Informed Consent

Study title: Comparative analysis of clinical efficacy of radiofrequency ablation for lower extremity varicose veins versus concurrent or staged management of perforating veins: A multicenter randomized controlled trial

Version: V1.0

Version date: June 12,2025

Dear Subject:

We invite you to participate in the multicenter randomized controlled study titled " Comparative Clinical Efficacy of Simultaneous or Staged Management of Branch Venes in Lower Extremity Varicose Vein Radiofrequency Ablation Surgery: A Multicenter Randomized Controlled Study", which has been reviewed and approved by the Ethics Committee of Sir Run Run Shaw Hospital, affiliated with Zhejiang University School of Medicine.

This informed consent form provides information to help you decide whether to participate in this clinical study. Your participation is entirely voluntary, and your decision will not affect your normal medical care or benefits at our hospital. If you choose to participate, our research team will make every effort to ensure your safety and rights throughout the study.

Please read carefully and ask the researcher in charge of the study if you have any questions.

I. Research Background, Significance and Purpose

1.1 Background

Varicose veins of the lower extremities (VVLE) are characterized by significantly enlarged, tortuous subcutaneous superficial veins with diameters exceeding 3mm. Clinical manifestations include pain, edema, pigmentation, pruritus, skin induration, and either healed or active venous ulcers, affecting approximately one-third of the global population. Treatment options encompass conservative approaches (e.g., compression therapy, pharmacological management) and various surgical interventions. The traditional surgical method is high ligation/stripping (HL/S) of the great saphenous vein. In recent years, minimally invasive techniques such as radiofrequency ablation (RFA), endovenous laser ablation (EVLA), and ultrasound-guided foam sclerotherapy (UGFS) have gained prominence. Among these, RFA and EVLA have largely replaced conventional surgery due to their advantages of shorter operation time and faster recovery. International guidelines recommend prioritizing intravascular thermal ablation for VVLE and main valve regurgitation, followed by UGFS, and HL/S as a last resort.

The 2023 Clinical Practice Guidelines for Lower Extremity Varicose Veins published by the American Venous Forum recommend ablative treatment for symptomatic reflux in superficial venous trunks, with concurrent phlebectomy or UFGS for associated perforating veins. When anatomical or medical contraindications prevent simultaneous procedures, ablative treatment of the superficial venous trunk alone should be performed, followed by at least 3 months of postoperative follow-up to assess whether staged phlebectomy or UFGS is required for persistent or recurrent symptoms. A significant number of experts endorse this approach, citing its superior efficacy and the convenience of a single surgical intervention for patients.Wang et al. divided recruited VVLE patients into two groups: one receiving combined endovenous laser ablation and foam sclerotherapy, and the other undergoing laser therapy alone. After a 6-month follow-up, no significant difference was observed in the incidence of complications (except bruising). The pain scores in the concurrent surgery group showed a marked increase at 4 weeks but decreased to the same level by 6 months. However, their number of residual varicose vein branches was significantly lower than that in the staged surgery group. Additionally, the reoperation rate was notably lower in the concurrent surgery group.

Lower rates of early quality of life improvement were observed. A systematic review of 15 studies found that both concurrent surgery and staged surgery groups demonstrated safety and efficacy with no significant differences in complications. The former showed a significantly lower rate of re-intervention compared to the latter, though this difference lacked statistical significance. Additionally, patients undergoing staged surgery exhibited better improvements in disease severity and quality-of-life scores at early stages. However, the study cautioned that these findings should be interpreted cautiously in real-world practice due to clinical heterogeneity and inherent biases from including 12 non-randomized studies. Evidence also suggests that patients opting for staged surgery had very low rates of secondary interventions, with no statistically significant differences in perioperative pain or postoperative recovery between the two approaches. In such cases, staged surgery may reduce costs.

In 1988, Professor Claude from France first proposed the hemodynamic theory of VVLE. Based on differences in venous anatomical location and function, the lower limb venous system can be classified from superficial to deep into five categories: deep veins (network1, N1), saphenous veins and Giacomini veins (network2, N2), saphenous vein branches (network3, N3), superficial veins connecting different regional saphenous veins (network4, N4), and microcirculatory venous networks (network5, N5). Approximately 90% of lower limb great saphenous vein varicose veins are classified as Type I and III, both showing N1 to N2 reflux. The distinction lies in the fact that Type I varicose veins consist entirely of saphenous veins with valve insufficiency from the return point to the reflux point, while Type III varicose veins initially feature a segment of saphenous vein with insufficiency, followed by the remaining portion composed of N2 branches. From a hemodynamic perspective, performing concurrent surgery that damages both the draining and returning branch veins may lead to tissue edema in the drainage area, resulting in increased postoperative swelling compared to preoperative levels. In staged surgery, only the main trunk of the saphenous vein is addressed during the initial phase while preserving its branches. Partially functional branches can continue to drain regional blood flow. Consequently, after initial surgery, the venous hypertension caused by reflux subsides, allowing most devascularized branches to gradually restore normal diameter and patency. This suggests that recurrence rates remain relatively low following staged surgical interventions. The "Clinical Practice Guidelines for Endovenous Thermocoagulation (2019)" issued by the Japanese Society of Venous Medicine and Hemotherapy classified this combined procedure as "no recommendation". Hicks et al. conducted a retrospective analysis of patients with great saphenous vein RFA combined with or without venectomy over two years, finding that compared to RFA alone, the incidence of endovenous heat-induced thrombosis (EHIT) was higher after RFA combined with venous puncture and vein resection. Kawahira et al. divided patients who received single RFA procedures, RFA combined with vein resection, or UGFS combined therapy between 2015 and 2021 at their hospital into two groups for short-term and medium-term efficacy comparison. The study found no statistically significant difference in recurrence rates or complications between the groups, indicating that RFA treatment alone can achieve expected outcomes.

According to current clinical studies, although guidelines and some experts believe that VVLE patients can be prioritized for ablation therapy and that concurrent venectomy or UGFS treatment is considered for varicocele, the available evidence for staged treatment does not demonstrate inferior clinical efficacy than concurrent.The limited number of existing literature and lack of detailed data on re-intervention rates, complication rates, and intraoperative pain scores have led us to advocate for further studies to evaluate the difference in efficacy between the two approaches. In this study, patients were randomly assigned to either intravenous RFA alone or RFA combined with UGFS for varicocele, followed by a 6-month follow-up.

1.2 Purpose of Research

1) The clinical efficacy of patients with lower extremity varicose veins treated with ultrasound-guided foam sclerosant therapy at the same time or in stages after radiofrequency ablation for great saphenous vein varicosity was compared within 6 months;

2) The expectation that concurrent or staged treatment of varicose veins is a surgical strategy for varicose veins provides strong evidence for the improvement of relevant guidelines and clinical practice.

II. RESEARCH PROCESS

2.1 Research Overview

This multicenter, randomized controlled clinical trial involves 206 participants, with our center expecting to enroll 30 subjects. By agreeing to participate, you will sign an informed consent form. We will then review your eligibility criteria. If you meet the criteria and don't fall under any exclusions, you'll be enrolled in the study and have a 50% chance of being assigned to either the experimental or control group.

If you are assigned to the trial group, you will only receive radiofrequency ablation of the main trunk of the great saphenous vein and no treatment for varicose veins of the branch.

If you are assigned to the control group, you will receive radiofrequency ablation of the main vein and ultrasound-guided foam sclerotherapy of the branch varicose veins.

Which group you are assigned to is determined by a computer-generated randomization, and neither you nor your physician can influence this assignment. Therefore, if you reject either of these two treatment options, you may choose not to participate in or withdraw from the study and discuss alternative treatment options with your physician again.

2.2 Cluster Interventions

Both groups underwent ultrasound-guided radiofrequency ablation for closure of the great saphenous vein trunk. In the experimental group, patients were positioned supine. A lower limb Doppler ultrasound was first performed on the affected great saphenous vein. After local anesthesia in the appropriate area, the Seldinger technique was employed under ultrasound guidance to puncture the great saphenous vein trunk 10cm above and below the knee joint. Following successful puncture, a guidewire was inserted, followed by the deployment of a 7-F blood vessel sheath (Tielmao) along the guidewire. The radiofrequency catheter was then introduced, with its tip fixed approximately 2cm from the femoral-saphenous junction. Under ultrasound guidance, an anesthetic solution was injected through the sheath to the femoral-saphenous junction. The distance between the catheter tip and the junction was re-measured using ultrasound until approximately 2cm was confirmed, after which the radiofrequency catheter was secured. The radiofrequency generator was activated to perform staged ablation of the great saphenous vein trunk. Prior to final segment ablation, the sheath was withdrawn early. Postoperative ultrasound confirmed venous closure. For the control group, post-ablation treatment included either injection of 1% polidocanol foam sclerosant or punctate stripping of pre-marked calf branches. Both groups required elastic bandages for 24 hours postoperatively and thigh-length Grade II compression stockings for one week after bandage removal.

2.3 Observing Indicators

The examination and evaluation items related to this study are all routine clinical examination and evaluation items.

There are 5 visits, and it will take you about 20 minutes to fill in the questionnaire at each follow-up. I hope you can cooperate with us.

Screening period (preoperative 7 days to 1 day): You will receive a consultation and routine examination from your attending physician to evaluate your baseline information, pain, quality of life, and clinical severity of varicose veins. The main items include VAS questionnaire, AVVQ questionnaire, and VCSS questionnaire.

Day of operation(day of operation, day 0): You will receive different surgical plans according to the results of the group. The VAS questionnaire will be used to record the pain during the operation, as well as the time of operation, the number of incisions, the amount of swelling

anesthetic, the amount of bleeding during the operation and the patient satisfaction.

One week after surgery (7 to 10 days after surgery): Outpatient visit, evaluation of VAS questionnaire, AVVQ questionnaire and VCSS questionnaire, recording the time to return to normal work, postoperative complications, and performing venous duplex ultrasound to check the target vein closure rate and whether the test group needs to be treated as a branch vein. If yes, record it.

3 months after surgery (90 to 95 days after surgery): Outpatient visit, VAS questionnaire, AVVQ questionnaire, and VCSS questionnaire were evaluated, postoperative complications were recorded, and the closure rate of the target vein and whether the trial group needed to treat the branch vein were recorded by intravenous duplex ultrasound.

6 months after surgery (180-185 days post-operation): Outpatient visit to evaluate VAS, AVVQ, and VCSS questionnaires, document postoperative complications, treatment costs, and patient satisfaction throughout the treatment process. Perform duplex ultrasound to assess the closure rate of the target vein and determine if the trial group requires management of collateral veins. Record any necessary interventions.

Additionally, during the 6-month follow-up period, you will need to closely monitor your daily life. If symptoms such as pain, swelling, or visible blood vessel dilation reappear due to disease progression, the researchers may recommend returning to our hospital for follow-up examinations and treatment, given their familiarity with your health status and treatment progress. We kindly request your cooperation. After the follow-up period begins, if the researchers continue to monitor your survival status, we hope you will continue to cooperate.

Your research information is used only for this study.

III. Possible Risks and Corresponding Measures

Potential adverse reactions/complications of this study include postoperative sensory abnormalities, skin burns/color changes, phlebitis, hematoma, infection, deep vein thrombosis, and pulmonary embolism. These risks are equivalent to those of conventional thermal ablation surgery. Extensive research has demonstrated that thermal ablation of lower extremity varicose veins offers superior safety and efficacy, with significantly lower postoperative complication rates and reduced risks.

If there is any damage, we will provide you with timely treatment.

3.1 Radiofrequency Ablation Related Adverse Events and Related Management Measures

3.1.1 Postoperative Sensory Abnormalities

Management: Previous data suggest that postoperative sensory abnormalities typically resolve during the follow-up period. When postoperative sensory abnormalities occur, appropriate treatment can be administered to alleviate patient distress.

3.1.2 Skin Burns/changes Color

Countermeasures: Radiofrequency therapy is a form of thermal treatment. Administering adequate amounts of swelling fluid can effectively prevent burns to the skin and surrounding tissues. In cases of skin burns, mild cases may require no treatment, while severe cases may need surgical dressing changes for healing.

3.1.3 Phlebitis

Management: Postoperative phlebitis following minimally invasive surgery typically causes mild pain at the affected site, with most patients not requiring analgesic treatment. For those experiencing postoperative pain, oral analgesics or sedatives may be administered to effectively relieve discomfort.

3.1.4 Hematoncus

Countermeasures: The most common complication related to puncture is radiofrequency ablation, and the most common one is subcutaneous hematoma. Once it occurs, elastic bandage compression can stop the bleeding and the development of hematoma.

3.1.5 Infect

Countermeasures: The incidence of infection after microsurgery is very low. Observe whether there is redness, swelling, heat, pain and tissue suppuration in the incision after operation. If there is, change the dressing in time, and use antibiotics in perioperative period to prevent infection.

3.1.6 Deep Venous Thrombosis

Management strategies: As a rare complication, postoperative varicose vein surgery is considered the most severe adverse reaction. Ensuring the catheter tip maintains ≥2cm distance from the femoral vein junction during procedure significantly reduces deep vein thrombosis (DVT) risk. Early ambulation after surgery effectively prevents this condition. Clinical monitoring through coagulation function tests, D-dimer levels, and lower extremity venous ultrasound enables timely diagnosis. When thrombosis occurs, implement standard therapeutic protocols for thrombosis management.

3.1.7 Pulmonary Embolism

Management Protocol: Pulmonary embolism is a rare but serious complication following radiofrequency ablation procedures. For patients presenting with postoperative pulmonary embolism symptoms (unexplained chest pain, blood-tinged sputum, dyspnea), clinicians should immediately consider this diagnosis and initiate prompt clinical evaluation with diagnostic tests. Early detection and treatment are crucial to control disease progression and safeguard the patient's health.

3.2 Adverse Events Related to Foam Sclerotherapy and Related Treatment Measures

3.2.1 Infect

Measures: The incidence of infection in micro incision is very low. Observe whether redness, swelling, heat, pain and tissue suppuration occur in the incision after surgery. If so, timely dressing change should be performed, and antibiotics should be used during the perioperative period to prevent infection.

3.2.2 Chromatosis

Measures to deal with it: Most of them are absorbed by themselves after 6 months after surgery, without special treatment. You can use topical drugs containing vitamin E whitening essence.

3.2.3 Inflammatory Response (redness, Pain, Induration, Etc.)

Measures to deal with it: Usually short, elastic bandages or compression bandages of elastic socks are adopted, and topical polysulfonic acid mucopolysaccharide ointment can be applied locally, and oral non-steroidal anti-inflammatory drugs can be taken to reduce inflammation and pain.

3.3 Other Information

During the study, other discomforts may occur. Please inform your investigator immediately, who will address any discomfort you experience.

IV. Expected Benefits

Based on current clinical research, radiofrequency ablation of the great saphenous vein trunk in the lower limbs can be performed first. Subsequent follow-up observations may determine whether treatment of the branch veins is necessary. Compared to the more common concurrent surgery approach, this method could potentially reduce pain, shorten operation time, and minimize postoperative complications. If these findings are confirmed and you happen to be assigned to the experimental group, you might benefit from this approach. Of course, you may not directly benefit from this study either. However, the data you provide will offer valuable insights for disease research, helping researchers better understand pathogenesis and explore potential therapeutic strategies. Ultimately, this could lead to improved diagnosis and treatment outcomes for you and similar patients in the future.

V. Replacement Therapy

In addition to the treatment protocol involved in this study, the following clinical treatment protocols can be used to treat the disease, including but not limited to: great saphenous vein high ligation, endoscopic laser ablation, etc.

VI. RESEARCH COSTS

Elastic socks will be provided free of charge after surgery.

During the study, if the patient needs to intervene in the calf branch vein after surgery, the study will provide the required sclerosing agent free of charge.

This study does not have additional examination and evaluation items, all the examination and evaluation items are clinical routine examination and evaluation items, so the related costs need to be borne by you.

Therefore, participation in this study will not add to your regular medical costs.

In addition, this study will provide you with a transportation subsidy of 200 yuan per follow-up.

VII. Compensation and Settlement of Damages

If any harm occurs, our research team will provide timely treatment. If the investigator determines that the harm is related to this study, we will cover the corresponding treatment costs and provide compensation (we will purchase clinical research insurance for you).

VIII. CONFIDENTIALITY

If you decide to participate in this study, your involvement in the trial and all personal information and related materials will be kept confidential. Your research-related data will be identified by a research number rather than your name. Information that could identify you will not be shared with anyone outside the research team unless you give your consent. All participants are required to maintain confidentiality regarding your identity and information. Your records will be stored in a locked file cabinet accessible only to researchers. To ensure the study is conducted properly, government regulators or ethics review committee members may review your personal data at the research site when necessary. When the study results are published, no personal information about you will be disclosed.

IX. Voluntary Nature

You may choose not to participate in this study, or you may withdraw from the study at any time by notifying the investigator. Your data will not be included in the study results, and your medical treatment and benefits will not be affected.

If you need additional treatment, or if you do not comply with the study protocol, or if you have a study-related injury, or for any other reason, the study physician may discontinue your participation in the study.

X. Obligations of the Subject

As a participant, you have the following responsibilities: Provide truthful information about your medical history and current physical condition; Inform the study doctor of any discomfort you experience during the study; Inform the study doctor of whether you have recently participated in or are currently participating in other studies.

11. Contact Information

You may access all relevant information and updates about this study at any time. Should you have questions or experience any discomfort or injuries during the research, please contact the research team (Dr. Zhu Yuefeng, 18867961156,12th Floor, Building 6, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, No.3 Qingchun East Road, Hangzhou, Zhejiang Province).

If you have any questions about the rights of a participant in the study, please contact the Ethics Committee of Sir Run Run Shaw Hospital, affiliated to Zhejiang University School of Medicine (0571-86006811).

informed consent

I have read this informed consent form on the signature page.

I was able to ask questions and all of them were answered.

I understand that participation in this study is voluntary.

I can choose not to take part in this study, or withdraw at any time after notifying the investigator without being discriminated against or retaliated against, and my medical treatment and rights will not be affected by this.

The study physician may discontinue my participation in this study if I require other treatment, or if I do not comply with the study plan, or if there is any study-related injury or for any other reason.

I will receive a copy of the signed informed consent form.

Name of subject (regular script): _____ Signature of the subject: _____

contact way： _____ date： _____ year _____moon _____ sun

If the subject is unable to read and sign the informed consent due to lack of capacity, or if the subject is a minor, his/her guardian shall act as the agent of the informed process and sign the informed consent.

Name of guardian (regular script): _____ Guardian's signature: _____

Relationship to the subject: _____

contact way： _____ date： _____ year _____moon _____ sun

If the subject is unable to read the informed consent form (e.g., illiterate subject), a witness shall witness the informed process and sign it.

Witness name (in regular script): _____ Witness signature: _____

contact way： _____ date： _____ year _____moon _____ sun

I have accurately informed the subject of this document, he/she has read the informed consent form accurately and I can confirm that the subject was offered an opportunity to ask questions. I can confirm that he/she consented voluntarily.

Name of researcher (regular script): _____ Researcher signature: _____

contact way： _____ date： _____ year _____moon _____ sun