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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059213
Article Type:	Protocol
Date Submitted by the Author:	12-Nov-2021
Complete List of Authors:	Li, Yong-jun ; Beijing Hospital, Vascular Surgery Wu, Weiwei; Beijing Tsinghua Changgung Hospital, Department of Vascular Surgery Li, Younan; Beijing Tsinghua Changgung Hospital, Department of Vascular Surgery Li, Jing; Beijing Sanhe Dingye Technology Company Sun, Mengnan; Beijing Sanhe Dingye Technology Company
Keywords:	Vascular medicine < INTERNAL MEDICINE, EPIDEMIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Manuscripts

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

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ABSTRACT

Introduction Endovenous microwave ablation (EMA) is a new minimally invasive surgery to treat GSV varicosis, but 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 minimally invasive surgery widely used in clinical practice.

Methods and Analysis This is a multicenter, randomized controlled non-inferiority trial to compare the efficacy and safety of EMA and EVLA in patients suffering from GSV varicosis. We will recruit 180 patients in 6 centers and randomly assign them into treatment group and control group in a 1:1 ratio. The treatment group is given EMA and the control group is given EVLA. The patients will return to the hospitals for follow-up visits at 7 days, 3 months and 6 months after the surgery. The primary outcome is the occlusion rate of GSV at 6 months after the surgery. The secondary outcomes are operative success rate, instrument performance evaluation, Venous Clinical Severity Score (VCSS), Aberdeen Varicose Vein Questionnaire (AVVQ) score, operation time. This study will assess the efficacy and safety of EMA, and verify whether EMA is not inferior to EVLA for the treatment of GSV varicosis.

Ethics and Dissemination This protocol has been approved by the Clinical Trial Ethics Committee of Beijing Tsinghua Chang Gung Hospital (SD-LC-001).

Keywords: GSV varicosis, endovenous laser ablation, endovenous microwave ablation, efficacy, safety.

Strengths and limitations of this study

- This is the first randomized controlled trial to explore the efficiency and safety of EMA and EVLA in patients with GSV varicosis.
- Our study will be performed in multi centers, which makes the results more reliable.
- For the missing data of efficacy indicators, the Worst Case Carry Forward (WCCF) strategy will be used to handle, indicating the results are interpreted cautiously.
- The lack of blinding of patients and surgeons is the limitation of this study.
- The surgery is performed by different doctors, which may cause some potential bias.

INTRODUCTION

Great saphenous vein (GSV) varicosis is a common peripheral vascular disease, and usually caused by incomplete venous valve closure, which makes the venous blood backflow and distal veins stasis and then results in the dilation, bulging and twisting of the GSV¹. The GSV is reported to affect about one-third of the adults, and mostly occurs in people who engage in sustained standing jobs, have high intensity of physical activity, or sit for a long time with less moving². The patients may suffer from occasional discomfort, itching, pigmentation, and skin ulceration, etc., impairing the quality of life³.

The common conventional surgical treatment for GSV varicosis is the high ligation and stripping (HLS), but the postoperative clinical recurrence is high and causes slow recovery and obvious incision scar^{4, 5}. In recent years, endovenous minimally invasive techniques are popular, and demonstrated to be more tolerance for patients, less invasive, and earlier return to normal activities than the conventional surgeries⁶⁻⁹. Endovenous laser ablation (EVLA) is a minimally invasive technique using different frequencies of laser¹⁰. Due to the good efficiency and high safety, it has been recommended as the first-line treatment for GSV varicosis¹¹. Endovenous microwave ablation (EMA) is a new minimally invasive technique, and its efficiency and safety in clinical practice have not been determined. A retrospective study from Mao *et al.* reported that the efficiency and safety of EMA was comparable to EVLA, and EMA showed a little higher occlusion rate than EVLA¹². Yang *et al.* reported that EMA displayed the similar efficiency and lower complications compared to EVLA,

and they recommended that randomized clinical trials (RCTs) should be designed to further compare the efficiency and safety because of potential selective bias in their cohort study¹³.

Herein, we aimed to perform a multicenter, randomized controlled non-inferiority trial to explore whether EMA can be an effective alternative to EVLA in the treatment of GSV varicosis.

METHODS AND ANALYSIS

Hypothesis

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

Study design

This is a multicenter, randomized controlled non-inferiority trial to 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 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.

Ethics and registration

This trial will be conducted according to the principles of Helsinki's Declaration, and approved by the Clinical Trial Ethics Committee of Beijing Tsinghua Chang Gung Hospital (SD-LC-001). The *ClinicalTrials.gov* identifier for this trial is NCT04726124, registered on January 22nd, 2021.

Participants

The participants will be recruited by the researchers through the recruitment posters in the six centers from January 26th to August 31st in 2021. The eligible participants will provide the informed consent and randomly allocated to EMA or EVLA group. After the surgery, the participants will be follow-up by returning to the centers at 7 days, 3 months and 6 months and by telephone at 1 month. During the trial, participants will not receive other relevant treatment and operation. Table 1 shows the time course for data collection and follow-up.

Inclusion criteria

Patients meeting all the following criteria will be included:

1. Patients with age ≥ 18 years, but not older than 80 years;
2. Patients clinically diagnosed as primary varicosis of GSV of the lower extremities;
3. Patients with Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) grade 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 diameter of target lesion vein < 2 mm or > 15 mm;
2. Patients with history of surgical treatment on the target lesion or patients with acute thrombosis;
3. Patients with deep 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 $\mu\text{mol/L}$);
6. Patients with known uncorrectable bleeding or severe coagulopathy;
7. Patients with anesthesia contraindications;
8. Patients with poorly controlled hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg) and diabetes mellitus (fasting glucose ≥ 10.0 mmol/L);
9. Patients with non-primary varicose veins caused by post-deep vein thrombosis syndrome, Klippel-Trenaunay syndrome, arteriovenous fistula, etc.
10. Patients with other diseases that may cause difficulty in the trial or the evaluation, such as mental illness, acquired immune deficiency syndrome (AIDS), malignant tumors, liver disease, cardiac insufficiency, etc., 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 calculations

The sample size will be calculated based on the occlusion rate of GSV at 6 months after the surgery. According to the data reported in relevant literature, the effective rate ranges from 92% to 98%^{14, 15}. After comprehensive consideration, the effective rate in this trial is preset as 95%. The non-inferiority cutoff value recognized 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 Devices¹⁶ 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 rate 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 central randomization 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. The allocation status of the participant is not possible to speculate before obtaining this information. 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 standardized objective measurement and standardized protocols will be used to limit the bias in other outcomes.

Inventions

The patients in each group will receive either EMA or EVLA. Both EVLA and EMA are thermal ablation therapy for target diseased blood vessels through thermal effect. Based on the similar working principles, EVLA is selected as the control group. The semiconductor laser treatment apparatus and disposable laser fiber (EUFOTON S. R. L., Trieste, Italy) is used for EVLA. The EMA is performed using microwave ablation

therapeutic apparatus (Sanhe Dingye Technology Company, Beijing, China). The analgesia or sedation will not be used before the surgery. Patients with bilateral varicosis will treat one leg by radiofrequency ablation, HLS and other methods before the random allocation.

EMA group

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

EVLV group

The laser fiber is transported through the vascular sheath to the GSV to drain into the opening of femoral vein under the guidance of ultrasound after injecting 1 % lidocaine, and then the fiber tip is retracted about 2 cm. After sufficient tumescent fluid is injected around the vein and the location of catheter tip is reconfirmed, the GSV is treated with

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4 ultrasound-guided laser ablation. The ablation power is set at 8W, and the withdrawal
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6 speed of optical fiber is 2-3mm/s. The occlusion is examined under the ultrasound after
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8 the EVLA.
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11 12 13 14 **Criteria for discontinuing the trail**

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

- 18 1. It is difficult to evaluate the efficacy due to the fatal mistakes in the protocol;
- 19 2. The significant deviation occurred during the implementation of the trial protocol;
- 20 3. Serious safety problems are found by investigators and unacceptable risks may
21 occur if the trial is continued;
- 22 4. Suspension/termination required by the sponsor or the drug administrative
23 department due to some reasons.
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35 Early suspension/terminating of the trial must be approved in writing by the principal
36 investigator and the sponsor. All trial data will be kept for future reference.
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43 **Data collection and management**

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

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48 The Worst Case Carry Forward (WCCF) strategy will be used to handle the missing
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50 data of efficacy indicators. The missing follow-up date will be filled with the planned
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52 date calculated in according to the last follow-up date. The other missing data, such as
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54 safety indicators and demographic data, will not be handled.
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Outcome measurement

Primary outcome

The primary outcome is the occlusion rate of GSV at 6 months after the surgery. The doppler ultrasonography is applied to check whether the GSV of patients is completely closed, and the results are recorded. At the end of the trail, the number statistics of patients with complete GSV occlusion will be performed and the complete GSV occlusion rate is calculated. The occlusion is defined that no discontinuous unclosed segments over 5 cm are observed after the examination of doppler ultrasonography showing the occlusion of entire treated GSV segment. The occlusion rate is calculated as number of patients with complete GSV in the group/number of total patients in the same group $\times 100\%$.

Secondary outcome

Operative success rate

The operative success rate is calculated by number of patients with successful operation in this group/total number of patients in this group $\times 100\%$.

Instrument performance evaluation

The instrument performance evaluation will be performed in soft microwave ablation catheter, hard microwave ablation catheter, and microwave ablation therapeutic apparatus host. The evaluation index for soft or hard microwave ablation catheter are flexibility (for soft), accuracy (for hard), passability, and convenience of use, and the grade 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 surgery.

Venous Clinical Severity Score (VCSS)

The VCSS¹⁷ is used during the screening period and at 30 days, 3 months, and 6 months after the surgery, and includes ten items, such as pain, varicose veins, edema, 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 total score is 30. Higher score indicates higher severity.

Aberdeen Varicose Vein Questionnaire (AVVQ) score

The AVVQ¹⁸ is applied during the screening period and at 30 days, 3 months, and 6 months after the surgery, and includes the scope of varicose veins, pain, edema, 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 wearing, work, life and sports, etc. Each problem is scored from 0 to 3 according to the severity. 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.

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,

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4 and 6 months after surgery. The laboratory parameters will be examined by routine
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6 blood, blood biochemistry, blood coagulation function, D-dimer, pregnancy check
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8 (only women in childbearing age), and electrocardiograph at the screening period. At 7
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10 days after surgery, only blood routine and blood biochemistry are examined. The
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12 abnormal laboratory results with clinical significance will be reviewed and followed up
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14 until return to normal or no clinical significance. The lower extremity vein is examined
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16 by B ultrasound at the screening period, 7 days, 3 months and 6 months after surgery.
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18 The images are collected and sorted by the researchers, and then submitted to the
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20 leading unit for analysis. The surgery-related complications will be observed and
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22 recorded from the beginning of the surgery to the end of follow-up, including peripheral
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24 nerve injury (such as skin numbness caused by cutaneous nerve injury), surrounding
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26 skin injury or burn, injury caused by microwave accessories entering accidentally the
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28 deep vein through the communicating branch; incision infection, deep venous
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30 thrombosis, superficial venous thrombosis. Other adverse events and serious adverse
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32 events are observed and recorded throughout the trial. Serious adverse events should be
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34 followed until the problem is resolved or estimated by investigators that have become
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36 chronic, stabilized or sufficient to account for the anomaly.
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51 **Statistical analysis**

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53 Statistical analysis will be performed using SAS software (version 9.4). The
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55 quantitative data are described as the mean, standard deviation, median, minimum,
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57 maximum, lower quartile (Q1), and upper quartile (Q3), and the classification data are
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described as the number and percentage. The quantitative data will be analyzed using the group t test (homogeneity of variance and normal distribution) or Wilcoxon rank sum test. The classification data will be analyzed using the chi-square test or Fisher's exact test, and the ranked data will be analyzed applying Wilcoxon rank sum test or CMH test. *P* value less than or equal to 0.05 was considered statistically significant.

Patient and public involvement

Patients have not been involved in the study design.

Dissemination

Results will be personally explained to all participants, and disseminated as articles published in international peer-reviewed journals. We will adhere to the official eligibility guidelines for authorship to publish, and do not plan to use professional writers.

Discussion

GSV is one of the most common diseases in surgery and more common in females than in man¹⁹. The symptoms of GSV are not only swelling and pain in the lower limbs, but also often combined with ulcers, eczema, phlebitis and other adverse reactions, which cause irreversible impact on patients' work and quality of life²⁰. Therefore, it is significant to search other suitable treatments for clinical application.

EVLA works on the basis that laser directly delivers into blood vessel lumen to

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4 produce heat energy to deform or inactivate the protein or enzymes in the blood vessel
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7 wall and destroy the structure of the vein wall with subsequent fibrosis, causing the
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10 blood vessels to contract and permanently close ²¹. Currently, EVLA, an endovenous
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12 thermal ablation, has been recommended as the first-line treatment for VVs ²². EMA is
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14 also an endovenous thermal ablation and has been confirmed as an effective and
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16 satisfactory new technique to treat GSV varicosis ⁶. The mechanism of EMA is to apply
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18 the microwave radiator directly to venous cavity wall to instantaneously produce high
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20 temperature with a certain penetration range, which can coagulate the tissues,
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22 extensively damage vascular endothelial cells and intima, induce thrombosis
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24 throughout the vein, and generate vascular fibrosis to make the blood vessel atresia ⁶.
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30 Mao et al. conducted a retrospective study to compare the efficiency and safety between
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32 EVLA and EMA ¹². The results showed that EMA brought lower ecchymosis
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34 complication but higher skin burn and paralysis complications than EVLA, although
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36 the operation time and length of hospital stay were no significant difference. Yang et
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38 al. reported that EMA had a shorter procedure time, lower incidence of induration and
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40 ecchymosis, and lower local recurrence below the knee compared to EVLA ¹³.
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46 However, the evidence whether EMA is not inferior to EVLA is still insufficient in
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48 clinical studies until now.
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51 We hope to conduct a multicenter, randomized controlled non-inferiority trial to
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53 evaluate the efficiency and safety of EMA in the treatment of GSV varicosis, and
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55 provide reliable evidence for the clinical application of EMA.
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Authors' contributions Y.J.L. and W.W.W. designed the study. Y.J.L. wrote the manuscript. Y.J.L., W.W.W., Y.N.L., J.L., and M.N.S. were responsible for the implementation of the study. W.W.W. critically reviewed, and edited the manuscript. All authors read and approved the final manuscript.

Funding None declared.

Competing Interests None.

Study sponsor

The sponsor is Beijing Tsinghua Changgung Hospital, located in No.168 Litang road, Changping District, Beijing 102218, P.R. China. The sponsor did not have a role in the design of the trial, collection, the intervention procedures, evaluation, and analysis of data.

Patient and Public Involvement statement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Data availability statement

No additional data available.

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Figure legends

Figure 1 The flow chart of study process.

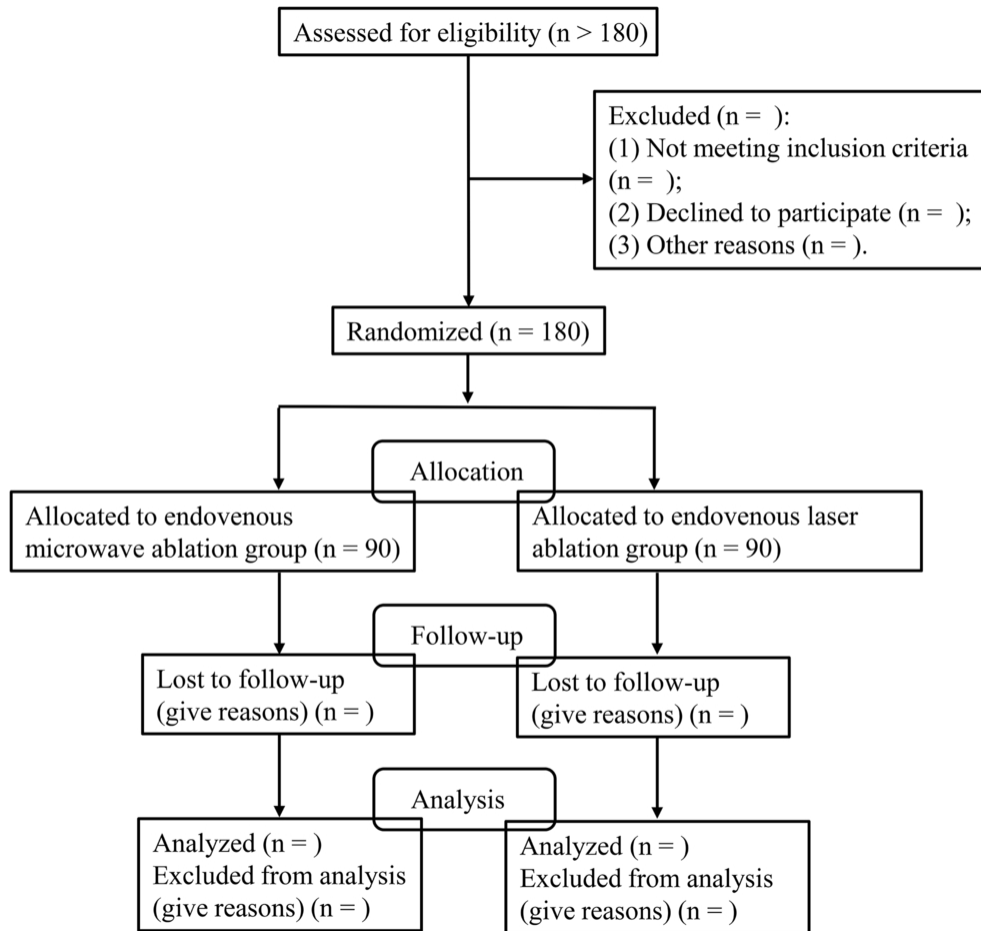
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Table 1 The time course for data collection and follow-up

Study period	Enrollment and allocation		Follow-up			
	Screening (-14~0 day)	Allocation (0 day)	7 day (±3 day)	1 month (±7 day)	3 month (±15 day)	6 month (±30 day)
Informed consent	X					
Demographics	X					
Allocation		X				
Vital signs	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					
Electrocardiograph	X					
B-mode ultrasound of lower extremity vein	X		X		X	X
VCSS	X			X	X	X
AVVQ	X			X	X	X
Instrument performance evaluation		X				
Drug use	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
	2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	-
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11-12
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5

1				
2	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
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4				
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6				
7				
8	Methods: Participants, interventions, and outcomes			
9				
10	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
11				
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15	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
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21	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
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26		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
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31		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-11
32				
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36		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
37				
38				
39	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
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48	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6 (see Table 1)
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54	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
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2 Recruitment 15 Strategies for achieving adequate participant enrolment to 6
3 reach target sample size
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5 **Methods: Assignment of interventions (for controlled trials)**
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7 Allocation:

8
9 Sequence generation 16a Method of generating the allocation sequence (eg, 9
10 computer-generated random numbers), and list of any
11 factors for stratification. To reduce predictability of a
12 random sequence, details of any planned restriction (eg,
13 blocking) should be provided in a separate document that
14 is unavailable to those who enrol participants or assign
15 interventions
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18 Allocation concealment 16b Mechanism of implementing the allocation sequence (eg, 9
19 central telephone; sequentially numbered, opaque, sealed
20 envelopes), describing any steps to conceal the sequence
21 until interventions are assigned
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24 Implementation 16c Who will generate the allocation sequence, who will enrol 9
25 participants, and who will assign participants to
26 interventions
27

28 Blinding 17a Who will be blinded after assignment to interventions (eg, 9
29 (masking) trial participants, care providers, outcome assessors, data
30 analysts), and how
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33 17b If blinded, circumstances under which unblinding is 9
34 permissible, and procedure for revealing a participant's
35 allocated intervention during the trial
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38 **Methods: Data collection, management, and analysis**

39 Data collection 18a Plans for assessment and collection of outcome, baseline, 11-12
40 methods and other trial data, including any related processes to
41 promote data quality (eg, duplicate measurements, training
42 of assessors) and a description of study instruments (eg,
43 questionnaires, laboratory tests) along with their reliability
44 and validity, if known. Reference to where data collection
45 forms can be found, if not in the protocol
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49 18b Plans to promote participant retention and complete follow- 6
50 up, including list of any outcome data to be collected for
51 participants who discontinue or deviate from intervention
52 protocols
53

54 Data 19 Plans for data entry, coding, security, and storage, 11-12
55 management including any related processes to promote data quality
56 (eg, double data entry; range checks for data values).
57 Reference to where details of data management
58 procedures can be found, if not in the protocol
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1				
2	Statistical	20a	Statistical methods for analysing primary and secondary	16
3	methods		outcomes. Reference to where other details of the	
4			statistical analysis plan can be found, if not in the protocol	
5				
6		20b	Methods for any additional analyses (eg, subgroup and	-
7			adjusted analyses)	
8				
9		20c	Definition of analysis population relating to protocol non-	12
10			adherence (eg, as randomised analysis), and any	
11			statistical methods to handle missing data (eg, multiple	
12			imputation)	
13				
14				
15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC);	12
18			summary of its role and reporting structure; statement of	
19			whether it is independent from the sponsor and competing	
20			interests; and reference to where further details about its	
21			charter can be found, if not in the protocol. Alternatively,	
22			an explanation of why a DMC is not needed	
23				
24				
25		21b	Description of any interim analyses and stopping	5
26			guidelines, including who will have access to these interim	
27			results and make the final decision to terminate the trial	
28				
29				
30	Harms	22	Plans for collecting, assessing, reporting, and managing	14-15
31			solicited and spontaneously reported adverse events and	
32			other unintended effects of trial interventions or trial	
33			conduct	
34				
35				
36	Auditing	23	Frequency and procedures for auditing trial conduct, if any, -	-
37			and whether the process will be independent from	
38			investigators and the sponsor	
39				
40	Ethics and dissemination			
41				
42	Research ethics	24	Plans for seeking research ethics committee/institutional	6
43	approval		review board (REC/IRB) approval	
44				
45	Protocol	25	Plans for communicating important protocol modifications	11
46	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
47			relevant parties (eg, investigators, REC/IRBs, trial	
48			participants, trial registries, journals, regulators)	
49				
50				
51	Consent or assent	26a	Who will obtain informed consent or assent from potential	6
52			trial participants or authorised surrogates, and how (see	
53			Item 32)	
54				
55		26b	Additional consent provisions for collection and use of	12
56			participant data and biological specimens in ancillary	
57			studies, if applicable	
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2	Confidentiality	27	How personal information about potential and enrolled	12
3			participants will be collected, shared, and maintained in	
4			order to protect confidentiality before, during, and after the	
5			trial	
6				
7	Declaration of	28	Financial and other competing interests for principal	18
8	interests		investigators for the overall trial and each study site	
9				
10	Access to data	29	Statement of who will have access to the final trial dataset,	12
11			and disclosure of contractual agreements that limit such	
12			access for investigators	
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15	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for	12
16	post-trial care		compensation to those who suffer harm from trial	
17			participation	
18				
19	Dissemination	31a	Plans for investigators and sponsor to communicate trial	16
20	policy		results to participants, healthcare professionals, the public,	
21			and other relevant groups (eg, via publication, reporting in	
22			results databases, or other data sharing arrangements),	
23			including any publication restrictions	
24				
25				
26		31b	Authorship eligibility guidelines and any intended use of	16
27			professional writers	
28				
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30		31c	Plans, if any, for granting public access to the full protocol,	11-12
31			participant-level dataset, and statistical code	
32				
33	Appendices			
34				
35	Informed consent	32	Model consent form and other related documentation	6
36	materials		given to participants and authorised surrogates	
37				
38	Biological	33	Plans for collection, laboratory evaluation, and storage of	12
39	specimens		biological specimens for genetic or molecular analysis in	
40			the current trial and for future use in ancillary studies, if	
41			applicable	
42				
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059213.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Mar-2022
Complete List of Authors:	Li, Yong-jun ; Beijing Hospital, Department of Vascular Surgery Wu, Weiwei; Beijing Tsinghua Changgung Hospital, Department of Vascular Surgery Li, Younan; Beijing Tsinghua Changgung Hospital, Department of Vascular Surgery Li, Jing; Beijing Sanhe Dingye Technology Co., Ltd. Sun, Mengnan; Beijing Sanhe Dingye Technology Co., Ltd.
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Public health
Keywords:	Vascular medicine < INTERNAL MEDICINE, EPIDEMIOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Manuscripts

Efficacy and safety of endovenous microwave ablation versus laser ablation for great saphenous vein varicosis: study protocol for a multicenter, randomized 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 multicenter, randomized controlled non-inferiority trial to compare the efficacy and safety of EMA and EVLA in patients suffering from GSV varicosis. We will recruit 180 patients in 6 centers 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.

Keywords: GSV varicosis, endovenous laser ablation, endovenous microwave ablation, efficacy, safety.

For peer review only

Strengths and limitations of this study

- Compared to previous studies, we use the randomized method to control confounders.
- Our study will be performed in multi centers, which makes the results more reliable.
- For the missing data of efficacy indicators, the Worst Case Carry Forward (WCCF) 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 that usually caused by incomplete venous valve closure, which makes the venous blood backflow and distal veins stasis and then results in the dilation, bulging and twisting of the GSV¹. The GSV varicosis affects about one-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 moving². The patients may suffer from occasional discomfort, itching, pigmentation, and skin ulceration, etc., impairing their quality of life³.

The common conventional surgical treatment for GSV varicosis is the high ligation and stripping (HLS), but it has been reported to cause a high postoperative clinical recurrence, slow recovery, and obvious incision scar^{4,5}. For the need of less invasive treatment, endovenous thermal ablation technique, 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 a high heat of local tissues contacting electrode catheter to produce endothelial damage⁸. For EVLA, the laser is converted into thermal energy through the optical fiber, which causes thermal injury to the target vein endothelium and its resultant occlusion⁹. Both RFA and EVLA showed good efficiency and high safety, whereas evidence indicated that EVLA is more cost-effective therapeutic option^{10,11}.

Endovenous microwave ablation (EMA) is a relatively novel method of thermal ablation treatment¹². Different from RFA, it does not use thermocouple to regulate the

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4 temperature at the venous wall ¹². Also, the way of EMA to generate thermal energy is
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6 different from EVLA. For EMA, the microwave ablation catheter is percutaneously
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8 inserted into the varicose veins, and penetrable microwave energy is released by the
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10 antenna radiation to make the polar molecules in the vascular tissues vibrate at a high-
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12 frequency under the action of microwave field to directly generate heat ¹³. The
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14 efficiency and safety of EMA in clinical practice have rarely been reported. A
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16 retrospective study from Mao *et al.* reported the short-term (6 months) occlusion rate
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18 of EMA and EVLA that EMA was little higher than EVLA ¹³. Yang *et al.* performed a
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20 cohort study comparing the efficiency of EMA with EMA, and found EMA displayed
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22 the similar occlusion rate and lower complications compared to EVLA ¹⁴. A limitation
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24 of this study is that it is not a randomized trial, which may cause some selective bias ¹⁴.
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33 Considering these, we aimed to conduct a multicenter randomized controlled trial
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35 (RCT) to further compare the efficacy and safety of EMA with EVLA in the treatment
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37 of GSV varicosis. Also, we not only assess the short-term outcome (6 months) but also
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39 the long-term outcome (12 months).
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46 **METHODS AND ANALYSIS**

47 **Hypothesis**

48 The efficiency and safety of EMA is not inferior to EVLA in treating GSV varicosis.
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56 **Study design**

57 This is a multicenter, randomized controlled non-inferiority trial to the efficacy and
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4 safety of EMA versus EVLA for GSV varicosis. This trial will be performed in Beijing
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6 Hospital, Peking Union Medical College Hospital, Beijing Tsinghua Changgung
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8 Hospital, Beijing Luhe Hospital. Capital Medical University, the First Hospital of Hebei
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10 Medical University, and the First Affiliated Hospital of Xi'an Jiaotong University. The
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12 flow chart of study process is shown in Figure 1. This study sets up a final analysis, and
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14 an interim analysis will not be performed. The trial will not be terminated on statistical
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16 grounds. The *ClinicalTrials.gov* identifier for this trial is NCT04726124, registered on
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18 January 22nd, 2021.
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28 **Participants**

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30 The participants will be recruited by the researchers through the recruitment posters in
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32 the six centers, and the estimated recruitment time is from January 26th to August 31st
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34 in 2021. The eligible participants will provide the informed consent (Supplementary
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36 file 1) and randomly allocated to EMA or EVLA group. After the treatment, the
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38 participants will be followed up by returning to the centers at 7 days, 3 months, 6
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40 months and 12 months, and by telephone at 1 month. During the trial, participants will
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42 not receive other relevant treatment and operation. Table 1 shows the time course for
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44 data collection and follow-up.
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53 **Inclusion criteria**

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55 Patients meeting all the following criteria will be included:
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- 58 1. Patients with age \geq 18 years, but not older than 80 years;
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2. Patients clinically diagnosed as primary GSV insufficiency with reflux lasting > 0.5 seconds on doppler ultrasonography;
3. Patients with Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) 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 diameter of target lesion vein < 2 mm or > 15 mm;
2. Patients with 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 $\mu\text{mol/L}$);
6. Patients with known uncorrectable bleeding or severe coagulopathy;
7. Patients with anesthesia contraindications;
8. Patients with poorly controlled hypertension (systolic blood pressure \geq 160 mmHg and/or diastolic blood pressure \geq 100 mmHg) and diabetes mellitus (fasting glucose \geq 10.0 mmol/L);
9. Patients with non-primary varicose veins caused by post-deep vein thrombosis

syndrome, Klippel-Trenaunay syndrome, arteriovenous fistula, etc.

10. Patients with other diseases that may cause difficulty in the trial or the evaluation, such as mental illness, acquired immune deficiency syndrome (AIDS), malignant tumors, liver disease, cardiac insufficiency, etc., 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 cutoff value recognized 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 Devices¹⁷ 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 rate 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 central randomization 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. The allocation status of the participants is impossible to speculate before the 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 standardized objective measurement and standardized 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 fiber (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). The analgesia or sedation will not be used before the treatment. Patients with bilateral disease will treat one leg by radiofrequency ablation, HLS and other methods before the random allocation. After they recover well and can walk normally, they will be randomly allocated into EMA group or EVLA group for the treatment of contralateral leg.

EMA group

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

ultrasound is used again to examine the occlusion.

EVLA group

The laser fiber is transported through the vascular sheath to the GSV to drain into the opening of femoral vein under the guidance of ultrasound after injecting 1 % lidocaine, and then the fiber tip is retracted about 2 cm. After sufficient tumescent fluid is injected around the vein and the location of catheter tip is reconfirmed, the GSV is treated with ultrasound-guided laser ablation. The wavelength of the laser is 1470nm. The ablation power is set at 8W, and the withdrawal speed of optical fiber is 2-3mm/s. The occlusion is examined under the 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. The significant deviation occurred during the implementation of the trial protocol;
3. Serious safety problems are found by investigators and unacceptable risks may occur if the trial is continued;
4. Suspension/termination required by the sponsor or the drug administrative department due to some reasons.

Early suspension/terminating of the trial must obtain the written approval by the principal investigator and the sponsor. All trial data will be kept for future reference.

Data collection and management

The data will be collected and filled in by the trained researchers. The data administrators establish the data management system based on the case report form (CRF), and set strict permissions for database access and independent accounts. All CRFs are confirmed to be correctly and completely filled in, and are 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 independently input the data and compare the consistency of the data files. For the data problems, such as missing, abnormal, and logic error, 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 our 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 all 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 (WCCF) 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 in according to the last follow-up date. The other 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 12 months after the treatment. The doppler ultrasonography will be used to examine the occlusion of target vein of participants. The successful operation is defined as the complete occlusion that doppler ultrasonography showing the entire treated target vein segment with no discrete segments of patency exceeding 5 cm¹⁸. At the end of the trial, patients with complete GSV occlusion will be collected and the complete GSV occlusion rate is calculated. The occlusion rate is calculated as 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 exceeds 5 cm¹⁸. The cases of occlusion failure will be collected and classified for statistics according to the closure types. The reasons for the failure will be detailly explored.

Secondary outcome

Venous Clinical Severity Score (VCSS)

The VCSS¹⁹ is used during the screening period and at 1 month, 3 months, 6 months, and 12 months after the treatment. The VCSS includes ten items, such as pain, varicose veins, edema, 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 total score is 30. Higher score indicates higher severity.

Aberdeen Varicose Vein Questionnaire (AVVQ) score

The 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. The AVVQ includes the scope of varicose veins, pain, edema, 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 wearing, work, life and sports, etc. Each item is scored from 0 to 3 according to the severity. 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 in soft microwave ablation catheter, hard microwave ablation catheter, and microwave ablation therapeutic apparatus host. The soft catheter is made of soft polymer material and mainly used for

the lesion of GSV trunk. The hard catheter is made of stainless steel material, which cannot be bent, and suitable for relatively superficial veins. The evaluation index for soft or hard microwave ablation catheter 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 in childbearing age), and electrocardiograph at the screening period. At 7 days after treatment, only blood routine and blood biochemistry are examined. The 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. The treatment-related complications will be observed and recorded from the beginning of the treatment to the end of follow-up, including 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, superficial venous thrombosis. Other adverse events and serious adverse events are observed and recorded throughout the trial. Serious adverse events should be followed until the problem is resolved or estimated by investigators that have become chronic, stabilized or sufficient to account for the anomaly.

Statistical analysis

Statistical analysis will be performed using SAS software (version 9.4). The quantitative data are described as the mean, standard deviation, median, minimum, maximum, lower quartile (Q1), and upper quartile (Q3), and the classification data are described as the number and percentage. The quantitative data will be analyzed using the group t test (homogeneity of variance and normal distribution) or Wilcoxon rank sum test. The classification data will be analyzed using the chi-square test or Fisher's exact test, and the ranked data will be analyzed applying Wilcoxon rank sum test or CMH test. *P* value less than or equal to 0.05 was considered statistically significant.

Patient and public involvement

Patients have not been involved in the study design.

Ethics and dissemination

This trial will be conducted according to the principles of Helsinki's Declaration, 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 disseminated 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 more common in females than in male²². The symptoms of GSV varicosis are not only swelling and pain in the lower limbs, but also often combined with ulcers, eczema, phlebitis and other adverse reactions, which cause irreversible impact on patients' work and quality of life²³. To improve this, exploring the suitable treatments for clinical application is important.

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, 27, 28}. For EVLA, laser delivers into blood vessel lumen to produce heat

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4 energy to deform or inactivate the protein or enzymes in the blood vessel wall and
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6 destroy the structure of the vein wall with subsequent fibrosis, causing the blood vessels
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8 to contract and permanently close ²⁹. EMA is a relatively novel endovenous thermal
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10 ablation technique ³⁰. The mechanism of EMA is to apply the microwave radiator
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12 directly to venous cavity wall to instantaneously produce high temperature with a
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14 certain penetration range, which can coagulate the tissues, extensively damage vascular
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16 endothelial cells and intima, induce vascular fibrosis to make the blood vessel atresia
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18 ³⁰. Mao et al. conducted a retrospective study to compare the efficiency and safety
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20 between EVLA and EMA ¹³. The results showed that EMA brought lower ecchymosis
21
22 complication but higher skin burn and paralysis complications than EVLA, although
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24 the operation time and length of hospital stay were no significant difference. Yang et
25
26 al. reported that EMA had a shorter procedure time, lower incidence of induration and
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28 ecchymosis, and lower local recurrence below the knee compared to EVLA ¹⁴. From
29
30 the current studies, the evidence whether EMA is not inferior to EVLA is still
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32 insufficient. Mao et al. mainly focuses on the short-term outcome, and the study of
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34 Yang et al. is not a randomized trial which may cause selective bias.
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46 Based on these, we hope to conduct a multicenter, randomized controlled non-
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48 inferiority trial to evaluate the long-term efficiency and safety of EMA in the treatment
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50 of GSV varicosis compared to EVLA, and provide reliable evidence for the clinical
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52 application of EMA.
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58 **Authors' contributions** Y.J.L. and W.W.W. designed the study. Y.J.L. wrote the
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manuscript. Y.N.L. refined the study protocol and study implementation. J.L. and M.N.S. provided methodological and statistical expertise. W.W.W. critically reviewed, and edited the manuscript. All authors read and approved the final manuscript.

Funding None declared.

Competing Interests All authors declared there is no competing interest.

Patient and Public Involvement statement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Data availability statement

No additional data available.

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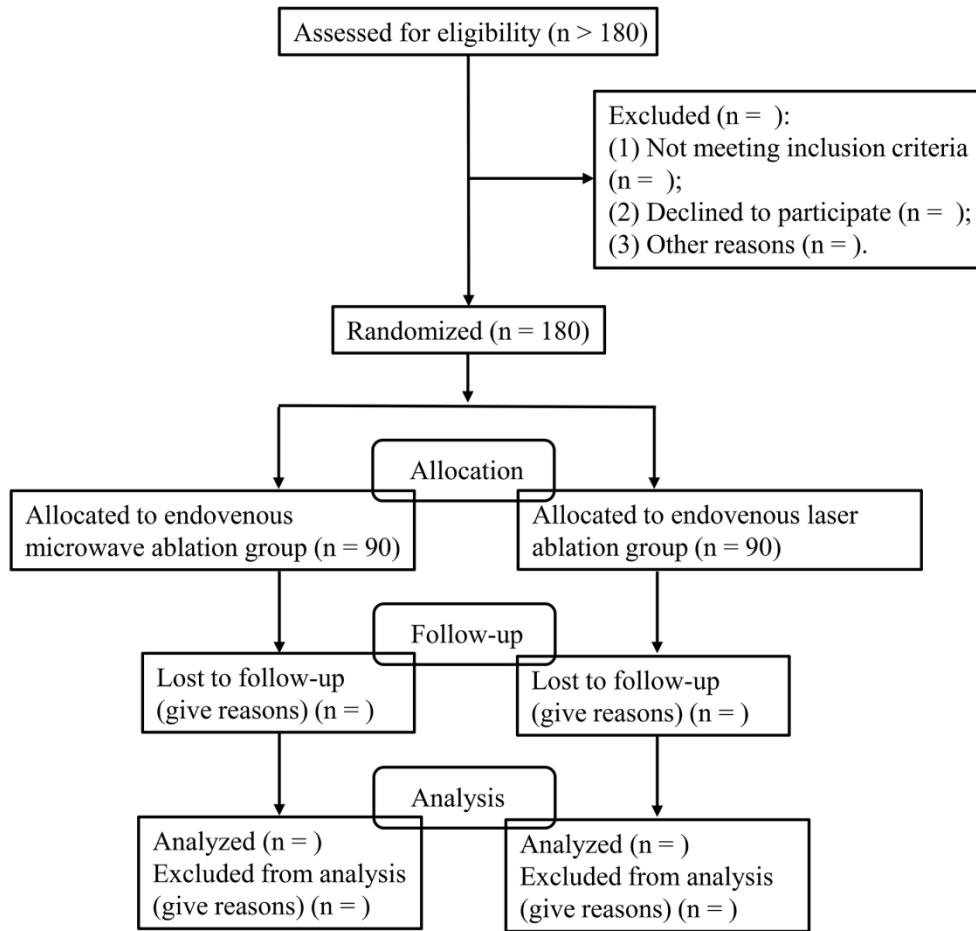
Figure legends

Figure 1 The flow chart of study process.

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

Study period	Enrollment and allocation		Follow-up				
	Screening (-14~0 day)	Allocation (0 day)	7 day (±3 day)	1 month (±7 day)	3 month (±15 day)	6 month (±30 day)	12 month (±30 day)
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						
Electrocardiograph	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



Informed Consent File

Name of Medical Apparatus Used in this Trial: Microwave ablation therapeutic apparatus and semiconductor laser therapeutic apparatus

Sponsor: Beijing Hospital (Beijing, China);

Peking Union Medical College Hospital (Beijing, China);

Beijing Tsinghua Changgung Hospital (Beijing, China);

Beijing Luhe Hospital.Capital Medical University (Beijing, China);

The First Hospital of Hebei Medical University (Shijiazhuang, China);

The First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China)

Name of Project: Efficacy and safety of endovenous microwave ablation versus laser ablation for great saphenous vein varicosis: a multicenter, randomized controlled non-inferiority trial

Number of Project: SD-LC-001

Version Number/Date: V1.0/2020-05-12

Clinical trial Institution: _____

Researcher: _____

Dear subjects:

Hello! You will be invited to participate in a clinical trial “Efficacy and safety of endovenous microwave ablation versus laser ablation for great saphenous vein varicosis: a multicenter, randomized controlled non-inferiority trial” conducted by 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 following describes the background, purpose, methods, benefits and possible risks or inconveniences brought to you during this trial, and your rights and interests. Please read this informed consent file carefully before participating in this trial. The information provided to you by this file can help you decide whether to participate in this trial. If you have any questions, please ask the doctors in charge of the trial to ensure that you have fully understood the content. Your participation in this trial is voluntary. If you agree to participate in this clinical trial, please sign the informed consent file.

1. Name and objective:

Trial name: Efficacy and safety of endovenous microwave ablation versus laser ablation for great saphenous vein varicosis: a multicenter, randomized controlled non-inferiority trial.

The objective is to compare the safety and efficacy of endovenous microwave ablation and endovenous laser ablation in the treatment of great saphenous vein varicosis.

2. Background

Varicose veins of lower limbs are a common peripheral vascular disease and the occurrence of great saphenous varicose vein is the most common. Studies have reported that its incidence is about 5% to 30%, with a higher incidence in man. It may be associated with increased intravascular pressure caused by various reasons such as congenital familial or acquired phlebitis, prolonged standing, and obesity, constipation or pregnancy. Varicose veins of the lower extremities often manifest as swelling, pain, and heaviness of the affected limbs as the disease progresses as well as skin dystrophic changes in foot and ankle, such as dermatitis, hyperpigmentation and repeated ulcers, severely affecting the patient's quality of life.

At present, the effective method for varicose veins of lower limbs above C2 stage is surgery. The main methods of surgical treatment are as follows:

- a. Traditional surgical method -- high ligation of great saphenous vein plus stripping
- b. Endovenous laser treatment (EVLT)

The main mechanism of laser is to scatter around through the end of the optical fiber, and be absorbed by surrounding groups and converted to heat through photothermal action, making the blood in the venous lumen boiling to produce vapor, and therefore deforming or inactivating the proteins or enzymes in the vascular wall and destroying the structure of the venous wall into fibrosis to make blood vessels constrict and permanently close, finally coming to the same effect with the traditional

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4 surgery.

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7 c. Endovenous microwave treatment (EMT)

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9 The main mechanism of EMT is to use the concentric circle thermal coagulation
10 release effect of microwave on the tissue, making the microwave radiator directly acting
11 on the venous vascular wall and enabling to achieve instantaneously (within a few
12 seconds) high temperature with a certain range of penetration within an area and thus
13 solidifying the tissue. In addition, heat effect causes extensive damage to vascular
14 endothelial cells and intima. Thrombosis is induced throughout the vein, followed by
15 vascular fibrosis that causes vascular atresia.
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27 d. Radiofrequency endovenous obliteration

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29 e. Mini-phlebectomy (TriVex™)

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31 f. Endovenous intracavitary electrocoagulation

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33 g. Subfascial endoscopic Perforator vein surgery

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35 h. Mechanized ablation
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40 The microwave ablation therapeutic apparatus (Beijing Sanhe Dingye Technology
41 Co., Ltd., Beijing, China) has been registered and inspected by a qualified medical
42 apparatus product quality inspection center. The inspection results are qualified and the
43 apparatus meet the requirements of clinical application.
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53 **3. Materials and methods**

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55 This study is a multicenter, randomized, controlled non-inferiority trial, with
56 semiconductor laser therapeutic apparatus developed by EUFOTON S.R.L. as a control
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4 apparatus. The subjects who meet the requirements of the trial after signing the
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6 informed consent will be randomly assigned to the experimental group or the control
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8 group. The microwave ablation therapeutic apparatus (Beijing Sanhe Dingye
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10 Technology Co., Ltd., Beijing, China) and semiconductor laser therapeutic apparatus
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12 (EUFOTON S. R. L., Trieste, Italy) will be used to perform EMT and EVLT,
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14 respectively.
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20 The clinical trial will be conducted in 6 centers, and a total of 180 subjects will be
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22 enrolled. Subjects will be randomly assigned to the experimental group (microwave
23
24 ablation therapeutic apparatus) and the control group (semiconductor laser therapeutic
25
26 apparatus), with the case ratio 1:1. It means that 90 of the 180 subjects will be randomly
27
28 assigned to the experimental group and 90 will be randomly assigned to the control
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30 group.
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35 The enrollment of the subjects and the operation conditions will be recorded
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37 during the study. Subjects in the study will be followed up at 7 days, 1 month, 3 months,
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39 6 months, and 12 months after the treatment.
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45 ***3.1 Inclusion criteria and exclusion criteria***

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48 Inclusion criteria: (1) patients with age \geq 18 years, but not older than 80 years; (2)
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50 patients clinically diagnosed as primary GSV insufficiency with reflux lasting $>$ 0.5
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52 seconds on doppler ultrasonography; (3) patients with Clinical-Etiologic-Anatomic-
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54 Pathophysiologic (CEAP) C2-C6; (4) patients who voluntarily participate in this trial,
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56 understand all the risks and benefits described in the informed consent document, and
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4 sign the written informed consent form.
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6 Exclusion criteria: (1) patients with diameter of target lesion vein < 2 mm or > 15
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8 mm; (2) patients with history of surgical treatment on the target lesion or patients with
9
10 acute thrombosis; (3) patients with deep vein thrombosis or superficial vein thrombosis;
11
12 (4) patients with acute systemic infectious diseases; (5) patients with severe liver and
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14 kidney dysfunction (alanine aminotransferase > 3 times the upper limit of normal value;
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16 creatinine > 225 $\mu\text{mol/L}$); (6) patients with known uncorrectable bleeding or severe
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18 coagulopathy; (7) patients with anesthesia contraindications; (8) patients with poorly
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20 controlled hypertension (systolic blood pressure \geq 160 mmHg and/or diastolic blood
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22 pressure \geq 100 mmHg) and diabetes mellitus (fasting glucose \geq 10.0 mmol/L); (9)
23
24 patients with non-primary varicose veins caused by post-deep vein thrombosis
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26 syndrome, Klippel-Trenaunay syndrome, arteriovenous fistula, etc; (10) patients with
27
28 other diseases that may cause difficulty in the trial or the evaluation, such as mental
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30 illness, acquired immune deficiency syndrome (AIDS), malignant tumors, liver disease,
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32 cardiac insufficiency, etc., or patients with expected life less than 1 year; (11) pregnant
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34 women, lactating women, or women preparing to be pregnant during the trial; (12)
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36 patients participated in clinical trials of other drugs or medical devices in the past 3
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38 months; (13) patients who will be deemed unsuitable for inclusion by the researchers
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40 due to other reasons.
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56 **4. Process and duration**

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58 The study will be divided into 7 visit stages including screening period (-14-0 days),
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4 operation day (0 day), 7 days after surgery (± 3 days), 1 month after surgery (± 7 days),
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7 3 months after surgery (± 15 days), 6 months after surgery (± 30 days), and 12 months
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9 after surgery (± 30 days). Specific contents to be completed at each visit stage were as
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11 follows:
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14 Screening period (-14-0 days): Informed consent is required for patients who meet
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16 the requirements for initial screening. After the subject and his/her family members
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18 agree and sign the informed consent voluntarily, the subject will be checked whether
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20 meet the inclusion criteria and then general demographic information, vital signs, past
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22 medical history, laboratory examination, electrocardiogram, doppler ultrasonography
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24 of lower limb vein, venous clinical severity score (VCSS) and aberdeen varicose vein
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26 questionnaire (AVVQ) evaluation will be collected. If all is correct, surgery can be
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28 arranged.
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35 Operation day (0 day): The patients will be randomly divided into experimental
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37 group and control group and then performed surgery with specific apparatus. The full
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39 process of operation will be recorded carefully. The performance of the apparatus
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41 should be evaluated, and defects, adverse events and serious adverse events should be
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43 timely processed and reported.
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49 7 days after surgery (± 3 days): Vital signs will be recorded and related laboratory
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51 examination will be performed. Doppler ultrasonography of lower limb vein will be
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53 performed. Adverse events and serious adverse events should be handled and reported
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55 in a timely manner.
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59 1 month after surgery (± 7 days): The follow-up will be conducted by telephone.
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4 VCSS and AVVQ will be collected. Adverse events and serious adverse events should
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6 be handled and reported in a timely manner.
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9 3 months after surgery (± 15 days): The follow-up will be conducted by clinical
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11 doctor. Vital signs should be recorded and VCSS and AVVQ will be collected. Doppler
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13 ultrasonography of lower limb vein will be performed. Adverse events and serious
14
15 adverse events should be handled and reported in a timely manner.
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19 6 months after surgery (± 30 days): The follow-up will be conducted by clinical
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21 doctor. Vital signs should be recorded and VCSS and AVVQ will be collected. Doppler
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23 ultrasonography of lower limb vein will be performed. Adverse events and serious
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25 adverse events should be handled and reported in a timely manner.
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29 12 months after surgery (± 30 days): The follow-up will be conducted by clinical
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31 doctor. Vital signs should be recorded and VCSS and AVVQ will be collected. Doppler
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33 ultrasonography of lower limb vein will be performed. Adverse events and serious
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35 adverse events should be handled and reported in a timely manner.
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39 Combined medication should be recorded at all stages.
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43 A total of 180 patients will be enrolled in this clinical trial, which will be conducted
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45 at 6 centers and the expected recruitment time is last for 8 months, with an overall
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47 duration of at least 24 months
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50 51 52 53 **5. Source of funding and conflict of interest**

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56 There is no funding, and there is no interest conflict with relevant hospitals and doctors.
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6. Potential benefits

You will not benefit directly from participating in this study, but your condition will be closely monitored by the doctors in charge of you during your participation. In addition, if the results of this study show that the microwave ablation therapy apparatus is effective and safe, the microwave ablation therapy apparatus will be helped to market in the future to help more patients with varicose veins of lower limb and bring certain social benefits.

7. Potential risks and discomfort

(1) Peripheral nerve injury, such as nerve damage to skin numbness

peripheral nerve injury can lead to body unconsciousness, and can lead to abnormal activities. Once peripheral nerve injury occurs after surgery, timely treatment should be carried out, and the researchers need to actively manage treatments and minimize the pain of the patients.

(2) Peripheral skin injury and burn

Microwave therapy is a thermal treatment. Operator is prone to burn skin due to poor technical mastery at early stage. Therefore, subcutaneous injection of normal saline should be performed before microwave ablation which can effectively prevent the burn to the skin and surrounding tissues. If skin burns occur, minor injuries need not be treated, while serious surgical need dressing change.

(3) Injury caused by microwave accessory straying into the deep vein via communicating branch

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4 Complications related to puncture are one of the complications after microwave
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6 ablation, and subcutaneous hematoma is the most common. Therefore, sufficient
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8 hemostasis should be performed to reduce further expansion of hematoma and stop
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10 intracavitary hemorrhage in case of large amount of bleeding, so as to ensure the safety
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12 of patients. If the blood vessels are perforated and the blood vessels are ruptured, the
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14 blood vessels can be blocked intravascular, and the blood vessels cannot be blocked by
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16 compression or surgical repair.
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22 (4) Wound infection

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24 Although the incidence of minimally invasive small incision infection is very low,
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26 postoperative observation of local incision redness, swelling, heat, pain and tissue
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28 suppuration is necessary. If the above happens, the dressing should be timely changed,
29
30 and antibiotics should be used in the perioperative period to prevent infection.
31
32
33
34

35 (5) Deep venous thrombosis

36
37 Deep vein thrombosis is the most serious adverse reaction after surgery for varicose
38
39 veins of lower limbs. Early postoperative ambulation can effectively prevent the
40
41 occurrence. To prevent this, aspirin can be taken orally. Timely diagnosis can be
42
43 confirmed through clinical observation, coagulation function detection, D-dimer and
44
45 venous ultrasound examination of lower limbs. Once it is confirmed, treatment should
46
47 follow the conventional treatment of thrombosis.
48
49
50
51

52 (6) Superficial vein thrombosis

53
54 Superficial vein thrombosis is the most serious adverse reaction after surgery for
55
56 varicose veins of lower limbs. Early postoperative ambulation can effectively prevent
57
58
59
60

1
2
3
4 the occurrence. Timely diagnosis can be confirmed through clinical observation,
5
6 coagulation function detection, D-dimer and venous ultrasound examination of lower
7
8 limbs. Once it is confirmed, treatment should follow the conventional treatment of
9
10 thrombosis.
11
12
13
14
15
16

17 **8. Treatment and financial compensation for trial-related injuries**

18
19 If you suffer any injury or death related to this study during the study period, the sponsor
20
21 will bear the corresponding treatment expenses and corresponding economic
22
23 compensation for you, except for the damage caused by the fault of the medical
24
25 institution and its medical staff during the diagnosis and treatment activities.
26
27
28
29
30
31

32 **9. Risk of Pregnancy**

33
34 Female subjects: If you become pregnant unexpectedly during the study period, the
35
36 doctor in charge of you will recommend termination of the pregnancy; If you insist on
37
38 pregnancy, all consequences will be borne by you.
39
40
41

42
43 Male subjects: If your partner become pregnant unexpectedly during the study period,
44
45 the doctor in charge of you will advise your partner to terminate of the pregnancy; If
46
47 your partner insists on pregnancy, all consequences will be borne by you and your
48
49 partner.
50
51
52
53
54
55

56 **10. Possible trial groups to be assigned**

57
58 You will be randomly assigned to either an experimental or a control group for surgery.
59
60

11. Alternative diagnosis and treatment methods other than this study

Participation in this clinical study is your voluntary behavior. You may choose to participate or not, which will not have any adverse impact on your access to regular treatment. At present, you can also choose other treatment methods according to your health condition. Your doctor will discuss with you the major risks and benefits associated with these treatments.

12. Confidentiality of medical records

Your personal information about participating in the study is confidential and will be kept confidential at all times. Only the study doctor will retain your basic information, and your initials and code will be used to identify you in other study documents. Your name and identification will not appear. However, the ethics committee, drug regulatory department, health committee or sponsor may access your personal data in accordance with prescribed procedures when necessary. Writing papers or reports will not disclose your identifying information, and any information used before your name and other letters may identify your information will be deleted.

13. Fee Description

You are selected for this study, so you can use the microwave ablation therapeutic apparatus (Beijing Sanhe Dingye Technology Co., Ltd., Beijing, China) and semiconductor laser therapeutic apparatus (EUFOTON S. R. L., Trieste, Italy) for free.

1
2
3
4 At the same time, you can enjoy the following diagnosis and treatment items and
5
6 subsidies:

- 7
8
9 ● Screening period (-14-0 days): Laboratory tests (blood routine, blood biochemistry,
10
11 clotting quadruple, D-dimer), pregnancy test (if applicable), Doppler ultrasonography
12
13 of lower limb vein, electrocardiogram. If the relevant examination has been performed
14
15 before the informed consent is signed and within 14 days before the operation, there is
16
17 no need to repeat the examination.
18
19
20 ● 7 days after surgery (± 3 days): Laboratory tests (blood routine, blood biochemistry),
21
22 Doppler ultrasonography of lower limb vein.
23
24
25 ● 3 months after surgery (± 15 days), 6 months after surgery (± 30 days), and 12
26
27 months after surgery (± 30 days): Doppler ultrasonography of lower limb vein.
28
29
30 ● We will reimburse you for the transportation cost of each visit to and from the
31
32 hospital, 200 yuan per person for each visit, a total of 3 visits, a total of 600 yuan.
33
34 Subsidies will be given at the end of each follow-up visit, and finally according to the
35
36 actual visit.
37
38
39
40
41
42

43 The sponsor will only provide you with the cost of relevant examinations that need
44
45 to collect data in the clinical study. Other examinations are routine diagnosis and
46
47 treatment that you must carry out, and relevant data do not need to be collected. This
48
49 part of the cost will be borne by you.
50
51
52
53
54
55

56 **14. Voluntary participation and withdrawal from the trial**

57
58 You may choose not to participate in the study or withdraw from the study at any time
59
60

1
2
3
4 after notifying the doctor. Your medical treatment and rights will not be affected by
5
6 discrimination or retaliation.
7

8
9 If you require additional diagnosis/treatment, or you are not following the study
10
11 plan, or have any other sound reasons, the study doctor may terminate your continued
12
13 participation in the study.
14
15

16
17 You will receive timely information that may affect your continued participation
18
19 in the study.
20
21

22
23 You may keep abreast of information and research progress related to this study,
24
25 if you have questions related to this study, or you have any discomfort or injury during
26
27 the study or questions about rights and interests of participants in this study, you can
28
29 contact the Ethics Committee at _____.
30
31

32 33 34 35 **Informed consent**

36
37 I have carefully read the informed consent form. I have a chance to ask questions and
38
39 all questions have been answered. I understand participating in this study is voluntary.
40
41
42 I can choose not to participate in the study, or quit at any time after notifying the doctor
43
44 without discrimination or revenge, and will not lead to any of my medical treatment
45
46 and the rights and interests are affected. The study doctor may terminate my
47
48 participation in the clinical trial if I require additional diagnosis/treatment, or if I do not
49
50 comply with the study plan, or for any other reasonable reason.
51
52
53
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1
2
3
4 I voluntarily agree to participate in the clinical trial and I will receive a signed copy of
5
6 the informed consent.
7

8
9 Subject name (in print): _____
10

11 Subject name (hand written): _____ Date: _____
12

13 Contact information: _____
14

15
16 If the subject is unable to sign the informed consent due to consciousness disorder,
17
18 paralysis of the subject's upper limbs or inability to write, or the subject is a child, the
19
20 legal representative shall sign the informed consent
21
22

23
24 Legal representative's signature (in print): _____
25

26
27 Subject name (hand written): _____ Date: _____
28

29
30 Contact information: _____ Relationship with subject: _____
31

32 Reason for subject unable to sign the informed consent: _____
33
34

35 36 37 Declaration of Researchers

38
39 I have informed the subjects of the informed consent accurately and answered their
40
41 questions. The subjects are willing to participate in this clinical trial.
42
43

44
45 Researcher name (in print): _____
46

47
48 Researcher name (hand written): _____ Date: _____
49

50 Contact information: _____
51
52
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
	2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	-
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11-12
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5

1				
2	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
3				
4				
5				
6				
7				
8	Methods: Participants, interventions, and outcomes			
9				
10	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
11				
12				
13				
14				
15	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
16				
17				
18				
19				
20				
21	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
22				
23				
24				
25				
26		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
27				
28				
29				
30				
31		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-11
32				
33				
34				
35				
36		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
37				
38				
39	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
40				
41				
42				
43				
44				
45				
46				
47				
48	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6 (see Table 1)
49				
50				
51				
52				
53				
54	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
55				
56				
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58				
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60				

1
2 Recruitment 15 Strategies for achieving adequate participant enrolment to 6
3 reach target sample size
4

5 **Methods: Assignment of interventions (for controlled trials)**
6

7 Allocation:

8
9 Sequence generation 16a Method of generating the allocation sequence (eg, 9
10 computer-generated random numbers), and list of any
11 factors for stratification. To reduce predictability of a
12 random sequence, details of any planned restriction (eg,
13 blocking) should be provided in a separate document that
14 is unavailable to those who enrol participants or assign
15 interventions
16
17

18 Allocation concealment 16b Mechanism of implementing the allocation sequence (eg, 9
19 central telephone; sequentially numbered, opaque, sealed
20 envelopes), describing any steps to conceal the sequence
21 until interventions are assigned
22
23

24 Implementation 16c Who will generate the allocation sequence, who will enrol 9
25 participants, and who will assign participants to
26 interventions
27

28 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, 9
29 trial participants, care providers, outcome assessors, data
30 analysts), and how
31
32

33 17b If blinded, circumstances under which unblinding is 9
34 permissible, and procedure for revealing a participant's
35 allocated intervention during the trial
36
37

38 **Methods: Data collection, management, and analysis**

39 Data collection methods 18a Plans for assessment and collection of outcome, baseline, 11-12
40 and other trial data, including any related processes to
41 promote data quality (eg, duplicate measurements, training
42 of assessors) and a description of study instruments (eg,
43 questionnaires, laboratory tests) along with their reliability
44 and validity, if known. Reference to where data collection
45 forms can be found, if not in the protocol
46
47
48

49 18b Plans to promote participant retention and complete follow- 6
50 up, including list of any outcome data to be collected for
51 participants who discontinue or deviate from intervention
52 protocols
53

54 Data management 19 Plans for data entry, coding, security, and storage, 11-12
55 including any related processes to promote data quality
56 (eg, double data entry; range checks for data values).
57 Reference to where details of data management
58 procedures can be found, if not in the protocol
59
60

1				
2	Statistical	20a	Statistical methods for analysing primary and secondary	16
3	methods		outcomes. Reference to where other details of the	
4			statistical analysis plan can be found, if not in the protocol	
5				
6		20b	Methods for any additional analyses (eg, subgroup and	-
7			adjusted analyses)	
8				
9		20c	Definition of analysis population relating to protocol non-	12
10			adherence (eg, as randomised analysis), and any	
11			statistical methods to handle missing data (eg, multiple	
12			imputation)	
13				
14				
15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC);	12
18			summary of its role and reporting structure; statement of	
19			whether it is independent from the sponsor and competing	
20			interests; and reference to where further details about its	
21			charter can be found, if not in the protocol. Alternatively,	
22			an explanation of why a DMC is not needed	
23				
24				
25		21b	Description of any interim analyses and stopping	5
26			guidelines, including who will have access to these interim	
27			results and make the final decision to terminate the trial	
28				
29				
30	Harms	22	Plans for collecting, assessing, reporting, and managing	14-15
31			solicited and spontaneously reported adverse events and	
32			other unintended effects of trial interventions or trial	
33			conduct	
34				
35				
36	Auditing	23	Frequency and procedures for auditing trial conduct, if any, -	-
37			and whether the process will be independent from	
38			investigators and the sponsor	
39				
40	Ethics and dissemination			
41				
42	Research ethics	24	Plans for seeking research ethics committee/institutional	6
43	approval		review board (REC/IRB) approval	
44				
45	Protocol	25	Plans for communicating important protocol modifications	11
46	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
47			relevant parties (eg, investigators, REC/IRBs, trial	
48			participants, trial registries, journals, regulators)	
49				
50				
51	Consent or assent	26a	Who will obtain informed consent or assent from potential	6
52			trial participants or authorised surrogates, and how (see	
53			Item 32)	
54				
55		26b	Additional consent provisions for collection and use of	12
56			participant data and biological specimens in ancillary	
57			studies, if applicable	
58				
59				
60				

1				
2	Confidentiality	27	How personal information about potential and enrolled	12
3			participants will be collected, shared, and maintained in	
4			order to protect confidentiality before, during, and after the	
5			trial	
6				
7	Declaration of	28	Financial and other competing interests for principal	18
8	interests		investigators for the overall trial and each study site	
9				
10	Access to data	29	Statement of who will have access to the final trial dataset,	12
11			and disclosure of contractual agreements that limit such	
12			access for investigators	
13				
14				
15	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for	12
16	post-trial care		compensation to those who suffer harm from trial	
17			participation	
18				
19	Dissemination	31a	Plans for investigators and sponsor to communicate trial	16
20	policy		results to participants, healthcare professionals, the public,	
21			and other relevant groups (eg, via publication, reporting in	
22			results databases, or other data sharing arrangements),	
23			including any publication restrictions	
24				
25				
26		31b	Authorship eligibility guidelines and any intended use of	16
27			professional writers	
28				
29				
30		31c	Plans, if any, for granting public access to the full protocol,	11-12
31			participant-level dataset, and statistical code	
32				
33	Appendices			
34				
35	Informed consent	32	Model consent form and other related documentation	6
36	materials		given to participants and authorised surrogates	
37				
38	Biological	33	Plans for collection, laboratory evaluation, and storage of	12
39	specimens		biological specimens for genetic or molecular analysis in	
40			the current trial and for future use in ancillary studies, if	
41			applicable	
42				
43				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.