RESEARCH PROTOCOL

Official Title

Comparison of Intraoperative Pain Scores Between Radiofrequency Ablation and Microwave Ablation for Lower Extremity Varicose Veins: A Prospective Single-Center Randomized Controlled Study

NCT Number

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Protocol version note: this is the revised edition of the protocol, in which four primary intraoperative pain assessment timepoints are defined — immediately after venous access and sheath insertion, immediately after tumescent local anesthesia injection, during catheter ablation, and at the end of surgery.

This document is an English translation of the original Chinese protocol, prepared for public availability on ClinicalTrials.gov. It does not contain the names or identifying information of any research participants.

Sponsor / Study Site

Department of Vascular Surgery, the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine

1 Background

1.1 Epidemiology and Current Management of Lower Extremity Varicose Veins

Lower extremity varicose veins are among the most common peripheral vascular diseases encountered in clinical practice. Globally, the prevalence of venous insufficiency in the adult population is approximately 25%–40%, and the prevalence of overt varicose veins is approximately 10%–25% [1,2]. In China, with population aging and the increasing prevalence of occupations and lifestyles involving prolonged standing or sitting, the prevalence of lower extremity varicose veins continues to rise. The disease not only impairs patients' quality of life but, in severe cases, may lead to complications such as skin pigmentation, eczema, and ulceration, imposing a substantial medical burden on patients and society.

Conventional high ligation and stripping (HLS) of the great saphenous vein (GSV) was previously the standard operation for lower extremity varicose veins; however, it is associated with greater surgical trauma, a longer recovery period, and more complications. Since the early 2000s, endovenous thermal ablation (EVTA) has gradually become the preferred treatment for GSV reflux owing to its minimally invasive nature, rapid recovery, and well-established efficacy [3,4]. The endovenous thermal ablation techniques commonly used in clinical practice mainly include radiofrequency ablation (RFA) and microwave ablation (MWA), in addition to endovenous laser ablation (EVLA).

1.2 Differences in Working Principles Between RFA and MWA

Radiofrequency ablation delivers radiofrequency energy at a frequency of approximately 460 kHz through electrodes at the catheter tip in direct contact with the vein wall; the resulting resistive heating raises the vein wall temperature to approximately 120 °C, causing collagen contraction, endothelial injury, and luminal occlusion. Taking the ClosureFast system as an example, ablation is performed segmentally, with each 20-second cycle treating one segment; temperature controllability is good, the depth of thermal penetration is relatively limited (approximately 2–3 mm), and indirect thermal damage to surrounding tissues is comparatively small [5]. Because heat conduction in RFA depends on direct contact, tumescent local anesthesia (TLA) must adequately infiltrate the perivenous space to separate the vein from surrounding tissues (particularly the skin and nerves) and thereby provide effective thermal insulation.

Microwave ablation uses electromagnetic microwaves at a frequency of 2450 MHz. The antenna radiates microwave energy, causing high-frequency oscillation of water molecules in the target tissue; the resulting dielectric heating coagulates the vein wall. Unlike the resistive heating of RFA, dielectric heating in MWA does not require direct contact between the electrode and the tissue; energy is propagated by radiation, heating is faster, higher tissue temperatures can be achieved, and the depth of thermal penetration is relatively greater [6,7]. Some clinical studies have suggested that MWA produces a more uniform and thorough ablation of the vein wall; however, the theoretically greater thermal spread may require more generous protection of surrounding tissues.

1.3 Sources of Intraoperative Pain and the Rationale for Its Assessment

Tumescent local anesthesia is an indispensable key step in endovenous thermal ablation. The standard formulation is usually 0.9% normal saline 1000 mL + 2% lidocaine 20–40 mL + epinephrine 1 mg + 5% sodium bicarbonate 10–20 mL, yielding a final lidocaine concentration of approximately 0.1% [8]. TLA serves three purposes in EVTA: (1) providing local anesthesia and analgesia; (2) producing epinephrine-induced vasoconstriction to reduce bleeding; and (3) creating a “liquid separation layer” around the vein with a large volume of fluid, separating the vein from the skin and surrounding nerves and preventing thermal injury.

During endovenous ablation performed under local anesthesia, patients remain awake throughout, and intraoperative pain is experienced across multiple stages of the procedure: the mechanical stimulation of ultrasound-guided venous puncture and sheath insertion; the distending pain of tissue infiltration during TLA injection; the thermal pain during the ablation phase; and the overall discomfort at the end of surgery. Studies have shown that pain scores (VAS) during the TLA injection phase are often higher than those during the ablation phase itself [9,10]. Factors influencing intraoperative pain include the total volume of TLA fluid, injection speed, fluid temperature, solution pH, needle gauge, vein diameter and depth, ablation energy parameters (power, temperature, pullback speed), and individual patient characteristics (anxiety level, pain sensitivity, sex, age, body mass index [BMI], etc.).

Because intraoperative pain involves multiple consecutive stages, assessment at a single timepoint cannot comprehensively reflect the patient’s intraoperative comfort. Therefore, timepoint-specific pain assessment at the key procedural nodes—immediately after venous access and sheath insertion, immediately after tumescent local anesthesia injection, during catheter ablation, and at the end of surgery—is required to systematically characterize the full profile of intraoperative pain associated with the two ablation modalities.

1.4 Potential Differences Between RFA and MWA in TLA Requirements

Owing to their different working principles, RFA and MWA may differ considerably with respect to TLA injection:

(1) Volume requirement: Because MWA has a greater depth of thermal penetration and faster heating, a larger TLA volume may be required to ensure adequate thermal insulation. If the total TLA volume required for MWA is larger, the injection will last longer and produce greater tissue distension, which may theoretically result in higher pain scores.

(2) Distribution requirement: In RFA, thermal energy is confined to the catheter–vein wall interface, and TLA mainly needs to be distributed evenly around the vein; in MWA, energy is propagated by radiation and may exert thermal effects on a wider area of surrounding tissue, requiring TLA to infiltrate a larger region. Expansion of the injection field may increase the need for multiple puncture sites or extensive fan-shaped injection from a single site, thereby affecting the pain experience.

(3) Injection technique: Different operators may adapt their TLA injection strategy (e.g., injection speed, volume per bolus, number of puncture sites) according to the ablation modality; these technical differences may directly affect the patient’s pain experience.

1.5 Differences Between RFA and MWA in Pain During the Ablation Phase

Pain during endovenous thermal ablation arises mainly from thermal stimulation of the vein wall and surrounding tissues. Owing to their different working principles, RFA and MWA may differ in the pain experienced during ablation:

(1) Mode of heat delivery: RFA relies on resistive heating with a controllable temperature (approximately 120 °C) and limited thermal penetration (2–3 mm), producing relatively mild thermal stimulation of surrounding tissues; MWA relies on dielectric heating, with faster tissue heating, higher achievable temperatures, and greater thermal penetration, which may generate stronger thermal stimulation and pain.

(2) Ablation mode: RFA is performed segmentally (20 seconds per segment) with well-defined heating–interval cycles, whereas MWA involves continuous pullback ablation with sustained thermal stimulation. The two modes may affect patients' pain experience differently.

(3) Differential protective effect of TLA: Because MWA has a greater depth of thermal penetration, the same TLA volume may not provide thermal insulation equivalent to that of RFA; patients in the MWA group may therefore perceive more transmitted heat energy during the ablation stage, resulting in higher pain scores.

1.6 Research Gap

Although numerous studies have compared RFA and MWA with respect to vein occlusion rate, postoperative complications, and patient satisfaction [11–13], no prospective clinical study has directly compared intraoperative pain between the two modalities in a timepoint-specific, whole-process manner. Previous studies mostly assessed intraoperative pain at a single timepoint (e.g., a retrospective worst-pain rating after surgery) and therefore could neither distinguish the respective contributions of venous access and sheath insertion, TLA injection, and catheter ablation to overall intraoperative pain, nor clarify the factors influencing pain at each stage and their interaction with the ablation modality.

In summary, this study uses a prospective, single-center, randomized controlled design to systematically compare intraoperative pain scores between RFA and MWA at four primary assessment timepoints—immediately after venous access and sheath insertion (T1), immediately after tumescent local anesthesia injection (T2), during catheter ablation (T3), and at the end of surgery (T4)—and to explore the interacting factors influencing pain at each timepoint, thereby providing evidence to support clinical practice.

2 Objectives

2.1 Primary Objective

To compare intraoperative pain scores (VAS) between patients with lower extremity varicose veins undergoing RFA and those undergoing MWA at the following four primary assessment timepoints:

(1) T1, immediately after venous access and sheath insertion: immediately after completion of ultrasound-guided GSV puncture and sheath insertion, to characterize pain during this procedural stage (the procedure is identical in both groups, and this timepoint serves as a reference for between-group balance and individual pain sensitivity);

(2) T2, immediately after TLA injection: immediately after completion of tumescent local anesthesia injection, to determine whether a statistically significant difference exists between the two ablation modalities in pain during the TLA injection stage;

(3) T3, during catheter ablation: immediately after completion of GSV trunk ablation, to assess pain during the ablation process and determine whether a statistically significant difference exists between the two modalities in pain during the thermal ablation stage;

(4) T4, at the end of surgery: immediately after completion of the operation, a retrospective global assessment of pain over the entire surgical procedure.

Among these, T2 (immediately after TLA injection) and T3 (during catheter ablation)—the two core timepoints at which the two modalities may differ—are designated co-primary endpoints; T1 serves as the reference timepoint and T4 as the global assessment timepoint for intraoperative pain. Together, the four timepoints constitute a complete intraoperative pain trajectory analysis.

2.2 Secondary Objectives

(1) To compare the overall intraoperative pain trajectories (T1–T4) between the two groups, using repeated-measures analysis to test the group × time interaction effect;

(2) To compare TLA injection-related parameters between the two groups: total injected volume (mL), injection time (min), and number of puncture sites;

(3) To compare ablation-related parameters between the two groups: total ablation time, ablation length, and ablation energy parameters;

(4) To compare pain scores at 2 hours and 24 hours after surgery between the two groups;

(5) To compare patient satisfaction with, and acceptance of, the operation between the two groups;

(6) To compare the incidence of intraoperative and postoperative adverse events between the two groups (e.g., thermal skin injury, paresthesia, hematoma, deep vein thrombosis);

(7) To explore the interacting factors influencing pain scores at each intraoperative timepoint and their interaction with the ablation modality (sex, age, BMI, vein diameter, TLA volume, injection time, ablation parameters, preoperative anxiety level, baseline pain sensitivity, etc.), in order to clarify the factors underlying the difference in intraoperative pain between the two catheter-based ablation modalities.

3 Study Design

3.1 Study Type

A prospective, single-center, open-label, randomized controlled clinical trial (RCT).

3.2 Study Center

Department of Vascular Surgery, the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine.

3.3 Study Groups

Participants are allocated in a 1:1 ratio:

RFA group: GSV trunk ablation performed with a radiofrequency ablation system (ClosureFast, Medtronic).

MWA group: GSV trunk ablation performed with a microwave ablation system (Nanjing ECO).

3.4 Overview of Study Procedures

Screening assessment → informed consent → randomization → preoperative baseline assessment → surgery (venous access and sheath insertion → TLA injection → catheter ablation) → intraoperative pain assessment (VAS at four timepoints: T1 immediately after venous access and sheath insertion; T2 immediately after TLA injection; T3 during catheter ablation; T4 at the end of surgery) → postoperative assessment (2 h, 24 h, 7 d, 30 d) → follow-up → data analysis.

4 Study Population

4.1 Inclusion Criteria

- (1) Age 18–75 years, either sex;
- (2) Doppler ultrasound-confirmed great saphenous vein (GSV) trunk reflux (reflux time > 0.5 s) in the affected lower limb;
- (3) CEAP classification C2–C6;
- (4) GSV trunk diameter (thigh segment) of 4–12 mm on measurement;
- (5) Planned for endovenous thermal ablation, willing to participate in this study, and provision of written informed consent.

4.2 Exclusion Criteria

- (1) History of deep vein thrombosis in the affected lower limb;
- (2) History of GSV surgery or ablation in the affected lower limb;
- (3) Acute superficial thrombophlebitis in the affected lower limb;
- (4) Coexisting lower extremity arterial disease (ABI < 0.7);
- (5) Pregnancy or lactation;
- (6) Allergy to amide-type local anesthetics such as lidocaine or ropivacaine;
- (7) Severe hepatic or renal dysfunction (ALT/AST > 3 × the upper limit of normal, eGFR < 30 mL/min/1.73 m²);
- (8) Severe heart failure (NYHA class III–IV) or uncontrolled severe arrhythmia;
- (9) Coagulation abnormality (INR > 1.5, platelet count < 80×10^9/L);
- (10) Severe psychiatric illness or cognitive impairment precluding VAS assessment;
- (11) Need for simultaneous ablation of multiple sites (e.g., bilateral same-session surgery);
- (12) History of chronic pain or long-term analgesic use;
- (13) Any other condition deemed by the investigator to make participation inappropriate.

4.3 Withdrawal Criteria

- (1) Voluntary withdrawal by the participant;
- (2) Intraoperative conversion to another surgical approach due to anatomical factors (e.g., severe vein tortuosity, failed puncture);
- (3) Occurrence of a serious adverse event requiring termination of surgery;
- (4) Protocol violation (e.g., intraoperative medication or procedures deviating from the protocol);
- (5) Loss to follow-up.

5 Interventions

5.1 Preoperative Assessment

All patients complete the following examinations before surgery:

- (1) Lower limb venous Doppler ultrasound (reflux location, GSV diameter, perforator status);
- (2) Complete blood count, coagulation panel, hepatic and renal function tests, and electrocardiogram;
- (3) CEAP classification and Venous Clinical Severity Score (VCSS);
- (4) Preoperative anxiety score (STAI-State scale);
- (5) Baseline VAS score (resting pain of the affected limb).

5.2 Standardized Surgical Procedures

5.2.1 Anesthesia

This study uses local tumescent anesthesia only; general anesthesia or neuraxial anesthesia is not used. Patients remain awake and capable of performing VAS scoring throughout (RASS score −1 to 0).

5.2.2 GSV Puncture and Catheter Insertion

- (1) Ultrasound-guided percutaneous puncture of the GSV (near the medial aspect of the knee);
- (2) Insertion of the vascular sheath and advancement of the ablation catheter to 2–3 cm below the saphenofemoral junction;
- (3) Ultrasound confirmation of catheter position.

[Pain assessment node T1] Immediately after completion of venous access and sheath insertion and ultrasound confirmation of the catheter position (before TLA injection), the first VAS assessment is performed (VAS-T1).

5.2.3 Tumescent Local Anesthesia (TLA) Injection

Standardized TLA formulation: 0.9% normal saline 500 mL + 2% lidocaine 25 mL + epinephrine 0.5 mg + 5% sodium bicarbonate 15 mL; final lidocaine concentration approximately 0.09%.

Standardized injection technique:

- (1) Fluid temperature: room temperature (22–25 °C), with no additional heating or cooling;
- (2) Injection route: under ultrasound guidance, along the course of the GSV, via multiple percutaneous punctures, to create a fluid envelope in the perivenous space;
- (3) Injection device: a unified setup comprising a 5 mL syringe needle connected via tubing to a peristaltic pump running at 300 revolutions per minute, controlled by a foot pedal;
- (4) Injection speed: as tolerated by the patient; the operator maintains a steady injection rate and avoids rapid boluses;
- (5) Target: ultrasound confirmation of circumferential perivenous fluid infiltration, with the vein separated from the skin and deep fascia by fluid;
- (6) TLA volume: determined by the operator according to vein length and diameter; the actual total volume injected (mL) is recorded.

Key control measures: To ensure consistency of TLA injection technique between the two groups, all surgeries are performed by the same surgeon (or by two surgeons who have completed uniform training). A unified operating specification and identical instruments are used during the TLA injection phase.

[Pain assessment node T2] Immediately after completion of TLA injection and ultrasound confirmation of satisfactory perivenous fluid infiltration (before ablation), the second VAS assessment is performed (VAS-T2).

5.2.4 Ablation Procedure

RFA group: A ClosureFast radiofrequency ablation system (or a comparable RFA device) is used; segmental ablation is performed according to the manufacturer's recommended parameters (20 seconds per segment, proceeding from proximal to distal), with a pullback interval of approximately 6.5 cm (per the catheter markings).

MWA group: A microwave ablation system (e.g., a domestically produced microwave ablation device) is used; continuous ablation is performed according to the manufacturer's recommended parameters (pullback speed approximately 1 cm per 7 seconds; specific parameters per the device instruction manual), with continuous pullback ablation proceeding from proximal to distal.

[Pain assessment node T3] Immediately after completion of GSV trunk ablation and withdrawal of the ablation catheter/antenna, the patient is asked to recall the pain experienced during ablation, and the third VAS assessment is performed (VAS-T3).

5.2.5 Postoperative Management

- (1) Elastic bandage compression dressing or class II medical compression stockings at the end of surgery;
- (2) Ambulation immediately after surgery;
- (3) No routine postoperative oral analgesics (acetaminophen 500 mg orally may be given if necessary);
- (4) Postoperative follow-up schedule: 2 hours, 24 hours, 7 days, and 30 days.

[Pain assessment node T4] Immediately after completion of all surgical procedures (including tributary treatment and compression bandaging), the patient is asked to recall the pain experienced over the entire surgical procedure, and the fourth VAS assessment is performed (VAS-T4).

6 Outcome Measures

6.1 Primary Assessment Timepoints and Primary Outcome Measures

Four primary assessment timepoints are established in this study. Intraoperative pain is assessed using the Visual Analog Scale (VAS; 0 = no pain, 10 = worst imaginable pain):

Time point	Name	Assessment timing	Content assessed	Endpoint designation
T1	Immediately after venous access and sheath insertion	Immediately after completion of puncture and sheath insertion and ultrasound confirmation of catheter position (before TLA injection)	Pain caused by the venous access and sheath insertion procedure	Reference timepoint (identical procedure in both groups)
T2	Immediately after TLA injection	Immediately after completion of TLA injection and ultrasound confirmation of satisfactory infiltration (before ablation)	Pain during the TLA injection stage (from the first puncture/injection to completion of injection)	Co-primary endpoint 1

Time point	Name	Assessment timing	Content assessed	Endpoint designation
T3	During catheter ablation	Immediately after completion of trunk ablation and withdrawal of the catheter/antenna	Pain during the ablation stage (from device activation to completion of trunk ablation; retrospective rating of the most pronounced pain in this stage)	Co-primary endpoint 2
T4	End of surgery	Immediately after completion of all procedures and compression bandaging	Retrospective global assessment of pain over the entire operation	Global assessment timepoint

Table 1. Primary intraoperative pain assessment timepoints.

Co-primary endpoint 1: VAS score immediately after TLA injection (VAS-T2)

Assessment instrument: VAS 0–10;
Assessment timing: immediately after completion of TLA injection (T2), scored verbally by the patient and recorded by an independent research assistant;
Definition: the TLA injection stage is defined as the entire period from the first puncture/injection to ultrasound-confirmed completion of injection and readiness to begin ablation; the patient reports the most pronounced pain experienced during this stage.

Co-primary endpoint 2: VAS score during catheter ablation (VAS-T3)

Assessment instrument: VAS 0–10;
Assessment timing: immediately after completion of GSV trunk ablation and withdrawal of the ablation catheter/antenna (T3), scored verbally by the patient and recorded by an independent research assistant;
Definition: the ablation stage is defined as the entire period from activation of the ablation device to completion of trunk ablation and withdrawal of the catheter/antenna; the patient reports the most pronounced pain experienced during this stage.

Notes on the reference timepoint (T1) and the global assessment timepoint (T4):

T1 (immediately after venous access and sheath insertion): the puncture and sheath insertion procedure is completely identical between the two groups, and no between-group difference is expected. This timepoint mainly serves to: (1) verify the baseline balance of pain sensitivity between groups; (2) provide a within-subject reference for individual pain sensitivity, used to adjust subsequent pain assessments; and (3) define the starting point of the intraoperative pain trajectory.

T4 (end of surgery): a retrospective global assessment of pain over the entire operation (including tributary treatment and bandaging), reflecting the patient's overall experience of intraoperative pain and completing the intraoperative pain trajectory together with T1–T3.

6.2 Secondary Outcome Measures

Measure	Assessment timepoint	Description
Intraoperative pain trajectory (T1–T4)	T1, T2, T3, T4	Repeated-measures analysis testing the group × time interaction effect
Total TLA volume (mL)	Intraoperative record	Actual total volume injected
TLA injection time (min)	Intraoperative record	From the first puncture to completion of injection
Number of TLA puncture sites	Intraoperative record	Number of percutaneous injection punctures

Measure	Assessment timepoint	Description
Total ablation time (min)	Intraoperative record	From device activation to completion of ablation
Ablation length (cm)	Intraoperative record	Length of the vein segment actually ablated
Ablation energy parameters	Intraoperative record	RFA: number of segments/temperature; MWA: power/pullback speed
Pain score (VAS) at 2 h postoperatively	2 h after surgery	At rest
Pain score (VAS) at 24 h postoperatively	24 h after surgery	At rest
Patient satisfaction score	24 h after surgery	0–10; 10 = most satisfied
Acceptance of surgery	24 h after surgery	Willingness to undergo the same type of surgery again (yes/no/unsure)
Preoperative anxiety score (STAI-State)	Before surgery	20–80; higher scores indicate greater anxiety
Baseline VAS score	Before surgery	Resting pain of the affected limb, used as a covariate
VCSS	Before surgery and 30 d postoperatively	Venous Clinical Severity Score
Adverse events	Intraoperatively to 30 d postoperatively	See Section 6.3

Table 2. Secondary outcome measures.

6.3 Safety Outcome Measures

The following adverse events are recorded intraoperatively and within 30 days after surgery: (1) thermal skin injury/burn; (2) paresthesia or numbness along the course of the GSV; (3) subcutaneous hematoma; (4) superficial thrombophlebitis; (5) deep vein thrombosis (DVT); (6) pulmonary embolism; (7) incision/puncture site infection; and (8) other surgery-related adverse events.

7 Sample Size Calculation

7.1 Rationale

This study has two co-primary outcome measures: (1) the VAS score immediately after TLA injection (VAS-T2) and (2) the VAS score during catheter ablation (VAS-T3). Both are continuous variables, and the sample size calculation is based on the comparison of two group means.

Because the research hypothesis is that pain scores in the MWA group are higher than those in the RFA group at both core timepoints (i.e., both endpoints must reach statistical significance), a Bonferroni correction is applied to control the family-wise type I error rate: the significance level for each endpoint is $\alpha' = 0.025$ (two-sided), with an overall $\alpha = 0.05$. Between-group comparisons at T1 (reference timepoint) and T4 (global assessment timepoint) are treated as secondary analyses and are not included in the multiplicity correction framework for the primary endpoints.

7.2 Parameter Settings

Parameter	VAS-T2 (immediately after TLA injection)	VAS-T3 (during catheter ablation)	Rationale
Significance level (α′)	0.025 (two-sided)	0.025 (two-sided)	Bonferroni correction; overall α = 0.05

Parameter	VAS-T2 (immediately after TLA injection)	VAS-T3 (during catheter ablation)	Rationale
Power (1 − β)	0.80	0.80	Conventional setting
Expected mean VAS in the RFA group (μ_1)	3.5	2.5	Based on previous studies of intraoperative pain during RFA [9,10]; ablation-stage pain is usually lower than TLA injection-stage pain
Expected mean VAS in the MWA group (μ_2)	5.0	4.0	MWA has greater thermal penetration; pain at both stages assumed higher than RFA
Expected between-group difference (δ)	1.5	1.5	A 1.5-point difference on the VAS is considered the minimal clinically important difference [14]
Pooled standard deviation (σ)	2.0	2.0	Based on the standard deviations of pain scores in comparable studies [9,10]
Attrition rate	15%	15%	Accounting for dropout and loss to follow-up

Table 3. Sample size parameters.

7.3 Calculation Formula

The sample size per group for the comparison of two means (two-sided test) is calculated as:

$$n \text{ per group} = 2 \times (Z_{\alpha'/2} + Z_{\beta})^2 \times \sigma^2 / \delta^2$$

With the Bonferroni-corrected $\alpha' = 0.025$: $Z_{\alpha'/2} = 2.24$ (two-sided, $\alpha' = 0.025$); $Z_{\beta} = 0.84$ ($\beta = 0.20$, power = 80%); $\sigma = 2.0$; $\delta = 1.5$.

Calculation: n per group = $2 \times (2.24 + 0.84)^2 \times 2.0^2 / 1.5^2 = 2 \times 9.49 \times 4 / 2.25 = 75.92 / 2.25 \approx 33.7 \approx 34$.

Adjusted for a 15% attrition rate: n adjusted = $34 / (1 - 0.15) = 34 / 0.85 \approx 40$.

Note: The two co-primary endpoints use identical parameter settings ($\sigma = 2.0$, $\delta = 1.5$) and therefore yield the same required sample size; the larger value is adopted as the final sample size per group. Even if the expected means differ between the two endpoints, the required sample size is identical as long as the difference δ and the standard deviation σ are the same. In addition, because the repeated-measures analysis of the four timepoints (T1–T4) involves multiple measurements, its statistical power is no lower than that of a single-timepoint comparison; a sample size of 40 per group therefore satisfies the requirements of the primary analysis.

7.4 Sample Size Conclusion

Required sample size per group: 40 participants; total sample size: 80 (RFA group 40 + MWA group 40).

Remark: If pilot data indicate a standard deviation greater than 2.0 or a between-group difference smaller than 1.5 points, the sample size should be increased accordingly. An interim assessment is recommended after 10 participants per group have been enrolled; if the observed standard deviation deviates markedly from the assumed value, the sample size should be recalculated and adjusted using the observed parameters.

7.5 Sensitivity Analysis of Sample Size

The following sample size estimates under different parameter combinations (Bonferroni-corrected $\alpha' = 0.025$, power = 80%, including 15% attrition) are provided for reference:

σ	δ = 1.0	δ = 1.5	δ = 2.0
1.5	85 per group	40 per group	23 per group
2.0	151 per group	68 per group	40 per group
2.5	235 per group	105 per group	61 per group

Table 4. Sample size sensitivity analysis.

8 Randomization and Allocation

8.1 Randomization Method

Block randomization is used, with block sizes of 4 or 6 (randomly varied to prevent prediction of future allocations). An independent statistician generates the randomization list using SAS 9.4 software (or R) and allocates participants to the RFA group or the MWA group in a 1:1 ratio.

8.2 Allocation Concealment

Allocation concealment is implemented using sealed opaque envelopes. After a participant has signed the informed consent form and eligibility has been confirmed, the research staff open the corresponding sealed envelope to obtain the allocation.

8.3 Blinding

Because the surgical equipment and operating procedures of RFA and MWA differ, blinding of the surgeon and the patient is not feasible (open-label design). To minimize measurement bias:

(1) Outcome assessor blinding: VAS scores at all four timepoints are collected and recorded by an independent research assistant who is unaware of the group assignment (assessor blinding);

(2) Data analyst blinding: the statistical analysis is performed by an independent statistician using the codes “Group A” and “Group B”; unblinding takes place after the analysis is completed.

9 Study Procedures

9.1 Study Timeline

Phase	Time	Main activities
Screening period	Within 7 days before surgery	Informed consent, eligibility screening, baseline assessment
Surgery day	Day 0	Randomization, surgery, intraoperative pain assessment (T1–T4, four timepoints)
Early postoperative period	2 h and 24 h after surgery	Pain assessment, adverse event monitoring
Postoperative follow-up	7 d and 30 d after surgery	Ultrasound examination, VCSS assessment, adverse event monitoring

Table 5. Study timeline.

9.2 Intraoperative VAS Assessment Timepoints (Primary Assessment Nodes)

Time point	Name	Assessment timing	Content assessed	Endpoint designation
T0	Preoperative baseline	Before the start of surgery (before puncture)	Baseline resting pain score (covariate)	Baseline

Time point	Name	Assessment timing	Content assessed	Endpoint designation
T1	Immediately after venous access and sheath insertion	Immediately after completion of puncture and sheath insertion and ultrasound confirmation of catheter position	Pain caused by the puncture and sheath insertion procedure	Primary assessment node (reference timepoint)
T2	Immediately after TLA injection	Immediately after completion of TLA injection	Pain during the TLA injection stage	Primary assessment node (co-primary endpoint 1)
T3	During catheter ablation	Immediately after completion of trunk ablation and withdrawal of the catheter/antenna	Pain during the ablation stage	Primary assessment node (co-primary endpoint 2)
T4	End of surgery	Immediately after completion of all procedures and compression bandaging	Retrospective global assessment of the entire operation	Primary assessment node (global assessment)

Table 6. Intraoperative VAS assessment timepoints.

VAS assessment method: at each timepoint, an independent research assistant (blinded to the group assignment) questions the patient and records the score. At T1, T2, and T3, patients rate the most pronounced pain at that moment or during that procedural stage; at T4, patients provide a retrospective global assessment of the entire operation. The intervals between assessments are sufficient (natural pauses exist between procedures), avoiding mutual interference between successive pain perceptions.

9.3 Follow-up Schedule

Follow-up timepoint	Assessments
2 h postoperatively	VAS, vital signs, puncture site condition
24 h postoperatively	VAS, satisfaction, acceptance of surgery, adverse events, ambulation status
7 d postoperatively	VAS, adverse events, ultrasound examination (DVT screening)
30 d postoperatively	VAS, VCSS, ultrasound examination (GSV occlusion status), adverse events

Table 7. Follow-up schedule.

10 Statistical Analysis

10.1 Analysis Populations

(1) Full analysis set (FAS): all randomized participants who underwent surgery, analyzed according to the intention-to-treat (ITT) principle;

(2) Per-protocol set (PPS): participants who completed all follow-up without major protocol violations;

(3) Safety set (SS): all participants who underwent surgery.

The primary analysis is based on the FAS; the PPS serves as a sensitivity analysis.

10.2 Statistical Methods

10.2.1 Comparison of Baseline Characteristics

Continuous variables are summarized as mean ± standard deviation or median (interquartile range), with between-group comparisons using the independent-samples t test or the Mann–Whitney U test. Categorical variables are summarized as frequency (percentage), with between-group comparisons using the chi-square test or Fisher's exact test.

10.2.2 Primary Endpoint Analysis

This study has two co-primary endpoints: VAS-T2 (the pain score immediately after TLA injection) and VAS-T3 (the pain score during catheter ablation).

Multiplicity correction: A Bonferroni correction is applied, with the significance level for each endpoint set at $\alpha' = 0.025$ (two-sided), so that the family-wise type I error rate is controlled at $\alpha = 0.05$. Only when both endpoints reach statistical significance ($P < 0.025$) can it be concluded that the intraoperative pain in the MWA group is overall higher than that in the RFA group.

Analysis of each endpoint:

(1) Between-group comparison using the independent-samples t test (if normality and homogeneity of variance are satisfied) or the Mann–Whitney U test (if they are not);

(2) Reporting of the between-group mean difference and its 95% confidence interval (CI) for each endpoint;

(3) Analysis of covariance (ANCOVA) to adjust for potential confounding factors (e.g., baseline VAS, VAS-T1, preoperative anxiety score, GSV diameter, TLA volume, ablation length), with VAS-T1 included as a covariate as the within-subject reference for individual pain sensitivity.

Intraoperative pain trajectory analysis (key supportive analysis):

(1) A linear mixed-effects model (LMM) is used for the repeated-measures analysis of VAS scores at the four timepoints (T1–T4), with fixed effects for group, time (timepoint), and the group × time interaction, and a random effect for the individual patient;

(2) A statistically significant group × time interaction indicates that the intraoperative pain trajectories of the two ablation modalities differ;

(3) Pain trajectory plots (T1–T4, mean ± standard error) are produced for both groups to visually present the pain contribution of each procedural stage.

Sensitivity analyses:

(1) If only one of the two endpoints reaches statistical significance, the result for that endpoint is reported and its clinical significance is discussed;

(2) The Hochberg step-up procedure is used as a sensitivity analysis for multiplicity correction;

(3) ANCOVA with VAS-T1 as a covariate serves as a sensitivity analysis of the primary analysis, adjusting for individual differences in pain sensitivity.

10.2.3 Secondary Endpoint Analysis

(1) Between-group comparisons of VAS scores at each timepoint (T1, T4, and 2 h and 24 h postoperatively): independent-samples t test or Mann–Whitney U test;

(2) TLA- and ablation-related parameters (fluid volume, injection time, number of puncture sites, ablation time, ablation length): independent-samples t test or Mann–Whitney U test;

(3) Categorical variables (satisfaction, adverse events, etc.): chi-square test or Fisher's exact test.

10.2.4 Analysis of Influencing Factors and Their Interactions

For secondary objective (7)—exploring the interacting factors underlying the difference in intraoperative pain between the two catheter-based ablation modalities—the following analyses are performed:

(1) Univariate analysis: with VAS-T1, VAS-T2, VAS-T3, and VAS-T4 as the dependent variables, respectively, and sex, age, BMI, GSV diameter, GSV depth (distance from the skin), vein segment (thigh/calf), total TLA volume, TLA injection time, number of TLA puncture sites, ablation length, total ablation time, ablation energy parameters, preoperative anxiety score (STAI-State), and baseline VAS as independent variables, Pearson/Spearman correlation analysis or univariate regression is performed to screen potential influencing factors;

(2) Multivariable linear regression: with VAS-T2 and VAS-T3 as the main dependent variables, the variables with $P < 0.10$ in the univariate analysis together with prespecified core variables (group, age, BMI, GSV diameter, TLA volume, preoperative anxiety score) are entered, and stepwise regression is used to identify the independent influencing factors of pain at each timepoint; regression coefficients β and their 95% CIs are reported;

(3) Group interaction analysis: "group × factor" interaction terms (e.g., group × TLA volume, group × GSV diameter, group × sex, group × age group) are introduced into the multivariable regression to test whether the effect of each factor on pain differs by ablation modality (RFA/MWA), thereby identifying the effect modifiers of the pain difference between the two modalities;

(4) Mediation analysis (exploratory): if the TLA volume differs between the two groups, mediation analysis is used to test the indirect pathway "ablation modality → TLA volume → injection pain";

(5) Subgroup analyses: stratified analyses are performed by sex, age (<60 vs ≥60 years), BMI (<28 vs ≥28 kg/m²), GSV diameter (<8 mm vs ≥8 mm), and preoperative anxiety level (split at the STAI median) to test the consistency of the pain difference between the two ablation modalities across subgroups, with interaction P values used to assess subgroup effects.

Multiplicity note: All influencing-factor analyses are exploratory; no multiplicity correction is applied. Results are presented as point estimates with 95% CIs, serve to generate hypotheses, and do not support confirmatory conclusions.

10.2.5 Statistical Software

Statistical analysis is performed using R (version 4.3.0 or later; packages lme4, nlme, interactions, and mediation) or SPSS 26.0. All statistical tests are two-sided, and $P < 0.05$ is considered statistically significant (for the primary endpoints, the corrected significance level of $\alpha' = 0.025$ applies).

10.3 Missing Data

(1) Multiple imputation is used to handle missing data for the primary endpoints;

(2) The repeated-measures analysis (LMM) uses maximum likelihood estimation, which naturally handles timepoint data that are missing at random;

(3) Last observation carried forward (LOCF) is used as a sensitivity analysis.

11 Quality Control

11.1 Surgical Standardization

(1) All surgeries are performed by the same surgeon with experience of at least 50 RFA and 50 MWA procedures, or by two surgeons who have completed uniform training, to ensure consistency of technique;

(2) A unified surgical standard operating procedure (SOP) is established before the study begins, and all surgeons strictly follow the SOP;

(3) The TLA formulation, injection devices, and injection technique are standardized;

(4) The venous access and sheath insertion procedure is completely identical between the two groups, ensuring the between-group comparability of pain assessment at T1.

11.2 Quality Control of Data Collection

(1) Data are collected using a standardized electronic case report form (eCRF);

(2) VAS scores at the four timepoints are collected by uniformly trained independent research assistants who are unaware of the patients' group assignments before collection;

(3) Key intraoperative parameters (TLA volume, injection time, number of puncture sites, ablation parameters, etc.) are recorded in real time by the circulating nurse, with the time of each VAS assessment recorded simultaneously;

(4) Data entry uses double entry and verification to confirm consistency.

11.3 Ultrasound Standardization

All ultrasound examinations are performed by sonographers with at least 3 years of vascular ultrasound experience, using the same ultrasound machine model, with GSV diameter, reflux time, and other measurements recorded according to unified measurement standards.

12 Adverse Event Monitoring and Management

12.1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a participant from the signing of the informed consent form until the 30-day postoperative follow-up, not necessarily having a causal relationship with the surgery.

12.2 Serious Adverse Events (SAEs)

Serious adverse events include, but are not limited to: deep vein thrombosis, pulmonary embolism, serious bleeding requiring transfusion or surgical intervention, serious infection, and any complication requiring hospitalization.

12.3 Reporting Procedures

(1) All AEs are recorded in the eCRF;

(2) SAEs are reported to the principal investigator and the ethics committee within 24 hours of the investigator becoming aware of them;

(3) The investigator assesses the causal relationship and severity of each AE.

12.4 Trial Stopping Criteria

The investigator may consider terminating the trial if: (1) a serious adverse event clearly related to the study procedures occurs (e.g., a fatal pulmonary embolism); (2) safety concerns are serious enough that continuing the trial would be unethical; or (3) the sponsor or the ethics committee requests termination.

13 Ethical Considerations

13.1 Ethics Review

This protocol is submitted to the Medical Ethics Committee of [name of hospital] for review and approval before implementation; recruitment of participants may begin only after approval has been obtained.

13.2 Informed Consent

(1) During the screening period, the investigator fully informs patients of the study purpose, procedures, expected benefits, and potential risks;

(2) Patients sign the written informed consent form entirely of their own free will;

(3) Participants have the right to withdraw from the study at any stage, without this affecting their subsequent medical care.

13.3 Privacy Protection

(1) All research data are identified by codes (subject numbers) instead of patients' names and other identifying information;

(2) Informed consent forms and the code-to-identity linking table are kept securely by the investigator and are accessible only to members of the research team;

(3) Published study results will not contain any information that could identify a participant's identity.

13.4 Clinical Trial Registration

This study is registered at https://register.clinicaltrials.gov/ before participant enrollment.

14 Data Management

(1) A standardized electronic database is established, with data entry using double entry and verification;

(2) The database includes logic checks and range checks to prevent the entry of abnormal data;

(3) Study data are retained for at least 5 years after study completion;

(4) After database lock, the data are transferred to an independent statistician for analysis.

15 Study Timeline

Phase	Expected time	Main activities
Protocol design and ethics review	Months 1–2	Protocol finalization, ethics review, clinical trial registration
Investigator training and preparation	Months 2–3	SOP development, eCRF setup, personnel training
Participant recruitment and surgery	Months 3–10	Expected enrollment of 8–10 participants per month
Follow-up and data collection	Months 3–11	Completion of 30-day postoperative follow-up

Phase	Expected time	Main activities
Data cleaning and statistical analysis	Months 11–12	Database lock, statistical analysis
Report writing and publication	Months 12–13	Study report writing, manuscript submission

Table 8. Study timeline.

16 Expected Results and Significance

Through systematic assessment at the four primary assessment timepoints—T1 (immediately after venous access and sheath insertion), T2 (immediately after TLA injection), T3 (during catheter ablation), and T4 (end of surgery)—this study is expected to fully characterize the intraoperative pain trajectories of RFA and MWA and to clarify the differences between the two modalities in pain during the TLA injection stage and the ablation stage.

If the pain scores in the MWA group at T2 and/or T3 are significantly higher than those in the RFA group, targeted optimization of the corresponding stages of MWA surgery would be indicated—for example, improving the TLA injection technique (adjusting the fluid formulation and injection speed, using finer puncture needles, or providing adjunctive analgesia) to reduce injection pain, or adjusting the ablation parameters (e.g., reducing power, optimizing the pullback speed, or increasing the TLA volume) to alleviate ablation pain. If no significant difference is observed between the two groups at either core timepoint, the findings would provide evidence of equivalence between the two procedures in terms of intraoperative comfort, contributing to a comprehensive consideration of procedure selection.

Through the influencing-factor analyses, this study will further clarify the independent factors influencing pain at each timepoint (e.g., TLA volume, GSV diameter, preoperative anxiety level) and their interactions with the ablation modality, and will identify patient subgroups that are more sensitive to pain with a given ablation modality (e.g., elderly patients, highly anxious patients, and patients with large-diameter veins), providing an evidence base for individualized procedure selection and intraoperative analgesia management.

The results of this study will provide an evidence base for anesthesia management, ablation parameter optimization, and patient expectation management in endovenous thermal ablation for lower extremity varicose veins, and are of clinical significance for improving patient satisfaction with surgery, enhancing the surgical experience, and accelerating postoperative recovery.

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