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# Efficacy and safety of endovenous microwave ablation versus laser ablation for great saphenous vein varicosis: study protocol for a multicentre, randomised controlled non-inferiority trial

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## ABSTRACT

**Introduction** Endovenous microwave ablation (EMA) is a relatively novel thermal ablation treatment for great saphenous vein (GSV) varicosis, and its efficacy and safety are rarely reported. This study aims to explore whether EMA can be comparable to endovenous laser ablation (EVLA), which is a widely used thermal ablation treatment in clinical practice.

**Methods and analysis** This is a multicentre, randomised controlled non-inferiority trial to compare the efficacy and safety of EMA and EVLA in patients with GSV varicosis. We will recruit 180 patients in 6 centres and randomly assign them into treatment group (EMA group) and control group (EVLA group) in a 1:1 ratio. The patients will return to the hospitals at 7 days, 3 months, 6 months and 12 months, and will be called at 1 month after the treatment for follow-up visits. The primary outcome is the occlusion rate of GSV immediately, at 6 months, and at 12 months after the treatment. The secondary outcomes are Venous Clinical Severity Score (VCSS), Aberdeen Varicose Vein Questionnaire (AVVQ) Score, operation time and instrument performance evaluation.

**Ethics and dissemination** This protocol has been approved by the Clinical Trial Ethics Committee of Beijing Hospital (2020BJYYEC-126–02), Peking Union Medical College Hospital (KS2020393), Beijing Tsinghua Changgung Hospital (No.20279-2-02), Beijing Luhe Hospital.Capital Medical University (2020-LHYW-030–01), the First Hospital of Hebei Medical University (No.2020249), and the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2021LSY-12). The trial results will be published in peer-reviewed journals.

**Trial registration number** NCT04726124.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Compared with previous studies, we use the randomised method to control confounders.
⇒ Our study will be performed in multiple centres, which makes the results more reliable.
⇒ For the missing data of efficacy indicators, the Worst Case Carry Forward strategy will be used to handle, indicating the results are interpreted cautiously.
⇒ The lack of blindness of patients and surgeons is the limitation of this study.
⇒ The treatment is performed by different doctors, which may cause some potential bias.

## INTRODUCTION

Great saphenous vein (GSV) varicosis is a common peripheral vascular disease usually caused by incomplete venous valve closure, which results in venous blood backflow and distal veins stasis and then dilation, bulging and twisting of the GSV.[1] GSV varicosis affects about a third of the adults, and mostly occurs in people engaging in sustained standing jobs, having high intensity of physical activity, or sitting for a long time with less movement.[2] The patients may suffer from occasional discomfort, itching, pigmentation and skin ulceration, impairing their quality of life.[3]

The common conventional surgical treatment for GSV varicosis is high ligation and stripping (HLS), but it has been reported to cause high postoperative clinical recurrence, slow recovery and obvious incision scar.[4 5] Because of the need of less invasive treatment, endovenous thermal ablation techniques, such as radiofrequency ablation (RFA) and endovenous laser ablation (EVLA), have been developed.[6 7] RFA generates thermal energy by radiofrequency generator and special electrode catheter, resulting in high heating of local tissues contacting the electrode catheter to produce endothelial damage.[8] For EVLA, the laser is converted into thermal energy through the optical fibre, which causes thermal injury to the target vein endothelium and its resultant occlusion.[9]

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Both RFA and EVLA have shown good efficiency and high safety, whereas evidence indicates that EVLA is a more cost-effective therapeutic option.[10 11]

Endovenous microwave ablation (EMA) is a relatively novel method of thermal ablation treatment.[12] It differs from RFA in that it does not use a thermocouple to regulate the temperature at the venous wall.[12] Also, EMA generates thermal energy in a different manner from EVLA. For EMA, the microwave ablation catheter is percutaneously inserted into the varicose veins, and penetrable microwave energy is released by the antenna radiation to make the polar molecules in the vascular tissues vibrate at a high frequency under the action of microwave field to directly generate heat.[13] The efficiency and safety of EMA in clinical practice have rarely been reported. A retrospective study from Mao *et al* reported the short-term (6 months) occlusion rate of EMA and EVLA, where EMA was a little higher than EVLA.[13] Yang *et al* performed a cohort study comparing the efficiency of EMA with EVLA, and found that EMA displayed a similar occlusion rate and lower complications compared with EVLA.[14] A limitation of this study is that it is not a randomised trial, which may cause some selective bias.[14]

Considering these, we aimed to conduct a multicentre randomised controlled trial to further compare the efficacy and safety of EMA with EVLA in the treatment of GSV varicosis. Also, we not only assess the short-term outcome (6 months) but also the long-term outcome (12 months).

## METHODS AND ANALYSIS

### Hypothesis

The efficiency and safety of EMA is not inferior to EVLA in treating GSV varicosis.

### Study design

This is a multicentre, randomised controlled non-inferiority trial of the efficacy and safety of EMA versus EVLA for GSV varicosis. This trial will be performed in Beijing Hospital, Peking Union Medical College Hospital, Beijing Tsinghua Changgung Hospital, Beijing Luhe Hospital, Capital Medical University, the First Hospital of Hebei Medical University, and the First Affiliated Hospital of Xi'an Jiaotong University. The flow chart of the study process is shown in figure 1. This study sets up a final analysis, and an interim analysis will not be performed. The trial will not be terminated on statistical grounds. The *ClinicalTrials.gov* identifier for this trial is NCT04726124, registered on 22 January 2021.

### Participants

The participants will be recruited by the researchers through recruitment posters at the six centres, and the estimated recruitment time is from 26 January to 31 August 2021. Eligible participants will provide informed consent (online supplemental file 1) and will be randomly allocated to the EMA or the EVLA groups. After the treatment, the participants will be followed up by returning to the centres at 7 days, 3 months, 6 months and 12 months, and by telephone at 1 month. During the trial, the participants will not receive other relevant treatment. Table 1 shows the time course for data collection and follow-up.

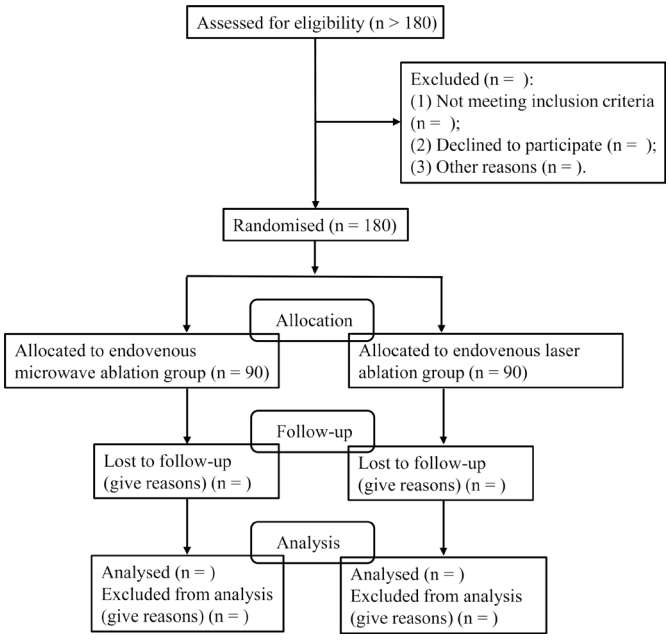


**Figure 1** The flow chart of study process.

### Inclusion criteria

Patients meeting all the following criteria will be included:

1. Patients aged ≥18 years, but not older than 80 years;
2. Patients clinically diagnosed as primary GSV insufficiency with reflux lasting >0.5 s on Doppler ultrasonography;
3. Patients with Clinical-Etiologic-Anatomic-Pathophysiologic C2–C6;
4. Patients who voluntarily participate in this trial, understand all the risks and benefits described in the informed consent document, and sign the written informed consent form.

### Exclusion criteria

Patients meeting one of the following criteria will be included:

1. Patients with a diameter of target lesion vein <2 mm or >15 mm;
2. Patients with a history of surgical treatment on the target lesion or patients with acute thrombosis;
3. Patients with deep vein thrombosis or superficial vein thrombosis;
4. Patients with acute systemic infectious diseases;
5. Patients with severe liver and kidney dysfunction (alanine aminotransferase >3 times the upper limit of normal value; creatinine >225 µmol/L);
6. Patients with known uncorrectable bleeding or severe coagulopathy;
7. Patients with anaesthesia contraindications;
8. Patients with poorly controlled hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood

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Table 1 The time course for data collection and follow-up

| Study period | Enrolment and allocation | | Follow-up | | | | |
|---|---|---|---|---|---|---|---|
| Time point | Screening (−14~0 day) | Allocation (0 day) | 7 days (±3 days) | 1 month (±7 days) | 3 months (±15 days) | 6 months (±30 days) | 12 months (±30 days) |
| Informed consent | X | | | | | | |
| Demographics | X | | | | | | |
| Allocation | | X | | | | | |
| Vital signs | X | X | X | | X | X | X |
| Previous medical history | X | | | | | | |
| Inclusion/exclusion assessment | X | | | | | | |
| Routine blood | X | | X | | | | |
| Blood biochemistry | X | | X | | | | |
| Pregnancy check | X | | | | | | |
| Blood coagulation function | X | | | | | | |
| D-dimer | X | | | | | | |
| ECG | X | | | | | | |
| Doppler ultrasonography of lower extremity vein | X | X | X | | X | X | X |
| VCSS | X | | | X | X | X | X |
| AVVQ | X | | | X | X | X | X |
| Instrument performance evaluation | | X | | | | | |
| Drug use | X | X | X | X | X | X | X |
| Adverse events | X | X | X | X | X | X | X |

AVVQ, Aberdeen Varicose Vein Questionnaire; VCSS, Venous Clinical Severity Score.

pressure ≥100 mm Hg) and diabetes mellitus (fasting glucose ≥10.0 mmol/L);

9. Patients with non-primary varicose veins caused by postdeep vein thrombosis syndrome, Klippel-Trenaunay syndrome, arteriovenous fistula, and so on.
10. Patients with other diseases that may cause difficulty in the trial or the evaluation, such as mental illness, AIDS, malignant tumours, liver disease, cardiac insufficiency and so on, or patients with expected life less than 1 year;
11. Pregnant women, lactating women or women preparing to be pregnant during the trial;
12. Patients participated in clinical trials of other drugs or medical devices in the past 3 months;
13. Patients who will be deemed unsuitable for inclusion by the researchers due to other reasons.

## Sample size calculation

The sample size will be calculated based on the occlusion rate of GSV at 6 months after the treatment. According to the data reported in relevant literature, the effective rate ranges from 92% to 98%.[15 16] After comprehensive consideration, the effective rate in this trial is preset as 95%. The non-inferiority cut-off value recognised by clinical experts is −10%. The α is 0.025, and the power is taken as 80%. The calculation formula for the sample size of the qualitative index non-inferiority design in the Guidelines for Clinical Trial Design of Medical Devices[17] is adopted:

$$n_T = n_C = \frac{(Z_{1-\alpha/2}+Z_{1-\beta})^2[(P_C(1-P_C)+P_T(1-P_T)]}{(|D|-\Delta)^2}$$

$P_T$ and $P_C$ are the expected occlusion rates of GSV in the EMA group and the EVLA group, respectively, and Δ refers to the non-inferiority test cut-off value (negative here). Based on this calculation formula, 75 patients are needed in each group. Considering a possible maximum dropout rate of 20% in each group during the trial, the planned number of patients in each group is increased to 90. As a result, the total number of patients enrolled in the two groups is 180.

## Randomisation

The enrolled patients will be randomly allocated into one of the two parallel treatment groups in a 1:1 ratio using the central randomisation system. The random number sequence will be generated in the Chinese Clinical Trial Registry using computer software, and the allocation sequence will be deposited in ResMan Clinical Trial Management Public Platform. It is not possible to speculate on the allocation status of the participants before the



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allocation. The other personnel, including clinical physicians, evaluator, research nurses are not entitled to apply for random numbers. Each process will be recorded and appropriately saved.

### Blinding

The outcome evaluator in this trial will be blinded to the allocation. The evaluation of outcomes will be carried out by an independent evaluator. The predetermined standardised objective measurement and standardised protocols will be used to limit the bias in other outcomes.

### Interventions

The patients in each group will receive either EMA or EVLA for the treatment of the trunk of the GSV. For the (large) tributaries, point-form-stripping treatment will be used. The semiconductor laser treatment apparatus and disposable laser fibre (EUFOTON S. R. L., Trieste, Italy) is used for EVLA. The EMA is performed using microwave ablation therapeutic apparatus (Sanhe Dingye Technology Co., Ltd., Beijing, China). Analgesia or sedation will not be used before the treatment. Patients with bilateral disease will treat one leg by RFA, HLS and other methods before the random allocation. After they recover well and can walk normally, they will be randomly allocated into the EMA group or the EVLA group for the treatment of the contralateral leg.

### EMA group

The microwave ablation catheter is transported to the GSV through the vascular sheath to drain into the opening of the femoral vein under the guidance of ultrasound after injecting a local anaesthetic (1% lidocaine), and then the catheter tip is retracted about 2 cm. After sufficient tumescent fluid is injected around the vein and the location of the catheter tip is reconfirmed, EMA will be conducted in the GSV under the guidance of ultrasound. The power of the soft catheter is set at 65 W. The time for single ablation is 3–5 s, and each withdrawal is about 1–1.5 cm. The hard catheter is recommended for smaller blood vessels below the knee, and the power is set at 35 W. The time for single ablation was 1–2 s, with each withdrawal of about 1 cm. After the EMA treatment, the ultrasound is used again to examine the occlusion.

### EVLA group

The laser fibre is transported through the vascular sheath to the GSV to drain into the opening of the femoral vein under the guidance of ultrasound after injecting 1% lidocaine, and then the fibre tip is retracted about 2 cm. After sufficient tumescent fluid is injected around the vein and the location of the catheter tip is reconfirmed, the GSV is treated with ultrasound-guided laser ablation. The wavelength of the laser is 1470 nm. The ablation power is set at 8W, and the withdrawal speed of the optical fibre is 2–3 mm/s. The occlusion is examined with the help of ultrasound after the EVLA.

### Criteria for discontinuing the trial

The trial will be suspended/terminated in advance if the following conditions happen:

1. It is difficult to evaluate the efficacy due to the fatal mistakes in the protocol;
2. Significant deviation occurs during the implementation of the trial protocol;
3. Serious safety problems are found by investigators and there are chances of unacceptable risks if the trial is continued;
4. Suspension/termination required by the sponsor or the drug administrative department due to some reasons.

Early suspension/termination of the trial must take place after obtaining written approval by the principal investigator and the sponsor. All trial data will be kept for future reference.

### Data collection and management

Data will be collected and filled in by trained researchers. The data administrators will establish the data management system based on the case report form (CRF), and set strict permissions for database access and independent accounts. All CRFs should be confirmed to be correctly and completely filled in, and should be consistent with the original data. If errors or omissions are found, the researchers should be informed to correct them in time, and the original records should be kept clear and visible. Two data administrators will independently input the data and compare the consistency of the data files. For data problems, such as missing, abnormal and logic errors, found in the verification, the data administrator will send questions to the researchers in time for answers. After confirming all data are correct, the database is locked, and then the locked data are exported for statistical analysis. Only investigators have access to the information, and they all will strictly maintain a privacy policy to protect confidentiality before, during and after the trial. The data monitoring committee is considered unnecessary because of the minimal risks of the interventions. The complete database and relevant documents will be transferred by the data management department to the sponsor after the clinical trial is completed, and kept by the sponsor until there is no use of the medical device. Each participant will receive a unique identifier when participating in the study, and this identifier will be used for the entire data documentation to ensure the participant's confidentiality. We only obtain consent to use data and samples for the research questions described in this protocol. Therefore, we do not intend to use participant data in ancillary studies.

### Statistical methods to handle missing data

The Worst Case Carry Forward strategy will be used to handle the missing data of efficacy indicators. The missing follow-up date will be filled with the planned date calculated according to the last follow-up date. The other

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missing data, such as safety indicators and demographic data, will not be handled.

## Outcome measurement

### Primary outcome

The primary outcome is the occlusion rate of GSV immediately, at 6 months and at 12 months after the treatment. Doppler ultrasonography will be used to examine the occlusion of the target vein of the participants. A successful operation is defined as the complete occlusion. The complete occlusion is denfined as Doppler ultrasonography showing the entire treated target vein segment with no discrete segments of patency exceeding 5 cm.[18] At the end of the trial, patients with complete GSV occlusion will be collected and the complete GSV occlusion rate calculated. The occlusion rate is calculated as the number of patients with complete GSV in the group/number of total patients in the same group ×100%. The occlusion failure is defined as the cumulative length of unclosed target vein segment exceeding 5 cm.[18] The cases of occlusion failure will be collected and classified for statistics according to the closure types. The reasons for the failure will be explored in detail.

### Secondary outcome

#### *Venous Clinical Severity Score*

VCSS[19] is used during the screening period and at 1 month, 3 months, 6 months and 12 months after the treatment. VCSS includes 10 items, such as pain, varicose veins, oedema, skin pigmentation, inflammation, skin induration, number of active ulcers, ulcer size, duration of ulcer and application of pressure therapy. Each item is scored from 0 to 3 according to the severity, and the total score is 30. Higher score indicates higher severity.

#### *AVVQ Score*

AVVQ[20 21] is applied to assess patients' quality of life during the screening period and at 1 month, 3 months, 6 months and 12 months after the treatment. AVVQ includes the scope of varicose veins, pain, oedema, itching, skin pigmentation, skin rashes, presence of ulcer, use of painkillers and stretch hose, presence of psychological concerns, and effect of varicose veins on daily wear, work, life and sports, and so on. Each item is scored from 0 to 3 according to the severity. A lower score indicates better quality of life.

## Operation time

The operation time is defined as the time between the initiation of the ablation after the device is inserted into the vein and the time after the ablation is completed.

## Instrument performance evaluation

The instrument performance evaluation will be performed using a soft microwave ablation catheter, a hard microwave ablation catheter and a microwave ablation therapeutic apparatus host. The soft catheter is made of soft polymer material and is mainly used for the lesion of the GSV trunk. The hard catheter is made of stainless steel material, which cannot be bent, and is suitable for relatively superficial veins. The evaluation indices for soft or hard microwave ablation catheters are flexibility (for soft), accuracy (for hard), passability and convenience of use. The grades are rated as excellent, good and poor. The evaluation index for microwave ablation therapeutic apparatus host is stability, and the grade is classified as yes or no. The manipulability of the instruments is evaluated by the investigator during or after the treatment.

## Safety assessment

The vital signs, including body temperature, respiration, heart rate and blood pressure, will be examined, observed and recorded at the screening period and 7 days, 3 months, 6 months and 12 months after the treatment. The laboratory parameters will be examined by routine blood, blood biochemistry, blood coagulation function, D-dimer, pregnancy check (only women of childbearing age) and ECG at the screening period. At 7 days after treatment, only blood routine and blood biochemistry are examined. Abnormal laboratory results with clinical significance will be reviewed and followed up until return to normal or no clinical significance. The lower extremity vein is examined by Doppler ultrasonography at the screening period, 7 days, 3 months, 6 months and 12 months after treatment. The images are collected and sorted by the researchers, and then submitted to the leading unit for analysis. During the treatment and follow-up, the complications caused by treatment will be observed and recorded, which includes peripheral nerve injury (such as skin numbness caused by cutaneous nerve injury), surrounding skin injury or burn, injury caused by microwave accessories entering accidentally the deep vein through the communicating branch; incision infection, deep venous thrombosis, and superficial venous thrombosis. Other adverse events and serious adverse events will be observed and recorded throughout the trial. Serious adverse events should be followed until the events are resolved or until investigators estimating the events has been chronic, stabilised, or explicable.

## Statistical analysis

Statistical analysis will be performed using SAS software (V.9.4). Quantitative data are described as the means, SDs, medians, minimum, maximum, lower quartile (Q1) and upper quartile (Q3), and the classification data are described as numbers and percentages. The quantitative data will be analysed using the group t test (homogeneity of variance and normal distribution) or Wilcoxon rank-sum test. The classification data will be analysed using the $\chi^2$ test or Fisher's exact test, and the ranked data will be analysed applying the Wilcoxon rank-sum test or Cochran-Mantel-Haenszel (CMH) test. A value of $p \leq 0.05$ is considered statistically significant.

## Patient and public involvement

Patients have not been involved in the study design.

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## ETHICS AND DISSEMINATION

This trial will be conducted according to the principles of the Declaration of Helsinki, and has been approved by the Clinical Trial Ethics Committee of Beijing Hospital (2020BJYYEC-126–02), Peking Union Medical College Hospital (KS2020393), Beijing Tsinghua Changgung Hospital (No.20279-2-02), Beijing Luhe Hospital.Capital Medical University (2020-LHYW-030–01), the First Hospital of Hebei Medical University (No.2020249) and the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2021LSY-12).

The study team will disclose results to all participants, and disseminate the results as articles published in international peer-reviewed journals. We will adhere to the official eligibility guidelines for authorship to publish.

## DISCUSSION

GSV varicosis is one of the most common venous diseases and is more common in women than in men.[22] The symptoms of GSV varicosis are not only swelling and pain in the lower limbs, but are also often combined with ulcers, eczema, phlebitis and other adverse reactions, which cause irreversible impact on patients' work and quality of life.[23] To improve this, it is important to explore suitable treatments for clinical application.

According to current guidelines,[24 25] EVLA and other endovenous thermal ablation techniques have replaced HLS as the first treatment option for incompetent saphenous veins, because they have been proven to be highly effective in many countries.[26–28] In the treatment of EVLA, laser is delivered into blood vessel lumen to produce heat energy, which deforms or inactivates the protein and enzymes in the blood vessel wall. After destroying the structure of the vein wall, the vein appears fibrosis, which makes the blood vessels contract and permanently close.[29] EMA is a relatively novel endovenous thermal ablation technique.[30] In the treatment of EMA, the microwave catheter is delivered into venous cavity to directly produce high temperature, which can coagulate the tissues, extensively damage vascular endothelial cells and intima, and induce vascular fibrosis to make the blood vessel atresia.[30] Mao *et al* conducted a retrospective study to compare the efficiency and safety between EVLA and EMA.[13] The results showed that EMA resulted in lower ecchymosis complications but higher skin burn and paralysis complications than EVLA, although the operation time and length of hospital stay had no significant difference. Yang *et al* reported that EMA had a shorter procedure time, lower incidence of induration and ecchymosis, and lower local recurrence below the knee compared with EVLA.[14] From the current studies, the evidence on whether EMA is not inferior to EVLA is still insufficient. Mao *et al* mainly focus on the short-term outcome, and the study of Yang *et al* is not a randomsied trial which may cause selective bias.

Based on these, we hope to conduct a multicentre, randomised controlled non-inferiority trial to evaluate the long-term efficiency and safety of EMA in the treatment of GSV varicosis compared with EVLA, and provide reliable evidence for the clinical application of EMA.

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**Contributors** YJL and WWW designed the study. YJL wrote the manuscript. YNL refined the study protocol and study implementation. JL and MNS provided methodological and statistical expertise. WWW critically reviewed, and edited the manuscript. All authors read and approved the final manuscript.

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