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

surgery.

c. Endovenous microwave treatment (EMT)

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

d. Radiofrequency endovenous obliteration

e. Mini-phlebectomy (TriVexTM)

f. Endovenous intracavitary electrocoagulation

g. Subfascial endoscopic Perforator vein surgery

h. Mechanized ablation

The microwave ablation therapeutic apparatus (Beijing Sanhe Dingye Technology Co., Ltd., Beijing, China) has been registered and inspected by a qualified medical apparatus product quality inspection center. The inspection results are qualified and the apparatus meet the requirements of clinical application.

3. Materials and methods

This study is a multicenter, randomized, controlled non-inferiority trial, with semiconductor laser therapeutic apparatus developed by EUFOTON S.R.L. as a control

apparatus. The subjects who meet the requirements of the trial after signing the informed consent will be randomly assigned to the experimental group or the control group. The microwave ablation therapeutic apparatus (Beijing Sanhe Dingye Technology Co., Ltd., Beijing, China) and semiconductor laser therapeutic apparatus (EUFOTON S. R. L., Trieste, Italy) will be used to perform EMT and EVLT, respectively.

The clinical trial will be conducted in 6 centers, and a total of 180 subjects will be enrolled. Subjects will be randomly assigned to the experimental group (microwave ablation therapeutic apparatus) and the control group (semiconductor laser therapeutic apparatus), with the case ratio 1:1. It means that 90 of the 180 subjects will be randomly assigned to the experimental group and 90 will be randomly assigned to the control group.

The enrollment of the subjects and the operation conditions will be recorded during the study. Subjects in the study will be followed up at 7 days, 1 month, 3 months, 6 months, and 12 months after the treatment.

3.1 Inclusion criteria and exclusion criteria

Inclusion criteria: (1) patients with age ≥ 18 years, but not older than 80 years; (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: (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 μmol/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.

4. Process and duration

The study will be divided into 7 visit stages including screening period (-14-0 days),

operation day (0 day), 7 days after surgery (±3 days), 1 month after surgery (±7 days), 3 months after surgery (±15 days), 6 months after surgery (±30 days), and 12 months after surgery (±30 days). Specific contents to be completed at each visit stage were as follows:

Screening period (-14-0 days): Informed consent is required for patients who meet the requirements for initial screening. After the subject and his/her family members agree and sign the informed consent voluntarily, the subject will be checked whether meet the inclusion criteria and then general demographic information, vital signs, past medical history, laboratory examination, electrocardiogram, doppler ultrasonography of lower limb vein, venous clinical severity score (VCSS) and aberdeen varicose vein questionnaire (AVVQ) evaluation will be collected. If all is correct, surgery can be arranged.

Operation day (0 day): The patients will be randomly divided into experimental group and control group and then performed surgery with specific apparatus. The full process of operation will be recorded carefully. The performance of the apparatus should be evaluated, and defects, adverse events and serious adverse events should be timely processed and reported.

7 days after surgery (±3 days): Vital signs will be recorded and related laboratory examination will be performed. Doppler ultrasonography of lower limb vein will be performed. Adverse events and serious adverse events should be handled and reported in a timely manner.

1 month after surgery (±7 days): The follow-up will be conducted by telephone.

VCSS and AVVQ will be collected. Adverse events and serious adverse events should be handled and reported in a timely manner.

3 months after surgery (±15 days): The follow-up will be conducted by clinical doctor. Vital signs should be recorded and VCSS and AVVQ will be collected. Doppler ultrasonography of lower limb vein will be performed. Adverse events and serious adverse events should be handled and reported in a timely manner.

6 months after surgery (±30 days): The follow-up will be conducted by clinical doctor. Vital signs should be recorded and VCSS and AVVQ will be collected. Doppler ultrasonography of lower limb vein will be performed. Adverse events and serious adverse events should be handled and reported in a timely manner.

12 months after surgery (±30 days): The follow-up will be conducted by clinical doctor. Vital signs should be recorded and VCSS and AVVQ will be collected. Doppler ultrasonography of lower limb vein will be performed. Adverse events and serious adverse events should be handled and reported in a timely manner.

Combined medication should be recorded at all stages.

A total of 180 patients will be enrolled in this clinical trial, which will be conducted at 6 centers and the expected recruitment time is last for 8 months, with an overall duration of at least 24 months

5. Source of funding and conflict of interest

There is no funding, and there is no interest conflict with relevant hospitals and doctors.

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

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

(4) Wound infection

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

(5) Deep venous thrombosis

Deep vein thrombosis is the most serious adverse reaction after surgery for varicose veins of lower limbs. Early postoperative ambulation can effectively prevent the occurrence. To prevent this, aspirin can be taken orally. Timely diagnosis can be confirmed through clinical observation, coagulation function detection, D-dimer and venous ultrasound examination of lower limbs. Once it is confirmed, treatment should follow the conventional treatment of thrombosis.

(6) Superficial vein thrombosis

Superficial vein thrombosis is the most serious adverse reaction after surgery for varicose veins of lower limbs. Early postoperative ambulation can effectively prevent

the occurrence. Timely diagnosis can be confirmed through clinical observation, coagulation function detection, D-dimer and venous ultrasound examination of lower limbs. Once it is confirmed, treatment should follow the conventional treatment of thrombosis.

8. Treatment and financial compensation for trial-related injuries

If you suffer any injury or death related to this study during the study period, the sponsor will bear the corresponding treatment expenses and corresponding economic compensation for you, except for the damage caused by the fault of the medical institution and its medical staff during the diagnosis and treatment activities.

9. Risk of Pregnancy

Female subjects: If you become pregnant unexpectedly during the study period, the doctor in charge of you will recommend termination of the pregnancy; If you insist on pregnancy, all consequences will be borne by you.

Male subjects: If your partner become pregnant unexpectedly during the study period, the doctor in charge of you will advise your partner to terminate of the pregnancy; If your partner insists on pregnancy, all consequences will be borne by you and your partner.

10. Possible trial groups to be assigned

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

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.

At the same time, you can enjoy the following diagnosis and treatment items and subsidies:

- Screening period (-14-0 days): Laboratory tests (blood routine, blood biochemistry, clotting quadruple, D-dimer), pregnancy test (if applicable), Doppler ultrasonography of lower limb vein, electrocardiogram. If the relevant examination has been performed before the informed consent is signed and within 14 days before the operation, there is no need to repeat the examination.
- 7 days after surgery (±3 days): Laboratory tests (blood routine, blood biochemistry), Doppler ultrasonography of lower limb vein.
- 3 months after surgery (±15 days), 6 months after surgery (±30 days), and 12 months after surgery (±30 days): Doppler ultrasonography of lower limb vein.
- We will reimburse you for the transportation cost of each visit to and from the hospital, 200 yuan per person for each visit, a total of 3 visits, a total of 600 yuan. Subsidies will be given at the end of each follow-up visit, and finally according to the actual visit.

The sponsor will only provide you with the cost of relevant examinations that need to collect data in the clinical study. Other examinations are routine diagnosis and treatment that you must carry out, and relevant data do not need to be collected. This part of the cost will be borne by you.

14. Voluntary participation and withdrawal from the trial

You may choose not to participate in the study or withdraw from the study at any time

after notifying the doctor. Your medical treatment and rights will not be affected by discrimination or retaliation.

If you require additional diagnosis/treatment, or you are not following the study plan, or have any other sound reasons, the study doctor may terminate your continued participation in the study.

You will receive timely information that may affect your continued participation in the study.

You may keep abreast of information and research progress related to this study, if you have questions related to this study, or you have any discomfort or injury during the study or questions about rights and interests of participants in this study, you can contact the Ethics Committee at _____.

Informed consent

I have carefully read the informed consent form. I have a chance to ask questions and all questions have been answered. I understand participating in this study is voluntary. I can choose not to participate in the study, or quit at any time after notifying the doctor without discrimination or revenge, and will not lead to any of my medical treatment and the rights and interests are affected. The study doctor may terminate my participation in the clinical trial if I require additional diagnosis/treatment, or if I do not comply with the study plan, or for any other reasonable reason.

I voluntarily agree to participate in the clinical trial and I will receive a signed copy of the informed consent.

Subject name (in print): _____

Subject name (hand written): _____ Date: _____

Contact information: _____

If the subject is unable to sign the informed consent due to consciousness disorder, paralysis of the subject's upper limbs or inability to write, or the subject is a child, the legal representative shall sign the informed consent

Legal representative's signature (in print): _____

Subject name (hand written): _____ Date: _____

Contact information: _____ Relationship with subject: _____

Reason for subject unable to sign the informed consent: _____

Declaration of Researchers

I have informed the subjects of the informed consent accurately and answered their questions. The subjects are willing to participate in this clinical trial.

Researcher name (in print): _____

Researcher name (hand written): _____ Date: _____

Contact information: _____