Official title：A prospective randomized controlled study on the safety and effectiveness of microscopic varicocele transposition surgery compared with simple ligation

NCT number：

Document date：Jun-3-2025

I. Research Background

Varicocele (VC) is a common urogenital disease affecting male fertility, characterized by abnormal dilation, elongation, and tortuosity of the pampiniform plexus within the spermatic cord. This pathology may lead to impaired testicular spermatogenesis, abnormal synthesis and secretion of testosterone, thereby causing male infertility [1, 2]. The prevalence of varicocele is approximately 15% in the general male population, 25.4% in men with abnormal semen, and 25%-35% in infertile men, with rates of 35% in primary infertility patients and 50%-81% in secondary infertility patients [35].

Traditional treatments for varicocele include open surgery, laparoscopic surgery, and interventional procedures [6], primarily aiming to block spermatic venous reflux. However, these methods have issues such as high recurrence rates and lack of long-lasting efficacy [7]. Therefore, finding more effective treatments has become a research focus. In recent years, with a deeper understanding of the pathophysiological mechanisms of varicocele, surgical methods have also progressed and innovated. Particularly, the development of microsurgical techniques has enabled more precise surgery, reducing damage to the testicular artery and lymphatics, thereby potentially better preserving testicular function. However, despite continuous advancements in surgical techniques, the surgical treatment of varicocele remains controversial, especially regarding the specific mechanisms of its improvement on fertility, which are not yet fully understood.

The new concept and surgical approach proposed in this study, namely surgery to reconstruct spermatic venous drainage, aims to provide more personalized treatment options for different etiologies and types of varicocele through different reconstruction methods. Based on the analysis of our center's 10-year experience, data, and follow-up of varicocele surgeries, we believe that reconstructing spermatic venous drainage will be a new direction for varicocele surgery in the future [8, 9]. This application does not currently involve new technology registration.

II. Research Objectives

1. **Primary Objective:**
   To explore and validate the effectiveness of the reconstructive spermatic vein

bypass surgery method in providing individualized treatment plans for varicocele of different etiologies and types, promoting it as a new direction in varicocele surgery.

2. **Secondary Objectives:**

   I. To clarify the specific mechanisms by which varicocele surgery (especially reconstructive spermatic vein bypass) improves fertility.

   II. To compare the reconstructive spermatic vein bypass surgical method with traditional treatments (open surgery, laparoscopic surgery, and interventional surgery), analyzing its advantages in reducing recurrence rates and improving long-term efficacy.

   III. To further refine the relevant theory and practical operation of the reconstructive spermatic vein bypass method based on our center's 10-year experience, data, and follow-up of varicocele surgeries.

III. Research Methods

1. **Study Design**

    1. **Research Center:** This study will be conducted at the Urology (Andrology) Center of Sichuan Provincial People's Hospital. This center has extensive experience in varicocele surgery, a professional medical team, and advanced surgical equipment. It has also accumulated a large amount of relevant surgical data and follow-up information over the past 10 years, providing a solid foundation for the study.
    2. **Type of Study Design:** A prospective, randomized controlled trial design will be used. Patients with varicocele who meet the inclusion criteria will be randomly divided into two groups: one group will undergo microscopic spermatic vein bypass surgery, and the other group will undergo microscopic simple ligation of the spermatic vein.
    3. **Randomization Method:** Grouping will be done using a computer-generated random number table. Patients will be numbered according to their order of enrollment and assigned to groups based on the random number table to ensure randomization and balance.

4. **Blinding Level:** A single-blind design will be used, meaning patients will not know which surgical treatment they receive, to reduce the influence of patient subjective factors on the study results. Surgeons and researchers will be aware of the group allocation to perform the surgery and collect data.
5. **Evaluation Methods:**

   I. **Surgical Effect Evaluation:** Assess postoperative spermatic vein blood flow using color Doppler ultrasound, including indicators such as venous diameter, reflux status, etc., at 1 month, 3 months, and 6 months postoperatively. The experimental group will also measure indicators such as anastomotic vessel diameter and flow velocity.

   II. **Testicular Function Evaluation:** Detect serum testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and other sex hormone levels, as well as perform routine semen analysis (including sperm concentration, motility, morphology, etc.), preoperatively and at 6 months postoperatively.

   III. **Recurrence Evaluation:** Record whether patients develop recurrence symptoms of varicocele, such as scrotal heaviness and pain, through regular follow-up, combined with ultrasound results to determine recurrence.

2. **Study Population (Clearly state the selection of research subjects and the rationale and feasibility of relevant criteria)**

   Patients with moderate to severe left varicocele presenting to Sichuan Provincial People's Hospital will be selected as research subjects. According to domestic and international varicocele treatment guidelines, moderate to severe varicocele affects patients' fertility and quality of life, indicating surgical intervention.

   Research Sample Size: Based on previous similar studies and the experience of this center, an estimated sample size of 142 cases per group, totaling 284 cases, is planned. The sample size determination comprehensively considers the study's statistical power (set to at least 80%), significance level ($\alpha=0.05$), and the expected magnitude of differences between groups. Statistical

calculations ensure that the given sample size can detect potential differences between the experimental and control groups, making the study results sufficiently persuasive. During the study, the sample size may be adjusted appropriately based on actual circumstances (such as loss to follow-up rate) to ensure the study's validity.

2.1 **Inclusion Criteria**

1. Diagnosed with varicocele by clinical examination (physical examination, ultrasound, etc.) and meeting surgical indications.
2. Male patients aged between 18 and 60 years.
3. Patients have the willingness to undergo treatment, voluntarily participate in this study, and sign the informed consent form.
4. Semen analysis shows abnormalities, such as reduced sperm count, decreased motility, abnormal morphology, etc., and related to varicocele.
5. No severe dysfunction of important organs such as heart, lungs, liver, kidneys, etc., and able to tolerate surgical treatment.
6. Have not received any treatment affecting varicocele condition or semen quality in the past 3 months.

2.2 **Exclusion Criteria**

1. Secondary varicocele (caused by other diseases such as retroperitoneal tumors, renal tumors, etc.).
2. Coexisting with other severe reproductive system diseases, such as epididymitis, orchitis, testicular tumors, etc.
3. Suffering from severe systemic diseases, such as uncontrolled hypertension, diabetes, malignant tumors, etc., which may affect surgical outcomes or prognosis.
4. Presence of coagulation dysfunction or taking medications affecting coagulation function.
5. History of allergy to drugs used during surgery (e.g., anesthetics).
6. Having mental illness or cognitive impairment, unable to cooperate to complete the study.
7. Already participating in other relevant clinical trials.

2.3 **Withdrawal Criteria**

1. **Inability to Complete Surgery:** During surgery, if severe anatomical variations, uncontrolled bleeding, etc., occur, preventing the successful completion of either the reconstructive spermatic vein bypass surgery or the traditional surgery, the patient will be withdrawn from the study. *Reason:* Surgery not performed as planned, subsequent evaluation of the surgical effect according to the study design is impossible, and the data would interfere with study results and not provide valid information.

2. **Patient Voluntary Withdrawal:** At any stage of the study, if the patient requests withdrawal due to personal reasons (e.g., concerns about surgical outcome, financial pressure, etc.), and signs a withdrawal consent form. *Reason:* To respect the patient's right to autonomy, protect patient rights, and avoid compromising study compliance and data quality due to reluctant participation.

3. **Significant Change in Medical Condition:** During the study, if the patient is diagnosed with another severe disease (e.g., new malignancy, severe cardiovascular disease, etc.), the change in condition may affect the evaluation of the varicocele surgery's efficacy, or the patient may be unable to continue according to the study protocol due to the need for treatment of the new disease. *Reason:* New severe diseases interfere with the evaluation of varicocele surgery treatment; the patient's treatment focus may shift, and continued participation may be detrimental to the patient and compromise the scientific validity of the data.

4. **Drug Allergy or Intolerance:** If the patient experiences a severe allergic reaction or intolerance to medications used during the perioperative period (e.g., anesthetics, antibiotics, etc.), affecting subsequent treatment and observation. *Reason:* This may alter the treatment plan, affect the evaluation of the surgery's inherent effect, and the patient's physical condition may be unsuitable to continue per the original research plan.

2.4 **Study Termination Criteria (for individual participants)**

1. **Postoperative Severe Complications:** Postoperative occurrence of severe complications such as testicular atrophy, testicular infarction, severe infection

(e.g., epididymitis, scrotal gangrene, etc.), affecting the accurate assessment of surgical efficacy. *Reason:* These severe complications alter the patient's physiological state and prognosis, making it difficult to solely evaluate the surgery's effect on varicocele, and may affect the patient's fertility and overall health, inconsistent with the study's intended evaluation purpose.

2. **Non-compliance with Follow-up:** The patient fails to undergo scheduled follow-up examinations such as color Doppler ultrasound, sex hormone testing, semen analysis, etc., at the specified times, or is lost to follow-up during the process. *Reason:* Follow-up data is crucial for evaluating surgical outcomes (including spermatic vein blood flow, testicular function recovery, recurrence, etc.). Non-compliance or loss to follow-up leads to missing data, affecting the completeness and accuracy of results, and prevents effective assessment of long-term effects.

3. **Receiving Other Related Treatment Midway:** During the study, the patient receives other treatments for varicocele besides the surgical treatment specified in this study (e.g., medication therapy, etc.). *Reason:* Other treatments may affect the varicocele condition and treatment outcomes, interfering with the isolated evaluation of the surgical method in this study, and preventing accurate judgment of its efficacy and safety.

4. **Occurrence of Serious Adverse Events:** Occurrence of surgery-related serious adverse events, such as deep vein thrombosis, pulmonary embolism, etc., endangering the patient's life and health, making continued participation unsuitable. *Reason:* These serious adverse events cause significant changes in the patient's health status, requiring primary focus and treatment. Continued participation may pose greater risks to the patient, and their subsequent condition would also affect the evaluation of surgical efficacy, violating ethical and scientific principles of research.

Research Content

3.1 **Study Interventions**

Screening Period:

Research Participant Selection: Screen eligible patients with left varicocele based on predefined inclusion and exclusion criteria.

Clinical Data and Sample Collection:

Detailed patient history taking, including onset time of left varicocele, symptom evolution, previous treatments, etc.

Comprehensive physical examination, focusing on the scrotum and left spermatic cord area, recording signs of varicocele.

Collect blood samples to test sex hormone levels (e.g., serum testosterone, FSH, LH), complete blood count, coagulation function, liver and kidney function, etc.

Collect semen samples for routine semen analysis, including sperm concentration, motility, morphology, liquefaction time, etc.

Perform color Doppler ultrasound to measure the presence of nutcracker phenomenon, left spermatic vein diameter, reflux velocity, reflux duration, etc., and record.

Intervention Period:

Group Assignment: Eligible patients will be randomly assigned to two groups using the random number table method.

Experimental Group: Microscopic Spermatic Vein Bypass Surgery.

Control Group: Microscopic Simple Spermatic Vein Ligation.

Experimental Group (Microscopic Spermatic Vein Bypass Surgery):

Surgical Technique: Continuous epidural or general anesthesia. Patient in supine position, routine disinfection and draping. Make an oblique incision approximately 3-5 cm long at the external inguinal ring. Incise skin, subcutaneous tissue, and external spermatic fascia layer by layer, freeing the spermatic cord. Under the operating microscope (magnification 8-15x), carefully dissect the internal spermatic vein, artery, and lymphatics. Based on the specific varicocele condition, select a suitable bypass vessel (e.g., inferior epigastric vein, superficial epigastric vein, etc.). Perform end-to-side or end-to-end anastomosis between the internal spermatic vein and the bypass vessel to reconstruct the spermatic venous drainage pathway. Carefully protect the testicular artery and lymphatics throughout the procedure to avoid injury.

Research Instruments:

Operating Microscope (Olympus Surgical Microscope) for precise intraoperative manipulation.

Vascular anastomosis instruments, including vascular clamps, vascular sutures, etc., for anastomosing the spermatic vein to the bypass vessel.

Standard surgical instruments, such as tissue forceps, scissors, hemostats, etc.

Control Group (Microscopic Simple Spermatic Vein Ligation):

Surgical Technique: Anesthesia and surgical incision same as the experimental group. Under the operating microscope, dissect the internal spermatic vein. After freeing a sufficient length, doubly ligate and transect the internal spermatic

vein using silk sutures or vascular clips to block venous reflux. Also, carefully protect the testicular artery and lymphatics during the procedure.

Research Instruments:

Operating Microscope (same as experimental group).

Standard surgical instruments, including tissue forceps, scissors, hemostats, etc., and silk sutures for ligating the internal spermatic vein.

Follow-up Period

1 Week Postoperatively: Conduct outpatient or telephone follow-up. Inquire about incision healing, presence of scrotal pain, increased swelling, etc. Examine the surgical incision for signs of infection, dehiscence, etc.

1 Month Postoperatively: Perform physical examination, focusing on the scrotum and spermatic cord area, assessing improvement in symptoms like scrotal heaviness and pain. Repeat color Doppler ultrasound to observe left spermatic vein blood flow, including presence of reflux, changes in venous diameter, etc.

3 Months Postoperatively: Repeat physical examination and color Doppler ultrasound. Retest serum sex hormone levels (testosterone, FSH, LH) and compare with preoperative levels. Collect semen sample for routine semen analysis to assess improvement in sperm quality.

6 Months Postoperatively: Repeat comprehensive physical examination, color Doppler ultrasound, sex hormone level testing, and semen routine analysis. Inquire in detail about the patient's fertility status (if applicable), understanding if successful conception has occurred.

Screening Period

History Collection: Detailed inquiry about the onset time of left varicocele to analyze the impact of disease duration. Record symptom evolution, including frequency and severity changes of discomfort like scrotal heaviness and pain, and association with posture, activity, etc. Ask about previous treatments (e.g., medication, physical therapy), their effects, and adverse reactions.

Physical Examination: Comprehensive physical exam, focusing on the scrotum and left spermatic cord. Observe scrotal appearance for swelling, skin color changes. Palpate the spermatic cord, recording signs of varicocele like cord texture, palpable "bag of worms" mass, its size, and extent.

Blood Sample Testing: Collect blood samples to test sex hormone levels (testosterone, FSH, LH), closely related to testicular function, reflecting varicocele's impact on the endocrine system. Test complete blood count to understand basic hematological status (RBC, WBC, platelet counts) and detect potential issues like anemia or infection. Test coagulation function (PT, APTT, etc.) to assess coagulation status for surgical risk assessment. Also test liver and kidney function indicators (ALT, AST, creatinine, BUN, etc.) to determine patient tolerance for surgery and medications.

Semen Sample Analysis: Collect semen samples for routine analysis. Measure sperm concentration (sperm count/mL), assessing sperm production ability. Measure sperm motility (progressive motility %, total motility %), reflecting sperm movement

ability. Analyze sperm morphology (normal morphology %). Record liquefaction time. These parameters are crucial for assessing varicocele's impact on fertility.

Color Doppler Ultrasound: Use color Doppler ultrasound to examine the left spermatic vein. Measure spermatic vein diameter, recording its degree of dilation. Detect reflux velocity, assessing the speed of blood reflux, reflecting impaired venous valve function. Measure reflux duration, determining the severity of the condition. These ultrasound indicators accurately diagnose left varicocele and provide baseline data for subsequent treatment efficacy evaluation.

Intervention Period

Intraoperative Observation: Closely observe surgical procedures during the operation.

For the Experimental Group (Bypass): Observe the suitability of bypass vessel selection, quality of vascular anastomosis (apposition, leakage), record total operative time (skin incision to closure), assess complexity and difficulty. Carefully note protection of the testicular artery and lymphatics, record any injuries and their management.

For the Control Group (Ligation): Observe dissection and ligation of the internal spermatic vein, accuracy of ligation points, completeness of reflux blockage. Carefully note protection of the testicular artery and lymphatics, record any injuries and management.

Perioperative Observation: Postoperatively, closely monitor vital signs (temperature, BP, HR, respiration) for complications like bleeding or infection. Observe the surgical incision: length, healing status, signs of redness, swelling, discharge, dehiscence. Assess patient's pain level using an appropriate scale (e.g., VAS), provide analgesia as needed. Observe scrotal swelling, measure size changes, assess for complications like scrotal hematoma.

Follow-up Period

1 Week Postoperatively: Via outpatient visit or phone call, inquire about incision healing, presence of pain, itching, etc. Examine incision for dryness, signs of infection (redness, swelling, purulent discharge). Ask about scrotal sensation, persistence of heaviness/pain, and changes in symptom severity.

1 Month Postoperatively: Perform physical examination of scrotum/spermatic cord, compare to preoperative status, assess improvement in symptoms like heaviness/pain. Repeat color Doppler ultrasound to observe left spermatic vein blood flow (diameter reduction, presence/degree of reflux), evaluating treatment efficacy.

3 Months Postoperatively: Repeat physical examination and color Doppler ultrasound, further observing symptom improvement and blood flow changes. Retest serum sex hormone levels, comparing to preoperative and 1-month postoperative results, understanding impact on testicular endocrine function. Collect semen sample for analysis, assessing changes in concentration, motility, morphology, etc., judging improvement in fertility potential.

6 Months Postoperatively: Repeat comprehensive physical examination, color Doppler ultrasound, sex hormone testing, and semen analysis. Detail patient's fertility status (if applicable), understanding successful conception, timing, and process. Comprehensively assess long-term efficacy, including varicocele cure, testicular function recovery, and fertility promotion.

Note: The costs of examinations and follow-up tests during the observation and follow-up periods are to be borne by the participants.
Permitted Concomitant Medications:

Analgesics: Postoperative pain may be managed with analgesics based on severity. Common analgesics include non-steroidal anti-inflammatory drugs (NSAIDs) like Ibuprofen, Diclofenac Sodium, etc.

Medications for Underlying Conditions: Patients may continue medications for pre-existing conditions like hypertension, diabetes, etc.

Prohibited Concomitant Medications:

Other Medications for Varicocele: Drugs potentially affecting spermatic vein blood flow or testicular function, such as Aescin/Horse Chestnut Seed Extract preparations, are not allowed during the study period.

Medications Affecting Sex Hormone Levels: Drugs like androgens, GnRH analogs, etc., other than the surgery itself, are not allowed during the study period.

Medications Affecting Semen Quality: Drugs such as certain chemotherapeutic agents, some psychotropic drugs, etc., are not allowed during the study period.

Specify Evaluation Endpoints/Study Endpoints (Primary, Secondary), Observation Times, Recording and Analysis. Interventional studies include efficacy evaluation, safety evaluation, and comprehensive efficacy evaluation.

- **Primary Endpoints:**
    1. **Improvement in Varicocele:** Assessed by changes in spermatic vein diameter, reflux velocity, and reflux duration measured via color Doppler ultrasound at 1 month, 3 months, and 6 months postoperatively. Compare ultrasound parameters between groups pre- and post-treatment to judge therapeutic efficacy. The experimental group will also measure anastomotic vessel diameter and flow velocity.
    2. **Improvement in Semen Quality (for patients with fertility needs):** Detect routine semen parameters (sperm concentration, sperm motility [progressive %, total %], sperm morphology [normal morphology %], liquefaction time). Analyze semen samples collected

preoperatively, and at 3 months and 6 months postoperatively. Compare the degree of improvement in semen quality between groups to assess the surgery's impact on fertility.

- **Secondary Endpoints:**
    1. **Relief of Scrotal Heaviness/Pain Symptoms:** Use the Visual Analogue Scale (VAS) or other suitable symptom rating scale for patients to subjectively rate the severity of scrotal heaviness, pain, etc. Assess preoperatively, and at 1 week, 1 month, 3 months, and 6 months postoperatively. Observe differences in symptom relief between groups.
    2. **Changes in Testicular Function-Related Sex Hormone Levels:** Detect serum testosterone, FSH, LH levels. Collect blood samples preoperatively, and at 3 months and 6 months postoperatively for testing. Analyze the impact of surgery on testicular endocrine function, compare changes in hormone levels between groups.
    3. **Incidence of Surgery-Related Complications:** Record complications occurring during surgery and postoperatively (e.g., intraoperative bleeding, testicular artery/lymphatic injury, postoperative scrotal hematoma, infection, varicocele recurrence). Record real-time during surgery. During follow-up, detect and record complications via physical exam, ultrasound, etc., noting time of occurrence, type, severity, and management. Compare complication incidence and severity between groups.
    4. **Improvement in Patient Quality of Life:** Use quality of life assessment scales (e.g., SF-36), evaluating multiple dimensions like physical function, psychological status, social function. Survey preoperatively, and at 3 months and 6 months postoperatively. Understand the impact of surgery on QoL, compare differences in QoL improvement between groups.
- **Observation Times**

- **Screening Period:** From patient enrollment to confirmation of eligibility and randomization completion, typically completed within days to weeks, depending on patient visits and test scheduling.
- **Intervention Period:** Surgical treatment phase, from surgery start to patient discharge, generally several days postoperatively, depending on patient recovery.
- **Follow-up Period:** Follow-up assessments at 1 week, 1 month, 3 months, and 6 months postoperatively to observe changes in the above indicators.

- **Recording and Analysis**
  - Establish dedicated research data recording forms. Trained research personnel will be responsible for recording all data.
  - Detailed records of clinical symptom scores, physical exam findings, etc., including specific situations and scores.
  - Color Doppler ultrasound results will be reported by professional ultrasonographers, recording spermatic vein parameter values.
  - Semen analysis and sex hormone test results will be performed by laboratory personnel following standard operating procedures, accurately recording values.
  - Complications will be promptly recorded (time of occurrence, manifestations, management, outcome).
  - Appropriate statistical methods will be used for data analysis.
    - **Quantitative Data (e.g., vein diameter, sperm concentration, hormone levels):** Based on data distribution, use t-tests, ANOVA, etc., to compare differences between groups.
    - **Categorical Data (e.g., complication rate, symptom relief rate):** Use Chi-square test or Fisher's exact test.
    - **Ordinal Data (e.g., symptom scores):** Use rank-sum tests (e.g., Mann-Whitney U) for comparison.
  - Statistical analysis will clarify the differences in efficacy, safety, and comprehensive outcomes between microscopic spermatic vein bypass

surgery and microscopic simple ligation for treating left varicocele, providing a scientific basis for clinical treatment.

- **Efficacy Evaluation:** Primarily based on the primary and secondary endpoints related to disease improvement, fertility enhancement, symptom relief, and testicular function. Compare the therapeutic effect of the two surgical methods on varicocele and their improvement on patient fertility and life aspects.
- **Safety Evaluation:** Based on the incidence of surgery-related complications. Analyze the incidence, severity, and recovery after management of complications in both groups to assess the safety of the two surgical methods.
- **Comprehensive Efficacy Evaluation:** Comprehensively consider the results of efficacy and safety evaluations, combined with factors like patient quality of life improvement, to conduct a holistic assessment of microscopic spermatic vein bypass surgery versus microscopic simple ligation, determining which surgical method is superior.

IV. Statistical Analysis

Use descriptive statistics to understand data distribution. Use t-tests, non-parametric tests, chi-square tests, or Fisher's exact test to compare baseline indicators between groups. For primary and secondary evaluation endpoints, quantitative data will be analyzed using independent samples t-test or non-parametric test based on normality and homogeneity of variance. Pre- and postoperative comparisons within the same group will use paired t-test or paired non-parametric test. Categorical data will use chi-square test. Repeated measures data will use analysis of variance (ANOVA), etc. Survival analysis will be used for outcomes changing over time. Subgroup analysis may be performed between different bypass surgeries. When multiple factors affect the outcome, Cox proportional hazards regression analysis will be used to control for confounding factors and clarify the independent association between surgical method and outcome.

V. Adverse Event Reporting, Handling, and Emergency Plans

1. **Definition of Adverse Event (AE):** Any untoward medical occurrence during the study, whether or not causally related to the research intervention

(microscopic spermatic vein bypass or microscopic simple ligation). This includes, but is not limited to, surgery-related complications, adverse drug reactions, unexpected changes in patient condition, etc.

2. **Expected Adverse Events in the Study**
    - **Surgery-Related Complications:**
        - Intraoperative Bleeding: Vascular injury during surgery affecting procedure and vital signs.
        - Testicular Artery or Lymphatic Injury: Accidental injury during dissection, potentially affecting testicular blood/lymph supply and function.
        - Postoperative Scrotal Hematoma: Bleeding from spermatic vein stumps or surgical area vessels accumulating in the scrotum, causing swelling/pain.
        - Infection: Including surgical site infection, epididymitis, seminal vesiculitis, potentially causing fever, local redness/swelling, increased pain.
        - Varicocele Recurrence: Reappearance of varicocele symptoms and ultrasound findings within the follow-up period.
    - **Adverse Drug Reactions:**
        - Antibiotic-related: Gastrointestinal upset (nausea, vomiting, diarrhea), allergic reactions (rash, pruritus, dyspnea).
        - Analgesic-related: NSAIDs may cause GI irritation, dizziness, drowsiness; weak opioids may cause constipation, respiratory depression.
    - **Other Adverse Events:**
        - Deep Vein Thrombosis (DVT): Prolonged bed rest post-surgery may lead to DVT, presenting as leg swelling, pain, skin color change.
        - Pulmonary Embolism (PE): Embolization of DVT clot to pulmonary artery, causing chest pain, dyspnea, hemoptysis.
3. **Judgment of Causality between AE and Intervention**

- An assessment team consisting of at least two physicians with extensive clinical experience (not involved in the surgery) will judge causality.
- Judgment based on: Temporal relationship between AE and intervention; consistency of AE with known effects of the intervention; improvement of AE upon stopping intervention or specific treatment.
- **Causality Categories:**
  - Definitely Related
  - Probably Related
  - Possibly Related
  - Probably Not Related
  - Not Related
  - Unassessable

4. **Recording, Handling, and Reporting of Adverse Events**
   - **Recording:** Researchers must immediately and accurately record AE details (time, manifestations, severity, actions taken) upon discovery. Records must be complete and timely, signed by the recorder. Include relevant lab data.
   - **Handling:** Take appropriate actions based on AE severity/nature. Mild AEs (e.g., mild GI upset) receive symptomatic treatment (e.g., GI protectants) and close monitoring. Severe AEs (e.g., major intraop bleed, PE) require immediate action (stop surgery if necessary), emergency measures (hemostasis, anti-shock, thrombolysis), and prompt specialist consultation. For ADRs, adjust dose or discontinue drug and treat accordingly.
   - **Reporting:** Report AEs promptly to the principal investigator (PI). **Serious Adverse Events (SAEs)** must be reported to the Institutional Review Board/Ethics Committee (IRB/EC), drug regulatory authorities (if applicable), and relevant institutions **within 24 hours**. Reports must include AE details, causality assessment, actions taken, and current status.

5. **Reporting Method, Handling Measures, Follow-up Method and Time for SAEs**
    - **Reporting Method:**
        - **Verbal Report:** Immediately report basic SAE details (patient name/ID, AE time, main manifestations) to the PI via phone or in person.
        - **Written Report:** Submit a detailed written report within 24 hours of the verbal report. Include full description, diagnostic basis, actions taken, treatment effect, causality judgment, and attach relevant reports/medical records. Submit to IRB/EC, regulatory authorities (if applicable), and relevant institutions.
    - **Handling Measures:** Initiate emergency treatment immediately. Organize expert consultation from relevant departments for optimal treatment. Closely monitor vital signs and condition, adjust treatment as needed. If SAE is possibly related to the intervention, consider pausing the study for further patient assessment/treatment.
    - **Follow-up Method and Time:**
        - **Method:** Outpatient visit, telephone call, inpatient visit as appropriate based on patient condition and AE nature.
        - **Time:** Follow-up at 1 week, 1 month, 3 months, 6 months post-SAE occurrence to assess recovery and sequelae. Increase frequency/extend duration for complex/slow-recovery cases.
6. **Emergency Plans**
    - **Intraoperative Bleeding:** Prepare adequate hemostatic materials/devices pre-op (gauze, vascular sutures, electrocautery). Upon significant bleeding: apply direct pressure, quickly identify source. If difficult to control, temporarily clamp vessels for meticulous hemostasis; consult vascular surgery if needed. Monitor vital signs (BP, HR, Hb); transfuse if necessary.
    - **Testicular Artery/Lymphatic Injury:** Emphasize meticulous protection during surgery. If injury occurs: attempt immediate repair (vascular anastomosis for artery; ligation/repair for lymphatics).

Postoperatively, closely monitor testicular perfusion/function via ultrasound (blood flow), hormone levels; detect/manage impaired function promptly.

- **Postoperative Scrotal Hematoma:** Monitor scrotum closely post-op. If rapid swelling/severe pain occurs, suspect hematoma. Perform immediate ultrasound to assess size/extent. Small hematomas: conservative management (cold compress, hemostatic drugs), close observation. Large or non-resolving hematomas: surgical evacuation, hemostasis, infection prevention.
- **Infection:** Strict aseptic postoperative care. Monitor temperature, incision, scrotum closely. At signs of infection (fever, red/swollen incision, discharge): perform bacterial culture/sensitivity. Start targeted antibiotics based on results; enhance local wound care. Severe infections (epididymitis, seminal vesiculitis): bed rest, scrotal elevation, symptomatic treatment.
- **DVT/PE:** Encourage early ambulation/leg exercises post-op. Use compression stockings/pneumatic devices for DVT prophylaxis if indicated. If leg swelling/pain occurs: perform urgent lower limb venous ultrasound. If DVT confirmed: start anticoagulation (e.g., LMWH); consider thrombolysis/IVC filter based on severity. If chest pain/dyspnea/hemoptysis occur: suspect PE; perform urgent diagnostic tests (e.g., CTPA). If PE confirmed: initiate thrombolysis/anticoagulation immediately; consult pulmonology/critical care.

VI. Quality Control and Quality Assurance

- Regularly calibrate and maintain testing instruments/equipment (color Doppler ultrasound, semen analyzer, biochemical analyzer, etc.). Establish equipment files recording calibration/maintenance times, content, and results. Ensure instruments are in good working order for accurate/reliable data.
- Laboratory testing personnel must possess relevant expertise and skills, undergo strict training, and be certified before performing tests. Organize

regular professional training and academic exchanges to improve skills. Strictly adhere to operating procedures during testing to ensure accuracy and repeatability.

- Develop detailed, clear specifications and procedures for all research stages (patient screening, surgery, perioperative care, follow-up). Ensure researchers have clear guidelines.
- Provide professional training for doctors and researchers on varicocele (diagnosis, treatment principles, surgical techniques). Invite field experts for lectures to enhance expertise.
- Provide ethics training for researchers to understand ethical principles, respect participant rights and privacy. Strictly adhere to ethical requirements throughout the study to ensure legality and morality.
- Before study commencement, thoroughly explain the study's purpose, methods, risks, and benefits to potential participants. Answer questions, address concerns to improve understanding and acceptance.
- Build a good doctor-patient relationship. Researchers should establish good communication and trust, care for participants' physical and mental well-being. Respond promptly to participant needs/questions to enhance satisfaction and compliance.
- Develop a detailed follow-up plan for regular participant follow-up (clinic visits, phone calls). Remind participants of scheduled examinations/treatments to ensure protocol adherence.

VII. Data Safety Monitoring

1. **Data Manager:** Responsible for daily data management and maintenance (data entry, verification, storage, backup). Perform checks/operations per the Data Safety Monitoring Plan (DSMP), promptly record and report issues.
2. **Data Safety Officer:** Overall responsibility for data safety monitoring. Develop/update the DSMP. Review data access permissions. Oversee security of data storage and processing. Investigate and handle data safety issues, reporting promptly to the PI.

3. **Principal Investigator (PI):** Provide overall guidance and supervision for data safety monitoring. Approve high-risk data access permissions. Coordinate resolution of major issues arising during monitoring.

VIII. Reporting Format of Study Results

Study results will be reported in multiple formats:

- **Academic Papers:** Submit to suitable journals in urology, andrology, etc., based on study novelty. Structure: Abstract, Introduction, Methods, Results, Discussion, Conclusion to present the full study and analysis.
- **Academic Conferences:** Present at renowned domestic/international conferences: 15-20 minute oral presentations with slides, or high-quality posters for peer exchange.
- **Clinical Study Report:** Submit to Ethics Committee, Drug Regulatory Agency, funding agencies, etc. Cover study overview, data results, adverse event analysis, conclusions, and recommendations.
- **Patient Report:** Provide understandable brochures, posters, or online documents summarizing the study, interpreting results, and offering guidance/recommendations for patients. Disseminate through multiple channels to provide clinical evidence and promote academic exchange and practical development.

IX. Ethics of Clinical Research

The clinical research will adhere to the World Medical Association's Declaration of Helsinki and other relevant regulations. Before study initiation, the protocol must be approved by the Institutional Review Board/Ethics Committee. Before enrolling each participant, the investigator is responsible for fully and comprehensively explaining the study's purpose, procedures, and potential risks to the participant or their legal guardian, and obtaining written informed consent. Participants must be informed of their right to withdraw from the study at any time. The signed informed consent form shall be retained as a clinical research document. The personal privacy and data confidentiality of participants will be protected throughout the research process.

X. Study Timeline

- **May - June 2025:** Team formation and training, obtain ethics approval, complete online registration, begin patient screening.
- **July 2025 - February 2027:** Patient recruitment, baseline data collection, randomization, surgery implementation, record treatment and recovery.
- **March 2027 - August 2027:** Conduct follow-up per plan, perform clinical observations, laboratory tests, safety assessments, record data.
- **September - October 2027:** Data collation, preliminary statistical analysis, evaluate surgical efficacy, safety, and comprehensive outcomes.
- **November - December 2027:** Write research report, prepare academic paper for submission, prepare conference presentations, submit clinical study report to relevant institutions.

XI. References

1. Minhas S, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC, Cocci A, Corona G, Dimitropoulos K, Gül M et al: European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2021 Update on Male Infertility. European urology 2021, 80(5):603620.
2. Esteves SC, Miyaoka R, Roque M, Agarwal A: Outcome of varicocele repair in men with nonobstructive azoospermia: systematic review and metaanalysis. Asian journal of andrology 2016, 18(2):246253.
3. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. World Health Organization. Fertility and sterility 1992, 57(6):12891293.
4. Gorelick JI, Goldstein M: Loss of fertility in men with varicocele. Fertility and sterility 1993, 59(3):613616.
5. Alsaikhan B, Alrabeeah K, Delouya G, Zini A: Epidemiology of varicocele. Asian journal of andrology 2016, 18(2):179181.
6. Baazeem A, Belzile E, Ciampi A, Dohle G, Jarvi K, Salonia A, Weidner W, Zini A: Varicocele and male factor infertility treatment: a new metaanalysis and review of the role of varicocele repair. European urology 2011, 60(4):796808.
7. Kroese AC, de Lange NM, Collins J, Evers JL: Surgery or embolization for varicoceles in subfertile men. The Cochrane database of systematic reviews 2012, 10:Cd000479.
8. Dou K, Yang Q, Song T, Zeng X, Yao J, Li Y: Microscopic internal spermaticinferior epigastric vein anastomosis for treating left varicocele. International urology and nephrology 2024, 56(10):32693276.
9. Li YT, Yang Q, Yao JC, Lv Q, Liu SQ, Dou K: Microsurgical gonadalinferior

epigastric vein anastomosis to treat the nutcracker phenomenon with left gonadal vein varices with reflux. International urology and nephrology 2020, 52(9):16291635.