BMJ Open  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 reflux including endovenous laser ablation (EVLA), radio frequency ablation (RFA), endovenous steam ablation (EVSA), mechaanochemical ablation (MOCA), cyanoacrylate injection and ultrasound-guided foam sclerotherapy (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 three 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-by-treatment interaction model.

Strengths and limitations of this study
► This review will include all relevant randomised controlled trials comparing outcomes between endovenous ablation and surgery from 2000 to September 2018.
► Stratified analysis by short-term 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 the prevalence rate of 30%–50%.1 2 This has led to significant health spending, and about 1%–2% of healthcare 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, a lower rate of surgical site infection, faster return to normal activities and work.7 However, they are accompanied by higher equipment costs.8 Therefore, many techniques of endovenous ablation have emerged including endovenous laser ablation (EVLA), radio frequency ablation (RFA), endovenous steam ablation (EVSA) and ultrasound-guided foam sclerotherapy (UGFS). Two novel techniques of non-tumescent non-thermal endovenous ablation (NTNT) including mechanochemical ablation (MOCA) and cyanoacrylate injection have been introduced for several years with promising early results.9

Directly related outcome after GSV ablation is an 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, mid-term and late failure when it occurs ≤3 days, ≤1 month, 1 year, 1–3 years and >3 years after the operation. Sources of recurrences could be neovascularisation and reflux in tributaries in which the former might occur more often after open surgery whereas the latter often occurs after endovenous ablation without high ligation (HL).\textsuperscript{10,11} Another important outcome is patient-reported outcome measurements, which measures patients’ perspective in both generic and specific quality of life.\textsuperscript{6}

Previous evidences about efficacy of these procedures had been pooled considering short-term to long-term outcomes. The first systematic review in 2012 included 28 randomised controlled trials (RCTs) to compare short-term/mid-term outcomes of endovenous procedures with surgery. It found benefits of endovenous procedures (ie, 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.\textsuperscript{7} Two other systematic reviews in 2017\textsuperscript{10,11} and 2018\textsuperscript{12} considered only long-term outcomes by including 12 and 9 RCTs with >5 years follow-up, respectively. Although the former meta-analysis\textsuperscript{12} considered only RCTs, they pooled outcome data (ie, success/recurrent reflux rates and mean difference (MD)) comparing before versus 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\textsuperscript{13} 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, that is, with or without HL.\textsuperscript{13-26} In addition, RCTs comparing among endovenous techniques including NTNT (ie, 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.\textsuperscript{27} Therefore, this systematic review and network meta-analysis is conducted which aims to, directly and indirectly, compare clinical outcomes between interventions stratifying by the 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 (ie, wound infection, haematoma, paresthesia, ecchymosis and deep venous thrombosis) will be pooled using all available data. In addition, source of recurrences (ie, neovascularisation and reflux in tributaries) and reintervention rates will also be pooled. A 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 Preferred Reporting Items for Systematic Reviews and Meta-analyses statement for reporting systematic reviews and meta-analyses\textsuperscript{28} and extension statement for systematic reviews incorporating network meta-analyses of healthcare interventions.\textsuperscript{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: ‘Variocose veins’[Mesh] OR ‘Saphenous vein’[Mesh] OR varicose OR saphenous NOT esophageal; radiofrequency OR RFA OR VVUS 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 mechemochemical OR mecano-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, the 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 (ie, EVLA, RFA and EVSA), endovenous non-thermal non-tumescent ablations (ie, MOCA, UGFS, cyanoacrylate injection) and surgery; had at least one following outcomes including anatomical success, postoperative pain, wound infection, haematoma, 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 (ie, saphenofemoral or HL with stripping of the GSV), endovenous thermal ablations (ie, EVLA, RFA and EVSA) and non-thermal non-tumescent endovenous ablation (ie, UGFS, MOCA, cyanoacrylate injection). EVLA ablates GSV using laser energy with varying wavelength such as 810, 940, 980, 1470 and 1560 nm.\textsuperscript{30,31} RFA generates heat by radio frequency energy. Both RFA and EVLA are usually performed with tumescent anaesthesia 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 the vein, which is injected to the GSV by either direct puncture or via a catheter. Foam sclerosant can be developed manually or by the 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 (eg, different sclerosants and/or concentrations for UGFS, short vs 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 a duplex scan. This outcome will be considered according to the time frame of follow-up, that is, periprocedural, early, mid-term and late failure.

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 (ie, haematoma, ecchymosis, paresthesia and deep vein thrombosis). Quality of life will be compared according to the 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 the intervention, duration of follow-up, type of anaesthesia, compression method, tumescent anaesthesia, primary outcome definition, concomitant phlebectomy and sclerotherapy will be extracted. These data will be used for exploring the source of heterogeneity. Mean (SD) and frequencies of outcomes data by intervention will be extracted for pooling. MD or risk ratio (RR) will be used in case of no summary data provided in the study. Inconsistent data will be solved by consensus with a third party (AT) and finalised. An 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 by two independent researchers (BS and SO). This tool consists of seven 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 a third party (AT).

Grading evidence
Quality of evidence will be graded separately for each outcome using a tool suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. 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 three studies for each comparison. RRs with 95% CI will be estimated for a 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 MD with 95% CI will be estimated and pooled across studies if outcome measures are the same and different scales, respectively. Mean and SD will be estimated from median and range/interquartile, if a study did not report mean and SD.

Heterogeneity will be assessed using a 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 (ie, concomitant phlebectomy or foam sclerotherapy, type of anaesthesia and compression method), different of interventional techniques in each type of endovenous ablation (ie, laser wavelength, catheter use in UGFS, and type of sclerosant and concentration), outcomes definition (ie, non-occlusion, non-occlusion with or without reflux) and patient's characteristics (ie, 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 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. The analysis will be performed by the following steps: first, relative intervention effect, that is, 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. A probability of being the best intervention will be estimated and ranked using surface under the cumulative ranking method, and rankogram will be plotted accordingly. Cluster rank plot will be constructed by comparing the probability of being risk and benefit.
The inconsistency assumption (ie, whether direct effects agree with the indirect effects) will be checked using a design-by-treatment interaction model. If this assumption is not met, an inconsistency factor (ie, ln(R-Rdirect)-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.

Analyses will be performed using STATA V.15.0. A p<0.05 will be considered as statistically significant, except heterogeneity test where p<0.10 will be used.

Patient and public involvement

Patients and public will not be involved in this study.

Ethics and dissemination

Results of the study will be presented in international meeting. The manuscript will be submitted to peer-reviewed journal.

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Contributors

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. AF designed review methods, wrote and commented on protocol.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

Ethical consideration and ethic committee approval are not required from the nature of systematic review and network meta-analysis.

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