein (GSV) reflux. These included endovenous laser ablation (EVLA), radiofrequency ablation (RFA), and ultrasound-guided foam sclerotherapy (UGFS). EVLA and RFA demonstrated similar anatomical success to surgery for short term outcome but controversial results for longer term (≥5 years). Additional evidences from randomized controlled trials (RCT) have been published with varying follow-up times. This study is therefore conducted to directly and indirectly compare outcomes among all procedures stratify by short and long term follow-up.

Methods and analysis. Medline and Scopus will be searched from 2000 to May 2018 with predefined search strategy. Interventions of interest are open surgery (i.e., saphenofemoral or high ligation (HL) with stripping) and endovenous abrasions (i.e., EVLA, RFA, and UGFS). The primary outcomes are anatomical success. Two independent reviewers will select studies, extract data, assess risk of bias of included studies. Disagreement will be adjudicated by the third party. Outcomes will be directly pooled if there are at least 3 studies in that comparison. A fixed effect model will be used unless heterogeneity is present, a random effect model will be applied. Source of heterogeneity will be explored using meta-regression analysis, sub-group analysis will be done accordingly. Publication bias will be assessed using Egger's test and funnel plot. A network meta-analysis will be applied to indirect compare all interventions including RFA, EVLA, EVLA with HL, UGFS, UGFS with HL, and HL with stripping. Probability being best intervention will be estimated and ranked. Inconsistency assumption be checked using a design-treatment interaction model.

Ethics and dissemination. Ethical approval is not required for systematic review and network meta-analysis. The study will be published in a peer-reviewed journal.

PROSPERO registration number. CRD42018096794

Keywords. Endovenous, stripping, varicose vein, saphenous vein reflux, saphenofemoral ligation, sclerotherapy

Article summary

Strengths and limitations of this study

- This review will include all relevant RCTs comparing outcomes between endovenous ablation and surgery since 2000 to March 2018.
- Stratify analysis by short and long term follow up will be performed
- Probability of being a best procedure will be estimated and provided

INTRODUCTION

Chronic venous disease is common condition affected both men and women with prevalence rate of 30-50%.[1 2] This has led to significant health spending, about 1%-2% of health care budgets had been spent for venous disease in European countries.[3] Great saphenous vein (GSV) reflux is the most common site of reflux accounting for about 80% of all reflux sites.[4] GSV ablation is recommended to improve symptoms and quality of life of patients.[5 6]

To ablate GSV, endovenous ablations are recommended over surgery as a new standard treatment.[6] The benefits over open surgery are less postoperative pain, lower rate of surgical site infection, faster return to normal activities and work.[7] However, it is accompanied with higher equipment costs.[8] Many techniques of endovenous ablation have therefore emerged including endovenous laser ablation (EVLA), radiofrequency ablation (RFA), and ultrasound-guided sclerotherapy (UGFS). Two novel techniques of non-

tumescent non-thermal endovenous ablation (NTNT) including mechanico-chemical ablation (MOCA) and cyanoacrylate injection had been introduced for several years with promising early results.[9]

Directly-related outcome after GSV ablation is anatomical success, which is patency of the GSV after ablation. It can be classified as technical failure, periprocedural, early, midterm, and late failure if it is occurred ≤ 3 days, ≤ 1 month, 1 year, 1-3 years, and > 3 years after operation. Another important outcome is patient's-reported outcome measurements or PROMs, which measured patients' perspective in both generic and specific quality of life.[6]

Previous evidences about efficacy of these procedures had been pooled considering short to long term outcomes. The first systematic review in 2012 included 28 RCTs to compare short-midterm outcomes of endovenous procedures with surgery. It found benefits of endovenous procedures (i.e. EVLA, RFA, and UGFS) over open surgery in postoperative pain, morbidity, and faster recovery with similar efficacies for EVLA and RFA but less efficacy for UGFS.[7] Other two systematic reviews in 2017[10] and 2018[11] considered only long term outcomes by including 12 and 9 RCTs with > 5 year follow up, respectively. Although the former meta-analysis[10] considered only RCTs, they pooled outcome data (i.e., success/recurrent reflux rates and mean difference before vs after of each intervention without directly compared these outcomes between groups. As a result, randomization may be broken and thus bias the results. The latest meta-analysis[11] could not detect whether recurrence rates between EVLA, RFA, and surgery were different due to small numbers of included studies and subjects.

Some additional RCTs comparing endovenous procedures and open surgery or comparing among endovenous ablations have been published with varying of follow up time

and also surgical techniques (with or without high ligation).[11-24] These data have not yet been updated in the aforementioned meta-analyses with long term outcomes. In addition, accurate and precise magnitude of benefit of endovenous procedures over surgery along time horizon of treatment is important for economic analysis.[25] Therefore, this systematic review and network meta-analysis is conducted which aim to directly and indirectly compare clinical outcomes between interventions stratifying by time of follow up including anatomical success, clinical recurrence, and quality of life. Other postoperative outcomes include postoperative pain, time to return to normal activities and work, and complications (i.e. wound infection, hematoma, paresthesia, ecchymosis, and deep venous thrombosis) are pooled using all available data. Probability being best intervention will be estimated and ranked for each outcome. Risk and benefit will be then compared.

METHODS

The protocol was developed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement for reporting systematic reviews and meta-analyses[26] and extension statement for systematic reviews incorporating network meta-analyses of health care interventions.[27]

Search strategy

Medline and Scopus will be searched from August 2011 to May 2018. Search terms are constructed according to patients and intervention/comparator as follows: "Varicose veins"[Mesh] OR "Saphenous vein"[Mesh] OR varicose OR saphenous NOT esophageal; radiofrequency OR RFA OR VNUS OR endovenous OR EVLT OR EVLA OR laser OR sclerotherapy[Mesh] OR foam sclerotherapy OR UGFS OR stripping OR sapheno-femoral ligation OR surgery. These search terms of the two domains will be combined with

AND with limited to clinical trial, human, and English articles. Reference lists from previous meta-analysis and all eligible papers will be reviewed for relevant studies.

Study selection

After remove duplicated studies, study selection will be done by two independent authors (BS and TB). Title and abstract will be screened for eligible criteria, full text will then be reviewed if decision cannot be made. Any disagreement will be adjudicated by a third party (AT). Data from multiple publication studies will be combined as one publication for analysis.

RCTs studied in patients with GSV reflux will be included if they meet following criteria: Had any pair of following interventions including endovenous ablation (i.e., EVLA, RFA, and UGFS) and surgery; had at least one following outcomes including anatomical success, postoperative pain, wound infection, hematoma, ecchymosis, deep vein thrombosis, time to return to normal activities and work, clinical recurrence, and quality of life. Studies will be excluded if they have insufficient data for pooling.

Interventions

Interventions of interest are open surgery (i.e., saphenofemoral or high ligation (HL) with stripping of the GSV) and endovenous abrasions (i.e., EVLA, RFA, and UGFS).
EVLA ablates GSV using laser energy with varying wavelength such as 810, 940, 980, 1470, and 1560 nm.[28] RFA generates heat by radiofrequency energy. Both RFA and EVLA are usually performed with tumescent anesthesia to prevent thermal injury to adjacent tissue. UGFS, damages endothelium causing occlusion of vein, is injected to the GSV by either direct puncture or via catheter.[29] HL might or might not be applied with endovenous procedures.

Outcomes

The primary outcome of interest is anatomical success, which originally defined according to individual studies as not having patency of GSV, occlusion, or reflux of GSV diagnosed by duplex scan. This outcome will be considered according to time frame of follow up, i.e., periprocedural, early, midterm, and late failure.[6]

Secondary outcomes of interest are clinical recurrence, postoperative pain, time to return to normal activities and work, quality of life, and postoperative complications (i.e. hematoma, ecchymosis, paresthesia, and deep vein thrombosis). Quality of life will be compared according to time frame of follow up. Clinical recurrence will be defined as clinical detected recurrence of varicose vein.

Data extraction

Two independent authors (BS and KS) will extract data using standardized data extraction forms. General characteristics of studies and interventions including patients' severity, age, detailed of intervention, duration of follow up, type of anesthesia, compression method, tumescent anesthesia, primary outcome definition, concomitant phlebectomy and sclerotherapy bwill be extracted. These data will be used for exploring source of heterogeneity. Mean (SD) and frequencies of outcomes data by intervention will be extracted for pooling. Mean difference or risk ratio will be used in case of no summary data provided in the study. Inconsistent data will be solved by consensus with third party (AT) and finalize. Author will contact corresponding authors twice for missing data.

Risk of bias assessment

Studies will be assessed for risk of bias using Cochrane Collaboration's tool [30] by two independent researchers (BS and SO). This tool consists of 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of

outcome assessors, incomplete outcome reports, selective outcome reports, and other source of bias. Disagreement will be resolved by third party (AT).

Grading evidence

Quality of evidence will be graded separately for each outcome using a tool suggested by the GRADE Working Group.[31] Five domains will be assessed including study limitations, consistency, indirectness, imprecision, and publication bias. The evidence will be downgraded one and two levels for serious and very serious concerns, respectively.

Statistical analysis

Direct meta-analysis

Data will be directly pooled if there are at least 3 studies for each comparison. Risk ratios (RR) with 95% confidence interval (CI) will be estimated for dichotomous outcome. A continuity correction will be used if there is a zero cell. The RRs will be pooled using inverse variance, and Dersimonian and Laird for data without and with heterogeneity, respectively. For continuous outcome, unstandardized or standardised mean difference (MD) with 95%CI will be estimated and pooled across studies if outcome measures are the same and different scales, respectively. Mean and standard deviation (SD) will be estimated from median and range/interquartile If study did not report mean and SD.[32]

Heterogeneity will be assessed using degree of heterogeneity (I^2) and Q test. If either $I^2 \geq 25\%$ or Q test is significant with $p < 0.10$, the results will be considered as heterogeneous and random effect model will be applied. Possible source of heterogeneity will be explored by fitting studies' characteristics (i.e., outcome definition, concomitant phlebectomy, type of anesthesia, and compression method), interventional techniques (i.e., laser wavelength, catheter use in UGFS), and patient's characteristics (i.e., age, severity) in a meta-regression model if data are sufficient for doing. Subgroup or sensitivity analysis will

be performed accordingly to factors that can reduce a degree of heterogeneity. Publication bias will be assessed by funnel plot an Egger test. If there is evidence of asymmetry of the funnel by either two, a contour-enhanced plot will be constructed to distinguish whether a source of asymmetry due to heterogeneity or missing studies.

Network meta-analysis

A network meta-analysis[33] will be performed to indirectly compare among interventions including RFA, EVLA, EVLA with HL, UGFS, UGFS with HL, and HL with stripping. HL with stripping will be used as a common comparator. Analysis will be performed as following steps: First, relative intervention effect, i.e., risk ratio (RR) along with its variance-covariance will be estimated by binary regression analysis. A multivariate random-effect meta-analysis with consistency mode will be then used to pool RRs across studies. Mixed intervention comparisons will be next estimated. Probability being best intervention will be estimated and ranked using surface under cumulative ranking (SUCRA) method, rankogram will be plotted accordingly. Cluster rank plot will be constructed by comparing probability being risk and benefit.

The inconsistency assumption (i.e., whether direct effects agree with the indirect effects) will be checked using a design-treatment interaction model. If this assumption does not meet, an inconsistency factor (IF, i.e., ln(RRdirect)-ln(RRindirect)) will be estimated and tested. In addition, a comparison-adjusted funnel plot taking into account different comparisons will be plotted to explore whether there is evidence of small study effect for the whole network.[33 34]

Analyses will be performed using STATA version 15.0. A *p* value of less than 0.05 will be considered as statistically significant, except heterogeneity test where p value <0.10 will be used.

ETHIC and DISSEMINATION

Ethical consideration and ethic committee approval are not required from the nature of systematic review and network meta-analysis. Results of the study will be presented in international meeting. The manuscript will be submitted to peer-reviewed journal.

AUTHOR CONTRIBUTIONS

BS generated research question, writing part of the protocol, KS wrote and register protocol, SO wrote and register protocol, TB wrote and comment on protocol, KR wrote and comment on protocol, and AT wrote and comment on protocol.

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

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

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		Reporting Item	Page Number
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	1
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11
	#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	
Sources	#5a	Indicate sources of financial or other support for the review	2
Sponsor	#5b	Provide name for the review funder and / or sponsor	2
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	-
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
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	8
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9-10
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9-10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9-10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9-10
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

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Endovenous ablation and surgery in great saphenous vein reflux. A systematic review and network meta-analysis of randomized controlled trials protocol.

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Abstract

Introduction. Endovenous ablations are the new standard procedures for treatment of great saphenous vein (GSV) reflux. These included endovenous laser ablation (EVLA), radiofrequency ablation (RFA), endovenous steam ablation (EVSA), mechano-chemical ablation (MOCA), cyanoacrylate injection, and ultrasound-guided foam sclerotherapy (UGFS). EVLA and RFA demonstrated similar anatomical success to surgery for short term outcome but controversial results for longer term (≥5 years). Additional evidences from randomized controlled trials (RCT) have been published with varying follow-up times. This study is therefore conducted to directly and indirectly compare outcomes among all procedures stratify by short and long term follow-up.

Methods and analysis. Medline and Scopus will be searched from 2000 to May 2018 with predefined search strategy. Interventions of interest are open surgery (i.e., saphenofemoral or high ligation (HL) with stripping) and endovenous ablations (i.e., EVLA, RFA, EVSA, MOCA, cyanoacrylate injection and UGFS). The primary outcomes are anatomical success. Two independent reviewers will select studies, extract data, assess risk of bias of included studies. Disagreement will be adjudicated by the third party. Outcomes will be directly pooled if there are at least 3 studies in that comparison. A fixed effect model will be used unless heterogeneity is present, a random effect model will be applied. Source of heterogeneity will be explored using meta-regression analysis, sub-group analysis will be done accordingly. Publication bias will be assessed using Egger's test and funnel plot. A network meta-analysis will be applied to indirect compare all interventions including RFA, EVLA, EVLA with HL, UGFS, UGFS with HL, and HL with stripping. Probability being best intervention will be estimated and ranked. Inconsistency assumption be checked using a design-treatment interaction model.

Ethics and dissemination. Ethical approval is not required for systematic review and network meta-analysis. The study will be published in a peer-reviewed journal.

PROSPERO registration number. CRD42018096794

Keywords. Endovenous, stripping, varicose vein, saphenous vein reflux, saphenofemoral ligation, sclerotherapy

Article summary

Strengths and limitations of this study

- This review will include all relevant RCTs comparing outcomes between endovenous ablation and surgery since 2000 to March 2018.
- Stratify analysis by short and long term follow up will be performed
- Probability of being a best procedure will be estimated and provided

INTRODUCTION

Chronic venous disease is common condition affected both men and women with prevalence rate of 30-50%.[1 2] This has led to significant health spending, about 1%-2% of health care budgets had been spent for venous disease in European countries.[3] Great saphenous vein (GSV) reflux is the most common site of reflux accounting for about 80% of all reflux sites.[4] GSV ablation is recommended to improve symptoms and quality of life of patients.[5 6]

To ablate GSV, endovenous ablations are recommended over surgery as a new standard treatment.[6] The benefits over open surgery are less postoperative pain, lower rate of surgical site infection, faster return to normal activities and work.[7] However, it is accompanied with higher equipment costs.[8] Many techniques of endovenous ablation have

therefore emerged including endovenous laser ablation (EVLA), radiofrequency ablation (RFA), endovenous steam ablation (EVSA), and ultrasound-guided sclerotherapy (UGFS). Two novel techniques of non-tumescent non-thermal endovenous ablation (NTNT) including mechano-chemical ablation (MOCA) and cyanoacrylate injection had been introduced for several years with promising early results.[9]

Directly-related outcome after GSV ablation is anatomical success, which is patency of the GSV after ablation. However, failure or recurrence cannot be avoided which is classified as technical failure, periprocedural, early, midterm, and late failure when it is occurred ≤ 3 days, ≤ 1 month, 1 year, 1-3 years, and > 3 years after operation. Sources of recurrences could be neovascularization and reflux in tributaries in which the former might occur more after open surgery whereas the later often occurred after endovenous ablation without high ligation.[10 11] Another important outcome is patient's-reported outcome measurements or PROMs, which measured patients' perspective in both generic and specific quality of life.[6]

Previous evidences about efficacy of these procedures had been pooled considering short to long term outcomes. The first systematic review in 2012 included 28 RCTs to compare short-midterm outcomes of endovenous procedures with surgery. It found benefits of endovenous procedures (i.e. EVLA, RFA, and UGFS) over open surgery in postoperative pain, morbidity, and faster recovery with similar efficacies for EVLA and RFA but less efficacy for UGFS.[7] Other two systematic reviews in 2017[10] and 2018[11] considered only long term outcomes by including 12 and 9 RCTs with > 5 year follow up, respectively. Although the former meta-analysis[12] considered only RCTs, they pooled outcome data (i.e., success/recurrent reflux rates and mean difference) comparing before vs after of each intervention without directly compared these outcomes between groups. As a result,

randomization may be broken and thus bias the results. The latest meta-analysis[11] could not detect whether recurrence rates between EVLA, RFA, and surgery were different due to small numbers of included studies and subjects.

Some additional RCTs comparing endovenous procedures and open surgery or comparing among endovenous ablations have been later published with varying follow up time and also surgical techniques (i.e., with or without high ligation).[13-26] In addition, RCTs comparing among endovenous techniques including NTNT (i.e., EVSA, MOCA, and cyanoacrylate injection) have also been published. These data have not yet been updated in the aforementioned meta-analyses with long term outcomes. In addition, accurate and precise magnitude of benefit of endovenous procedures over surgery along time horizon of treatment is important for economic analysis.[27] Therefore, this systematic review and network meta-analysis is conducted which aim to directly and indirectly compare clinical outcomes between interventions stratifying by time of follow up including anatomical success, clinical recurrence, and quality of life. Postoperative outcomes include postoperative pain, time to return to normal activities and work, and complications (i.e. wound infection, hematoma, paresthesia, ecchymosis, and deep venous thrombosis) will be pooled using all available data. In addition, source of recurrences (i.e., neovascularization, and reflux in tributaries) and reintervention rates will also be pooled. Probability being best intervention will be estimated and ranked for each outcome. Risk and benefit will be then compared.

METHODS

The protocol was developed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement for reporting systematic reviews and

meta-analyses[28] and extension statement for systematic reviews incorporating network meta-analyses of health care interventions.[29]

Search strategy

Medline and Scopus will be searched from August 2011 to September 2018, and will be updated every 3 months till August 2019. Search terms are constructed according to patients and intervention/comparator as follows: "Varicose veins"[Mesh] OR "Saphenous vein"[Mesh] OR varicose OR saphenous NOT esophageal; radiofrequency OR RFA OR VNUS OR endovenous OR EVLT OR EVLA OR laser OR sclerotherapy[Mesh] OR foam sclerotherapy OR UGFS OR stripping OR sapheno-femoral ligation OR surgery OR steam OR glue OR cyanoacrylate OR clarivein OR mechanochemical OR mechano-chemical. These search terms of the two domains will be combined with AND with limited to clinical trial, human, and English articles. Reference lists from previous meta-analysis and all eligible papers will be reviewed for relevant studies.

Study selection

Study selection will be done by two independent authors (BS and TB). Title and abstract will be screened for eligible criteria, full text will then be reviewed if decision cannot be made. Any disagreement will be adjudicated by a third party (AT). Data from multiple publication studies will be combined as one publication for analysis.

RCTs studied in patients with GSV reflux will be included if they meet following criteria: Had any pair of following interventions including endovenous thermal ablation (i.e., EVLA, RFA, and EVSA), endovenous non-thermal non-tumescent ablations (i.e., MOCA, UGFS cyanoacrylate injection), and surgery; had at least one following outcomes including anatomical success, postoperative pain, wound infection, hematoma, ecchymosis, deep vein

thrombosis, time to return to normal activities and work, clinical recurrence, and quality of life. Studies will be excluded if they have insufficient data for pooling.

Interventions

Interventions of interest are open surgery (i.e., saphenofemoral or high ligation (HL) with stripping of the GSV), endovenous thermal ablations (i.e., EVLA, RFA, and EVSA), and non-thermal nontumescent endovenous ablation (i.e. MOCA, cyanoacrylate injection). EVLA ablates GSV using laser energy with varying wavelength such as 810, 940, 980, 1470, and 1560 nm.[30 31] RFA generates heat by radiofrequency energy. Both RFA and EVLA are usually performed with tumescent anesthesia to prevent thermal injury to adjacent tissue. EVSA used heat from steam to ablate GSV. MOCA both mechanically and chemically injured endothelium of targeted vein. Cyanoacrylate was polymerized into solid form to occlude vein after injection. UGFS damages endothelium causing occlusion of vein, is injected to the GSV by either direct puncture or via catheter.[32] Foam sclerosant can be developed manually or by manufacture. HL might or might not be applied with endovenous procedures. Comparison of interests will be any pair among different types of ablations or the same type of ablations but different techniques (e.g., different sclerosants and/or concentrations for UGFS, short versus long wavelengths or pull back types for laser) if data are sufficient for pooling and there are common comparators in the network mapping.

Outcomes

The primary outcome of interest is anatomical success, which variously defined according to original studies as incomplete stripping (in open surgery), non-occlusion of GSV, partially opened without reflux, or reflux of GSV diagnosed by duplex scan. This outcome will be considered according to time frame of follow up, i.e., periprocedural, early, midterm, and late failure.[6]

Secondary outcomes of interest are clinical recurrence, postoperative pain, time to return to normal activities and work, self-reported quality of life, reintervention rate, and postoperative complications (i.e. hematoma, ecchymosis, paresthesia, and deep vein thrombosis). Quality of life will be compared according to time frame of follow up. Clinical recurrence will be defined as clinical detected recurrence of varicose vein. Neovascularization and reflux in tributaries will also be extracted and compared.

Data extraction

Two independent authors (BS and KS) will extract data using standardized data extraction forms. General characteristics of studies and interventions including patients' severity, age, detailed of intervention, duration of follow up, type of anesthesia, compression method, tumescent anesthesia, primary outcome definition, concomitant phlebectomy and sclerotherapy will be extracted. These data will be used for exploring source of heterogeneity. Mean (SD) and frequencies of outcomes data by intervention will be extracted for pooling. Mean difference or risk ratio will be used in case of no summary data provided in the study. Inconsistent data will be solved by consensus with third party (AT) and finalize. Author will contact corresponding authors twice for missing data.

Risk of bias assessment

Studies will be assessed for risk of bias using Cochrane Collaboration's tool [33] by two independent researchers (BS and SO). This tool consists of 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome reports, selective outcome reports, and other source of bias. Disagreement will be resolved by third party (AT).

Grading evidence

Quality of evidence will be graded separately for each outcome using a tool suggested by the GRADE Working Group.[34] Five domains will be assessed including study limitations, consistency, indirectness, imprecision, and publication bias. The evidence will be downgraded one and two levels for serious and very serious concerns, respectively.

Statistical analysis

Direct meta-analysis

Data will be directly pooled if there are at least 3 studies for each comparison. Risk ratios (RR) with 95% confidence interval (CI) will be estimated for dichotomous outcome. A continuity correction will be used if there is a zero cell. The RRs will be pooled using inverse variance, and Dersimonian and Laird for data without and with heterogeneity, respectively. For continuous outcome, unstandardized or standardised mean difference (MD) with 95%CI will be estimated and pooled across studies if outcome measures are the same and different scales, respectively. Mean and standard deviation (SD) will be estimated from median and range/interquartile If study did not report mean and SD.[35]

Heterogeneity will be assessed using degree of heterogeneity (I^2) and Q test. If either $I^2 \geq 25\%$ or Q test is significant with $p < 0.10$, the results will be considered as heterogeneous and random effect model will be applied. Possible source of heterogeneity will be explored by fitting studies' characteristics (i.e., concomitant phlebectomy or foam sclerotherapy, type of anesthesia, and compression method), different of interventional techniques in each type of endovenous ablation (i.e., laser wavelength, catheter use in UGFS, and type of sclerosant and concentration), outcomes definition (i.e., non-occlusion, partially opened without reflux, and reflux) and patient's characteristics (i.e., age, severity) in a meta-regression model if data are sufficient for doing. Subgroup or sensitivity analysis

will be performed accordingly to factors that can reduce a degree of heterogeneity. Publication bias will be assessed by funnel plot an Egger test. If there is evidence of asymmetry of the funnel by either two, a contour-enhanced plot will be constructed to distinguish whether a source of asymmetry due to heterogeneity or missing studies.

Network meta-analysis

A network meta-analysis[36] will be performed to indirectly compare among interventions including RFA, EVLA, EVLA with HL, UGFS, UGFS with HL, EVSA, MOCA, cyanoacrylate injection, and HL with stripping. HL with stripping will be used as a common comparator. Analysis will be performed as following steps: First, relative intervention effect, i.e., risk ratio (RR) along with its variance-covariance will be estimated by binary regression analysis. A multivariate random-effect meta-analysis with consistency mode will be then used to pool RRs across studies. Mixed intervention comparisons will be next estimated. Probability being best intervention will be estimated and ranked using surface under cumulative ranking (SUCRA) method, rankogram will be plotted accordingly. Cluster rank plot will be constructed by comparing probability being risk and benefit.

The inconsistency assumption (i.e., whether direct effects agree with the indirect effects) will be checked using a design-treatment interaction model. If this assumption does not meet, an inconsistency factor (IF, i.e., ln(RRdirect)-ln(RRindirect)) will be estimated and tested. In addition, a comparison-adjusted funnel plot taking into account different comparisons will be plotted to explore whether there is evidence of small study effect for the whole network.[36 37]

Analyses will be performed using STATA version 15.0. A *p* value of less than 0.05 will be considered as statistically significant, except heterogeneity test where p value <0.10 will be used.

Patient and public involvement

Patients and public will not involve in the study.

ETHIC and DISSEMINATION

Ethical consideration and ethic committee approval are not required from the nature of systematic review and network meta-analysis. Results of the study will be presented in international meeting. The manuscript will be submitted to peer-reviewed journal.

AUTHOR CONTRIBUTIONS

BS generated research question, writing part of the protocol, KS wrote and register protocol, SO wrote and register protocol, TB wrote and comment on protocol, KR wrote and comment on protocol, and AT wrote and comment on protocol.

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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-P reporting guidelines, and cite them as:

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		Reporting Item	Page Number
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	1
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11
	#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	
Sources	#5a	Indicate sources of financial or other support for the review	2
Sponsor	#5b	Provide name for the review funder and / or sponsor	2
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	-
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
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	8
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9-10
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9-10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9-10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9-10
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

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Primary Subject Heading:	Surgery
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Keywords:	endovenous, saphenous vein reflux, stripping, saphenofemoral ligation, sclerotherapy

Endovenous ablation and surgery in great saphenous vein reflux: A systematic review and network meta-analysis of randomised controlled trials protocol.

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Abstract

Introduction. Endovenous ablations are the new standard procedures for treatment of great saphenous vein (GSV) reflux including endovenous laser ablation (EVLA), radiofrequency ablation (RFA), endovenous steam ablation (EVSA), mechano-chemical ablation (MOCA), cyanoacrylate injection, and ultrasound-guided foam sclerotherapy (UGFS). EVLA and RFA have demonstrated similar anatomical success for short term outcome, but results are controversial for longer term (≥5 years). Additional evidences from randomised controlled trials (RCT) have been published. This study is therefore conducted to directly and indirectly compare outcomes among all procedures stratifying by short and long term follow-up.

Methods and analysis. Medline and Scopus will be searched from 2000 to September 2018 with predefined search strategy. Interventions of interest are open surgery (i.e., saphenofemoral or high ligation (HL) with stripping) and endovenous ablations (i.e., EVLA, RFA, EVSA, MOCA, cyanoacrylate injection and UGFS). The primary outcome is anatomical success. Two independent reviewers will select studies, extract data, and assess risk of bias. Disagreement will be adjudicated by the third party. Outcomes will be directly pooled if there are at least 3 studies in that comparison. A fixed-effect model will be used unless heterogeneity is present, in which case a random-effect model will be applied. Sources of heterogeneity will be explored using meta-regression analysis, and sub-group analysis will be done accordingly. Publication bias will be assessed using Egger's test and funnel plot. A network meta-analysis will be applied to indirect compare all interventions including RFA, EVLA, EVLA with HL, UGFS, UGFS with HL, and HL with stripping. Probability of being best intervention will be estimated and ranked. Inconsistency assumption will be checked using a design-treatment interaction model.

Ethics and dissemination. Ethical approval is not required for systematic review and network meta-analysis. The study will be published in a peer-reviewed journal.

PROSPERO registration number. CRD42018096794

Keywords. Endovenous, stripping, varicose vein, saphenous vein reflux, saphenofemoral ligation, sclerotherapy

Article summary

Strengths and limitations of this study

- This review will include all relevant RCTs comparing outcomes between endovenous ablation and surgery since 2000 to September 2018.
- Stratified analysis by short and long term follow up will be performed
- Probability of being the best procedure will be estimated and provided

INTRODUCTION

Chronic venous disease is a common condition which affects both men and women with prevalence rate of 30-50%.[1 2] This has led to significant health spending, and about 1%-2% of health care budgets have been spent for venous disease in European countries.[3] Great saphenous vein (GSV) reflux is the most common site of reflux accounting for about 80% of all reflux sites.[4] GSV ablation is recommended to improve symptoms and quality of life of patients.[5 6]

To ablate GSV, endovenous ablations are recommended over surgery as a new standard treatment.[6] The benefits over open surgery are less postoperative pain, lower rate of surgical site infection, faster return to normal activities and work.[7] However, they are accompanied with higher equipment costs.[8] Therefore, many techniques of endovenous

ablation have emerged including endovenous laser ablation (EVLA), radiofrequency ablation (RFA), endovenous steam ablation (EVSA), and ultrasound-guided sclerotherapy (UGFS). Two novel techniques of non-tumescent non-thermal endovenous ablation (NTNT) including mechano-chemical ablation (MOCA) and cyanoacrylate injection have been introduced for several years with promising early results.[9]

Directly-related outcome after GSV ablation is anatomical success, which is patency of the GSV after ablation. However, failure or recurrence cannot be avoided which is classified as technical failure, periprocedural, early, midterm, and late failure when it occurs ≤ 3 days, ≤ 1 month, 1 year, 1-3 years, and > 3 years after operation. Sources of recurrences could be neovascularisation and reflux in tributaries in which the former might occur more after open surgery whereas the later often occurs after endovenous ablation without high ligation.[10 11] Another important outcome is patient's-reported outcome measurements or PROMs, which measures patients' perspective in both generic and specific quality of life.[6]

Previous evidences about efficacy of these procedures had been pooled considering short to long term outcomes. The first systematic review in 2012 included 28 RCTs to compare short-midterm outcomes of endovenous procedures with surgery. It found benefits of endovenous procedures (i.e. EVLA, RFA, and UGFS) over open surgery in postoperative pain, morbidity, and faster recovery with similar efficacies for EVLA and RFA, but less efficacy for UGFS.[7] Two other systematic reviews in 2017[10] and 2018[11] considered only long term outcomes by including 12 and 9 RCTs with > 5 year follow up, respectively. Although the former meta-analysis[12] considered only RCTs, they pooled outcome data (i.e., success/recurrent reflux rates and mean difference) comparing before vs after of each intervention without directly comparing these outcomes between groups. As a result, randomisation may be broken and thus bias the results. The latest meta-analysis[11] could not

detect whether recurrence rates between EVLA, RFA, and surgery were different due to small numbers of included studies and subjects.

Some additional RCTs comparing endovenous procedures and open surgery or comparing among endovenous ablations have been published later with varying follow up times and also surgical techniques, i.e., with or without high ligation.[13-26] In addition, RCTs comparing among endovenous techniques including NTNT (i.e., EVSA, MOCA, and cyanoacrylate injection) have also been published. These data have not yet been updated in the aforementioned meta-analyses with long term outcomes. In addition, accurate and precise magnitude of benefit of endovenous procedures over surgery along time horizon of treatment is important for economic analysis.[27] Therefore, this systematic review and network meta-analysis is conducted which aims to directly and indirectly compare clinical outcomes between interventions stratifying by time of follow up including anatomical success, clinical recurrence, and quality of life. Postoperative outcomes including postoperative pain, time to return to normal activities and work, and complications (i.e. wound infection, hematoma, paresthesia, ecchymosis, and deep venous thrombosis) will be pooled using all available data. In addition, source of recurrences (i.e., neovascularisation and reflux in tributaries) and reintervention rates will also be pooled. Probability of being the best intervention will be estimated and ranked for each outcome. Risk and benefit will be then compared.

METHODS

The protocol was developed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement for reporting systematic reviews and meta-analyses[28] and extension statement for systematic reviews incorporating network meta-analyses of health care interventions.[29]

Search strategy

Medline and Scopus will be searched from 2000 to September 2018, and will be updated every 3 months until August 2019. Search terms are constructed according to patients and intervention/comparator as follows: "Varicose veins"[Mesh] OR "Saphenous vein"[Mesh] OR varicose OR saphenous NOT esophageal; radiofrequency OR RFA OR VNUS OR endovenous OR EVLT OR EVLA OR laser OR sclerotherapy[Mesh] OR foam sclerotherapy OR UGFS OR stripping OR sapheno-femoral ligation OR surgery OR steam OR glue OR cyanoacrylate OR clarivein OR mechanochemical OR mechano-chemical. These search terms of the two domains will be combined with AND with limited to clinical trial, human, and English articles. Reference lists from previous meta-analysis and all eligible papers will be reviewed for relevant studies.

Study selection

Study selection will be done by two independent authors (BS and TB). Title and abstract will be screened for eligible criteria, full text will then be reviewed if a decision cannot be made. Any disagreement will be adjudicated by a third party (AT). Data from multiple publication studies will be combined as one publication for analysis.

RCTs studied in patients with GSV reflux will be included if they meet the following criteria: had any pair of the following interventions including endovenous thermal ablation (i.e., EVLA, RFA, and EVSA), endovenous non-thermal non-tumescent ablations (i.e., MOCA, UGFS cyanoacrylate injection), and surgery; had at least one following outcomes including anatomical success, postoperative pain, wound infection, hematoma, ecchymosis, deep vein thrombosis, time to return to normal activities and work, clinical recurrence, and quality of life. Studies will be excluded if they have insufficient data for pooling.

Interventions

Interventions of interest are open surgery (i.e., saphenofemoral or high ligation (HL) with stripping of the GSV), endovenous thermal ablations (i.e., EVLA, RFA, and EVSA), and non-thermal nontumescent endovenous ablation (i.e. UGFS, MOCA, cyanoacrylate injection). EVLA ablates GSV using laser energy with varying wavelength such as 810, 940, 980, 1470, and 1560 nm.[30 31] RFA generates heat by radiofrequency energy. Both RFA and EVLA are usually performed with tumescent anesthesia to prevent thermal injury to adjacent tissue. EVSA uses heat from steam to ablate GSV. MOCA both mechanically and chemically injured endothelium of targeted vein. Cyanoacrylate is polymerised into solid form to occlude vein after injection. UGFS damages endothelium causing occlusion of vein, which is injected to the GSV by either direct puncture or via catheter.[32] Foam sclerosant can be developed manually or by manufacture. HL might or might not be applied with endovenous procedures. Comparison of interests will be any pair among different types of ablations or the same type of ablations, but different techniques (e.g., different sclerosants and/or concentrations for UGFS, short versus long wavelengths or pull back types for laser), if data are sufficient for pooling and there are common comparators in the network mapping.

Outcomes

The primary outcome of interest is anatomical success, which was originally defined as incomplete stripping for open surgery and non-occlusion of GSV with or without reflux diagnosed by duplex scan. This outcome will be considered according to time frame of follow up i.e., periprocedural, early, midterm, and late failure.[6]

Secondary outcomes of interest are clinical recurrence, postoperative pain, time to return to normal activities and work, self-reported quality of life, reintervention rate, and postoperative complications (i.e. hematoma, ecchymosis, paresthesia, and deep vein

thrombosis). Quality of life will be compared according to time frame of follow up. Clinical recurrence will be defined as clinical detected recurrence of varicose vein. Neovascularisation and reflux in tributaries will also be extracted and compared.

Data extraction

Two independent authors (BS and KS) will extract data using standardised data extraction forms. General characteristics of studies and interventions including patients' severity, age, details of intervention, duration of follow up, type of anesthesia, compression method, tumescent anesthesia, primary outcome definition, concomitant phlebectomy and sclerotherapy will be extracted. These data will be used for exploring source of heterogeneity. Mean (SD) and frequencies of outcomes data by intervention will be extracted for pooling. Mean difference or risk ratio will be used in case of no summary data provided in the study. Inconsistent data will be solved by consensus with third party (AT) and finalised. Author will contact corresponding authors twice for missing data.

Risk of bias assessment

Studies will be assessed for risk of bias using Cochrane Collaboration's tool [33] by two independent researchers (BS and SO). This tool consists of 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome reports, selective outcome reports, and other source of bias. Disagreement will be resolved by third party (AT).

Grading evidence

Quality of evidence will be graded separately for each outcome using a tool suggested by the GRADE Working Group.[34] Five domains will be assessed including study limitations, consistency, indirectness, imprecision, and publication bias. The evidence will be downgraded one and two levels for serious and very serious concerns, respectively.

Statistical analysis

Direct meta-analysis

Data will be directly pooled if there are at least 3 studies for each comparison. Risk ratios (RR) with 95% confidence interval (CI) will be estimated for dichotomous outcome. A continuity correction will be used if there is a zero cell. The RRs will be pooled using inverse variance, and Dersimonian and Laird for data without and with heterogeneity, respectively. For continuous outcome, unstandardised or standardised mean difference (MD) with 95%CI will be estimated and pooled across studies if outcome measures are the same and different scales, respectively. Mean and standard deviation (SD) will be estimated from median and range/interquartile, if a study did not report mean and SD.[35]

Heterogeneity will be assessed using degree of heterogeneity (I^2) and Q test. If either $I^2 \geq 25\%$ or Q test is significant with $p < 0.10$, the results will be considered as heterogeneous and random effect model will be applied. Possible source of heterogeneity will be explored by fitting studies' characteristics (i.e., concomitant phlebectomy or foam sclerotherapy, type of anesthesia, and compression method), different of interventional techniques in each type of endovenous ablation (i.e., laser wavelength, catheter use in UGFS, and type of sclerosant and concentration), outcomes definition (i.e., non-occlusion, non-occlusion with or without reflux) and patient's characteristics (i.e., age, severity) in a meta-regression model, if data are sufficient. Subgroup or sensitivity analysis will be performed accordingly to factors that can reduce the degree of heterogeneity. Publication bias will be assessed by funnel plot and Egger test. If there is evidence of asymmetry of the funnel by either of these two, a contour-enhanced plot will be constructed to distinguish whether a source of asymmetry is due to heterogeneity or missing studies.

Network meta-analysis

A network meta-analysis[36] will be performed to indirectly compare among interventions including RFA, EVLA, EVLA with HL, UGFS, UGFS with HL, EVSA, MOCA, cyanoacrylate injection, and HL with stripping. HL with stripping will be used as a common comparator. Analysis will be performed by the following steps: First, relative intervention effect, i.e., risk ratio (RR) along with its variance-covariance will be estimated by binary regression analysis. A multivariate random-effect meta-analysis with consistency mode will then be used to pool RRs across studies. Mixed intervention comparisons will be next estimated. Probability of being the best intervention will be estimated and ranked using surface under cumulative ranking (SUCRA) method, and rankogram will be plotted accordingly. Cluster rank plot will be constructed by comparing probability of being risk and benefit.

The inconsistency assumption (i.e., whether direct effects agree with the indirect effects) will be checked using a design-treatment interaction model. If this assumption is not met, an inconsistency factor (IF, i.e., ln(RRdirect)-ln(RRindirect)) will be estimated and tested. In addition, a comparison-adjusted funnel plot taking into account different comparisons will be plotted to explore whether there is evidence of small study effect for the whole network.[36 37]

Analyses will be performed using STATA version 15.0. A *p* value of less than 0.05 will be considered as statistically significant, except heterogeneity test where p value <0.10 will be used.

Patient and public involvement

Patients and public will not be involved in this study.

ETHIC and DISSEMINATION

Ethical consideration and ethic committee approval are not required from the nature of systematic review and network meta-analysis. Results of the study will be presented in international meeting. The manuscript will be submitted to peer-reviewed journal.

AUTHOR CONTRIBUTIONS

BS initiated research question design review methods, and wrote the protocol, KS wrote and registered protocol, SO wrote and registered protocol, TB wrote and commented on protocol, KR wrote and commented on protocol, and AT designed review methods, wrote and commentted on protocol.

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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-P reporting guidelines, and cite them as:

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		Reporting Item	Page Number
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	1
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	11
	#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	
Sources	#5a	Indicate sources of financial or other support for the review	2
Sponsor	#5b	Provide name for the review funder and / or sponsor	2
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	-
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6-7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
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	8
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9-10
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9-10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9-10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9-10
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9