Research protocol

Study name: Comparison of radiofrequency ablation surgery for varicose veins in the lower extremities with concurrent or staged treatment of branch veins
Clinical efficacy: a multicenter randomized controlled study
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Research Department: General Surgery
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Comparison of clinical efficacy of radiofrequency ablation for varicose veins in the same or staged treatment of branch veins: A multicenter randomized controlled study

Research Programme

I. RESEARCH CONTEXT

Varicose veins of the lower extremities (VVLE) are characterized by dilated superficial veins forming twisted clusters with diameters exceeding 3mm[1]. Clinical manifestations include pain, edema, pigmentation, pruritus, skin induration, and chronic or active venous ulcers. Approximately one-third of the global population is affected by this condition[2]. Treatment options encompass both conservative approaches (such as compression therapy and pharmacological management) and surgical interventions. While traditional high ligation stripping (HL/S) remains the gold standard, modern medicine has embraced minimally invasive techniques including radiofrequency ablation (RFA), endovenous laser ablation (EVLA), and ultrasound-guided foam sclerotherapy (UGFS). Notably, RFA and EVLA have largely replaced conventional surgery due to their advantages of shorter operation times and faster recovery[3-6]. Foreign guidelines suggest that for VVLE and main valve regurgitation, intravenous thermal ablation should be preferred, followed by UGFS, and finally HL/S[7].

The Clinical Practice Guidelines for Lower Limb Varicose Veins (2023) issued by the American Forum on Venous Medicine recommend endovenous ablation for symptomatic main superficial veins accompanied by varicocelectomy or UGFSS for associated branch varicose veins. When concurrent surgery is not feasible due to anatomical or medical constraints, ablation of the main varicose vein should be performed, followed by postoperative monitoring for at least three months to assess potential need for staged varicocelectomy or UGFSS for persistent/recurrent symptoms[8, 9]. Many experts endorse this approach, considering it more effective and better suited for patients seeking single-surgery outcomes[10]. Wang et al. conducted a comparative study of VVLE patients undergoing combined endovenous laser ablation with foam sclerotherapy versus laser therapy alone. Six-month follow-up showed no significant difference in complication rates (except bruising). While the combined treatment group experienced higher pain scores at four weeks, these levels normalized by six months. Notably, the combined treatment group had significantly fewer residual branch varicose veins, lower readmission rates, and improved quality of life outcomes compared to the staged surgery cohort[11].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 group showed a markedly lower rate of re-intervention compared to the latter, though this difference lacked statistical significance. Additionally, patients undergoing staged surgery exhibited better improvements in early disease severity and quality-of-life scores. However, the study cautioned that these results should be interpreted cautiously in real-world practice, as the inclusion of 12 non-randomized studies introduced clinical heterogeneity and inherent biases[12]. Evidence also suggests that patients opting for staged surgery had very low rates of secondary interventions, with no statistically

significant differences observed between the two approaches regarding perioperative pain or postoperative recovery. In such cases, staged surgery may reduce costs[13-15].

In 1988, Professor Claude of France first articulated the hemodynamic theory of VVLE[16]. Based on venous anatomical location and function, the lower limb venous system can be divided into five layers from superficial to deep: deep veins (network 1, N1), saphenous veins and Giacomini veins (network 2, N2), saphenous branch veins (network 3, N3), superficial veins connecting different saphenous regions (network 4, N4), and venous networks in microcirculation (network 5, N5).90% of lower extremity great saphenous vein varicosities are classified as type I or III, both involving N1-to-N2 reflux. The distinction lies in the former's superficial venous segment from the reflux point to the return point being entirely composed of saphenous veins with valve insufficiency, while the latter's shunt initially involves a segment of saphenous vein dysfunction followed by N2 branch veins. From a hemodynamic perspective, simultaneous surgery destroying both return and reflux branch veins may cause tissue edema in the reflow area, leading to postoperative swelling worse than preoperative levels. Staged surgery focuses on treating the main saphenous vein while preserving branches, allowing partially functional branches to continue draining the area. Consequently, after initial surgery, the venous hypertension caused by reflux subsides, and most dilated branches gradually regain normal diameter. This suggests a low recurrence rate for staged interventions.The Venous Society of Japan's 2019 Clinical Practice Guidelines for Venous Thermal Ablation (VAT) categorize this combined procedure as "Not Recommended"[17].Hicks et al. conducted a retrospective analysis of patients undergoing RFA with or without venectomy on the great saphenous vein of the lower limb over two years, revealing a higher incidence of endothermic heat-induced thrombosis (EHIT) following RFA combined with venous puncture and resection compared to standalone RFA[18].Kawahira et al. compared short-term and mid-term outcomes between two groups of patients treated with single RFA, RFA with venectomy, or RFA combined with UGFS between 2015 and 2021 at the same hospital. The study found no statistically significant differences in recurrence rates or complications between groups, demonstrating that standalone RFA treatment achieves comparable outcomes[19].

Current clinical research indicates that while guidelines and some experts recommend prioritizing ablation therapy for VVLE patients with concurrent subcutaneous varicocele or superficial varicocele (UGFS) treatment, existing evidence for staged therapy does not demonstrate inferior clinical outcomes compared to simultaneous approaches. The limited literature available lacks detailed data on reintervention rates, complication incidence, and intraoperative pain scores. Therefore, we advocate for further studies to evaluate the efficacy differences between these methods. In this study, patients will be randomly assigned to either intravenous-only RFA therapy or RFA combined with UGFS for subcutaneous varicocele, followed by a 6-month follow-up period.

II. Research Objectives

1) The clinical efficacy of foam sclerosing agent therapy under ultrasound guidance in the same period or in stages after radiofrequency ablation for varicose veins of great saphenous vein was compared in patients with varicose veins of lower extremities 6 months;

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

III. RESEARCH DESIGN AND METHODOLOGY

3.1 Design Type

This study is a prospective, multicenter, randomized, controlled study.

In this study, only the data analysts were blinded, not the doctors and the subjects.

3.2 Subject Investigated

This study aims to include patients diagnosed with primary lower extremity great saphenous vein varicose veins who received treatment at multiple centers, including the Sir Run Run Shaw Hospital affiliated to Zhejiang University School of Medicine (lead institution). The inclusion and exclusion criteria are as follows.

3.2.1 Include Criteria

① 18 to 80 years old (inclusive).

② Primary unilateral varicose veins of the great saphenous vein of the lower extremity.

③ Clinical classification C2 to C4.

④ The branch veins originate within 15cm below the knee.

⑤ Hemodynamic classification includes types I and III involving collateral branches.

⑥ The main trunk of the great saphenous vein in the thigh has a diameter ranging from ≥3 mm to ≤15mm.

⑦ Volunteer to participate in this study and sign the informed consent form.

3.2.2 Exclusion criteria

① Body mass index ≥35kg/m ^{2}.

② The main trunk of the great saphenous vein is extremely twisted or adherent to the subcutaneous tissue.

③ A history of varicose vein surgery on the same side of the lower extremity (controlled by the investigator).

④ Prior deep vein thrombosis or calf muscle vein thrombosis.

⑤ Uncorrectable coagulation dysfunction or significant blood abnormalities (platelets ≤30× ^{9} 10 /L).

⑥ Known allergy to lidocaine or sclerosing agents.

⑦ Ankle-brachial index <0.6 and/or absolute ankle pressure <60mmHg.

⑧ Pregnant or breastfeeding, or planning to become pregnant within the next year.

⑨ The diameter of the anterior vena cava origin is> 3.5mm.

⑩ Vulnerable groups, including people with mental illness, cognitive impairment, critically ill patients, minors, pregnant women, illiterates, etc.

⑪The researchers believe there are other reasons why they are not suitable for the study.

3.2.3 Exit criteria

①The subject withdrew from the study voluntarily.

②The researchers concluded that the subjects were not fit to continue the study.

3.3 research contents

3.3.1 Groups of Subjects

Patients will be randomly assigned to different treatment groups using a random number table (generated by Excel's random function). After enrollment, patients are sequentially numbered. Following this process, a computer generates a unique random number for each participant. Those assigned odd numbers are placed in the experimental group, while those with even numbers are assigned to the control group.

In the pilot group, patients received only RFA treatment of the main great saphenous vein, but no treatment of the branch veins.

The control group patients will receive RFA treatment of the main vein and UGFS treatment of the branch vein.

3.3.2 Intervention Process

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 (DUS) was first performed on the affected great saphenous vein. After local anesthesia in the appropriate area, 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 segmental ablation, the blood vessel sheath was withdrawn early. Postoperative ultrasound confirmed complete closure of the great saphenous vein.

Following this protocol, the control group will receive either 1% polidocanol foam sclerotherapy or punctate stripping therapy on pre-marked great saphenous vein branches in the calf after ablation. Both groups must use elastic bandages on the affected limb within 24 hours post-surgery and wear thigh-length Grade II compression stockings for one week after bandage removal.

3.3.3 Observing Indicators

The relevant examination and evaluation items in this study are all routine clinical examination and evaluation items, and there is no additional examination and evaluation items in this study.

3.3.3.1 Key Observation Indicators

Reintervention rate: The proportion of patients in both groups who require treatment of varicose veins in branches assessed by duplex ultrasound within 6 months. Reintervention rate = Number of cases requiring treatment of varicose veins in branches/total number of cases in the group.

3.3.3.2 Secondary Indicators

1) Treatment cost: calculated after 6 months review.

2）Target vein closure rate: Target vein closure was evaluated by dual-function ultrasound scanning (closure was defined as total length of non-closed proximal venous segment in thigh ≤5 cm).

3）Surgery time: The time from the start of the puncture to the closure of the incision.

4）Number of surgical incisions.

5）Blood loss during surgery.

6）Amount of swelling anesthesia.

7）Quality of Life: The Assessment of Disease-Specific Quality of Life (AVVQ) questionnaire was used to evaluate patients. This instrument identifies four key health factors: pain and functional impairment, appearance, severity of varicose veins, and complications. Health status is assessed based on symptoms and their impact on daily activities. A total score ranges from 0 to 100 points, where 0 indicates the best quality of life and 100 represents the worst[21,22]. See Table 1.

8）Pain: The Visual Analog Score (VAS) scale was used for pain assessment. The scale was a 10-point scale, where 0 represented no pain and increased progressively up to 10, representing the most severe pain imaginable[20]. Pain needs to be divided into intraoperative pain and postoperative pain. See Figure 1.

9）Venous Clinical Severity Score (VCSS) is used to evaluate the severity of venous disease characteristics. The questionnaire contains 10 questions, with each item scored as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). The total score ranges from 0 to 100 points, where 100 indicates the most severe venous lesion[23]. See Table 2.

10）Postoperative complications: including postoperative edema, skin abnormal sensation, bruising, phlebitis, hematoma, infection, deep vein thrombosis and pulmonary embolism.

11）Time to return to work: Patients will be asked a uniform question about the time (days) required from surgery to return to normal life, work or both.

12）Patient satisfaction: divided into two stages, the surgical process and the whole treatment process. Relevant data will be collected during the operation and at the 6-month follow-up, including two questions: "Was the quality of the treatment you received good?" and "Did the treatment you received meet your expectations?" [24]

Figure 1 VAS Visual Analog Scoring Method

Table 1 AVVQ disease-specific quality of life questionnaire

问题	0分	1分	2分	3分
1.在过去的两周里，您静脉曲张分布的位置？			请绘制。	
2.在过去的两周里，静脉曲张导致您疼痛了多少天？	0天	1—5天	6-10天	＞10天
3.在过去的两周里，静脉曲张最疼的时候是？	不疼	在上午	在下午和/或晚上	夜里
4.在过去的两周里，您用了多少天的止痛药来治疗静脉曲张？	0天	1—5天	6-10天	＞10天
5.在过去的两周里，您有过脚踝肿胀吗？	没有	轻微的脚踝肿胀	中度脚踝肿胀(如：您需要坐着抬脚)	严重的脚踝肿胀(如：您穿鞋困难)
6.在过去的两周里，您有没有穿弹力袜？	没有	是的，我自己买的弹力袜，没有医生的推荐	是的，在医生建议下买了弹力袜，我偶尔会穿	是的，在医生建议下买了弹力袜，我每天都穿
7.如果您的脚踝肿了，有没有吃消肿药物？	没有	有		
8.在过去的两周里，您有没有因为静脉曲张而发痒？	没有	有，但仅限于膝盖以上	有，但仅限于膝盖以下	有，整条腿都有
9.您皮肤细小血管区域是否出现与静脉曲张有关的紫色病变？	没有	有		
10.您的脚踝有皮疹或湿疹吗？	没有	有，不需要医生的治疗	有，需要医生的治疗	
11.您是否有与静脉曲张相关的皮肤溃疡？	没有	有		
12.静脉曲张的出现引起您的关注了吗？	没有	有，轻微关注	有，中度关注	有，重度关注
13.您静脉曲张的外观会影响您对包括紧身衣在内的服装的选择吗？	不会	偶尔	经常	总是
14.在过去的两周里，静脉曲张是否影响了您的工作、家务或其他日常活动？	没有	是，我还能工作，但我的工作受到了轻度影响	是，我还能工作，但我的工作受到了中度影响	是，静脉曲张导致我一天/一天以上无法工作
15.在过去的两周里，静脉曲张是否影响了您的休闲活动(包括运动、爱好和社交生活)？	没有	是，受到了轻度影响	是，受到了中度的损害	是，我不能参加任何休闲活动
分数				
总分数				

Table 2 Venous Clinical Severity Score VCSS

症状	0分	1分	2分	3分
疼痛	无	偶发，不需止痛	每日发作，偶需止痛剂	重度，规律使用止痛剂
静脉曲张	无	少，静脉分支曲张	多，大隐静脉曲张于大腿或小腿	大量，大腿和小腿，大小隐静脉均受累
静脉性水肿	无	傍晚，仅有踝部水肿	午后，踝上水肿	晨起，踝上水肿，需减少活动抬高患肢
色素沉着	无或点状	散在、局限、褐色、陈旧	弥漫，小腿下1/3或新鲜（紫色）	广泛分布，超过小腿下1/3或新近出现
炎症	无	轻度，局限于溃疡周边	中度，累及小腿下1/3	重度，累及小腿下1/3以上，静脉性湿疹
硬结	无	局限、踝部、5cm以内	内侧或后侧，小腿下1/3	小腿下1/3以上
溃疡数量	0	1	2	>2
溃疡直径	无	<2cm	2~6cm	>6cm
持续时间	无	<3个月	3~12个月	>12个月
压迫性治疗	无	间歇使用弹力袜	长期使用弹力袜	长期使用弹力袜+抬高患肢

3.3.4 Statistical Analysis

3.3.4.1 Statistical Description

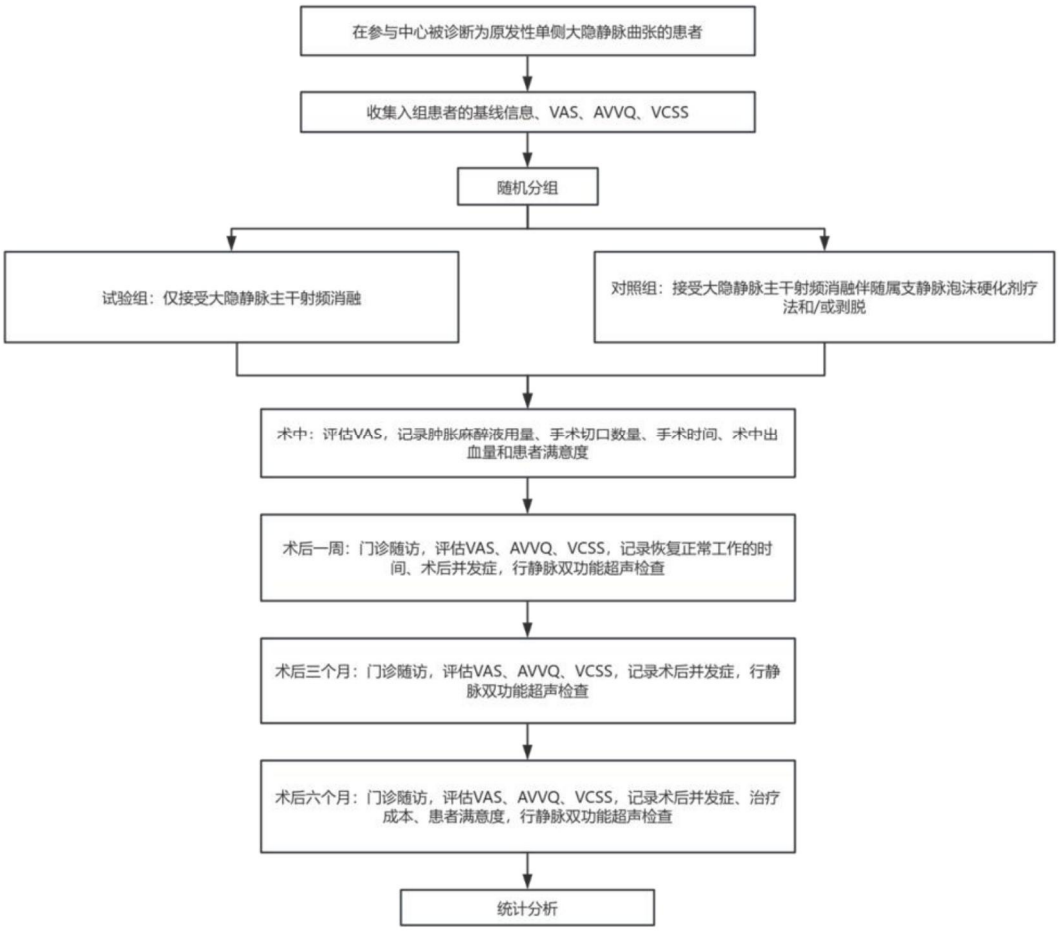
Quantitative variables are described by mean ± standard deviation or median and fourfold interquartile range, and categorical variables by frequency or

Percentage is used for description.

3.3.4.2 Statistical Analysis

For inter-group comparisons, the independent samples t-test or Mann-Whitney U test is employed based on specific circumstances, applicable to both parametric and non-parametric data. Categorical data are compared using chi-square tests or Fisher's exact tests. For repeated measurements, generalized estimating equations (GEE) are utilized to analyze post-intervention differences. The GEE model establishes primary effects across different groups and time series while evaluating their interactions (with baseline data serving as covariates).

3.4 Research Flow Chart



Note: VCSS, venous clinical severity score; AVVQ, Aberdeen Varicose Veins Questionnaire score; VAS, visual analog pain scale.

IV. Sample Size Calculation

Based on previous research findings[11], the reoperation rate was 4.9% for concurrent surgeries and 21.9% for staged surgeries. This randomized controlled trial allocated patients in a 1:1 ratio between groups. With 90% statistical power and a two-tailed 0.05 significance level, each group required at least 82 participants. Considering the extended follow-up period and a 20% dropout rate, the total sample size was expanded to 206 patients, with 103 participants per group. The follow-up lasted 6 months, with the study continuing for 18 months.

As this study is a multicenter study, the number of participants from each center will be evenly distributed as far as possible during the actual enrollment to ensure that

Sample representativeness. However, considering feasibility and enrollment progress, the study will adopt a competitive enrollment approach. During the study period, the enrollment numbers at each center will be adjusted according to actual conditions, and the final enrollment number at any specific center should not exceed 50% of the total cases.

V. DATA MANAGEMENT AND CONFIDENTIALITY

The study data were sourced from hospital medical records and questionnaires, with data entry performed by two individuals using Epidata3.1 software. Final data were verified by a third researcher. Data analysis was conducted using R4.3.3 software. All participant identity records were kept confidential and not disclosed beyond legal or regulatory requirements. All collected materials, including electronic versions (stored on USB drives) and paper questionnaires, were securely stored in password-protected cabinets at each center for at least 10 years. Data collected during the study remained strictly confidential and was accessible only to research team members (or individuals affiliated with the sponsor organization or center site).

VI. INFORMED CONSENT

Prior to enrollment in this study, the investigator responsible for obtaining informed consent must provide participants with a comprehensive written explanation detailing the study's objectives, nature, procedures, potential benefits, and risks. Participants must be fully informed of their right to withdraw from the study at any time. Before enrollment, each participant should receive adequate information and sufficient time to consider their participation. Only those who voluntarily agree and sign the informed consent form may be included in the study.

VII. Adverse Events and Related Measures

Potential adverse reactions/complications of this study may include postoperative sensory abnormalities, skin burns/color changes, phlebitis, hematoma, infection, deep vein thrombosis, pulmonary embolism, etc. However, extensive prior research has demonstrated that lower extremity varicose vein thermal ablation offers superior safety and efficacy, with a low incidence of postoperative complications and minimal associated risks.

7.1 Radiofrequency Ablation Related Adverse Events and Related Management Measures

7.1.1 Postoperative Sensory Abnormalities

Countermeasures: Previous data show that postoperative sensory abnormalities usually disappear during the follow-up period. When postoperative sensory abnormalities occur, corresponding treatment can be given to reduce the patient's distress.

7.1.2 Skin Burns/changes

Countermeasures: Radiofrequency therapy is a form of thermal therapy. Giving a sufficient dose of swelling fluid can effectively prevent burns to the skin and surrounding tissues. If skin burns occur, mild cases do not require treatment, while severe cases require surgical dressing changes for healing.

7.1.3 Phlebitis

Countermeasures: The phlebitis after microsurgery is easy to cause pain at the site but is mild, and most patients do not need pain relief

Treatment. A small number of patients can take oral analgesics or sedatives to relieve pain after surgery.

7.1.4 Hematoncus

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

7.1.5 Infect

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

7.1.6 Deep Venous Thrombosis

Management strategies: As a rare adverse event, postoperative complications are the most severe complication following varicose vein surgery in the lower extremities. Ensuring the catheter tip is at least 2cm away from the popliteal fossa junction during surgery can significantly reduce the incidence of deep vein thrombosis (DVT). Early ambulation after surgery effectively prevents this complication. Clinical monitoring through coagulation function tests, D-dimer levels, and lower extremity venous ultrasound allows for timely diagnosis. Once DVT develops, standard therapeutic protocols should be promptly implemented.

7.1.7 Pulmonary Embolism

Management Protocol: Pulmonary embolism represents a rare but critical complication following radiofrequency ablation procedures. For patients exhibiting postoperative pulmonary embolism indicators (unexplained chest pain, blood-tinged sputum, dyspnea), clinicians should urgently consider this diagnosis. Immediate clinical evaluation and diagnostic imaging are imperative to facilitate early detection and intervention, thereby controlling disease progression and safeguarding patient life quality.

7.2 Adverse Events Related to Foam Sclerotherapy and Related Treatment Measures

7.2.1 Infect

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

7.2.2 Chromatosis

Countermeasures: 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.

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

Countermeasures: Usually short, elastic bandage or elastic sock pressure dressing, topical polysulfonic acid mucopolysaccharide cream, etc., oral nonsteroidal anti-inflammatory drugs to reduce inflammation and pain.

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