Study Protocol and Statistical Analysis Plan

Official Title: Anesthetic Effect of Ropivacaine on Local Infiltration Anesthesia in Arteriovenous Fistula Surgery: a Randomized Controlled Trial

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1.0 PROTOCOL SYNOPSIS

- Title: Anesthetic Effect of Ropivacaine on Local Infiltration Anesthesia in Arteriovenous Fistula Surgery: a Randomized Controlled Trial
- Investigational Site: Lianyungang First People's Hospital
- Study Design: Prospective, double-blind, randomized, parallel-group, active-controlled clinical trial.
- Sample Size: 40 participants scheduled for primary radiocephalic arteriovenous fistula creation.
- Interventions:
  - Experimental Group: 0.375% Ropivacaine (75 mg in 20 mL)
  - Active Comparator Group: 0.67% Lidocaine (100 mg in 15 mL)
- Primary Outcomes: Intraoperative pain scores (Visual Analog Scale, 0-10).
- Study Status: Participant enrollment is completed. The study is active, not recruiting, with ongoing long-term follow-up. Anticipated study completion date is June 2026.

2.0 BACKGROUND AND RATIONALE

Arteriovenous fistula (AVF) is the preferred vascular access for patients with end-stage renal disease requiring hemodialysis. The surgery is commonly performed under local infiltration anesthesia. Lidocaine is a frequently used local anesthetic, but its duration of action is relatively short. Ropivacaine is a long-acting amide local anesthetic known for its sensory-motor blockade separation and lower cardiotoxicity. Theoretically, it may provide more prolonged and stable intraoperative and postoperative analgesia for AVF surgery and potentially improve long-term patency rates by reducing vasospasm. However, high-quality evidence directly comparing ropivacaine to the standard lidocaine in this specific surgical context remains limited. This study aims to systematically evaluate the efficacy and safety of ropivacaine for local infiltration anesthesia in AVF surgery through a rigorously designed randomized controlled trial.

3.0 OBJECTIVES

3.1 Primary Objective: To compare the intraoperative analgesic efficacy of 0.375% ropivacaine versus 0.67% lidocaine for local infiltration anesthesia in radiocephalic arteriovenous fistula creation.

3.2 Secondary Objectives:

- To compare postoperative pain scores at 24 hours between the two groups.
- To compare the operative time between the two groups.

- To assess the need for supplemental anesthesia in both groups.
- To evaluate the incidence of postoperative vasospasm in both groups.
- To compare the surgical success rate and postoperative complications (hematoma, bleeding) between the two groups.
- To assess and compare fistula maturation at 8 weeks postoperatively.
- To assess and compare primary unassisted patency rates at 1 year and 5 years postoperatively.

4.0 STUDY DESIGN

4.1 Overall Design: Single-center, prospective, randomized, double-blind, parallel-group, active-controlled clinical trial.

4.2 Study Flowchart: Screening → Informed Consent → Randomization → Intervention (Group A/B) → Surgery & Intraoperative Assessment → Postoperative Follow-up (24h, 48h, 8 weeks, 1 year, 5 years) → Data Analysis.

4.3 Bias Control: Randomized allocation with allocation concealment to control selection bias; Double-blinding (participants, surgeons, outcome assessors) to control performance and detection bias.

5.0 SUBJECT SELECTION

5.1 Inclusion Criteria:

1. Adult patients (aged ⩾18 years) scheduled for primary radiocephalic arteriovenous fistula creation.
2. Diagnosed with end-stage renal disease requiring hemodialysis.
3. American Society of Anesthesiologists (ASA) physical status I-III.
4. Willing and able to provide written informed consent.

5.2 Exclusion Criteria:

1. History of arteriovenous fistula on the ipsilateral limb.
2. Impaired communication abilities or inability to complete questionnaires due to language barriers, or missing essential data.
3. Preoperative ultrasound findings of:
   - Radial or brachial artery diameter <1.8 mm.
   - Cephalic vein diameter <2 mm at the wrist or <3 mm at the elbow (without tourniquet application).
4. Known allergy to local anesthetics (ropivacaine or lidocaine).
5. Coagulopathy or bleeding disorders.

6. Local infection at the planned anesthesia or surgical site.
7. Severe peripheral neuropathy or neurological disorders affecting upper limb function.
8. Significant thrombosis or severe stenosis in the proximal major veins or central veins of the limb.
9. Pregnancy or breastfeeding.
10. Participation in another clinical trial within 30 days.

6.0 INTERVENTION

6.1 Investigational Product:

- Experimental Group: 0.375% Ropivacaine solution, total volume 20 mL, total dose 75 mg.
- Active Comparator Group: 0.67% Lidocaine solution, total volume 15 mL, total dose 100 mg.
- Study solutions will be prepared by personnel not involved in participant management or outcome assessment to ensure identical appearance.

6.2 Administration: Local infiltration anesthesia will be administered subcutaneously along the planned surgical incision area by the same experienced surgeon using a standardized technique.

6.3 Concomitant Medication/Rescue: If the participant reports intolerable pain (VAS score $\geqslant 7$) during surgery, supplemental local anesthetic may be administered per protocol, and this will be recorded as "Need for supplemental anesthesia."

6.4 Blinding: The randomization code will be kept in sequentially numbered, opaque, sealed envelopes. Group assignment will be blinded to the participants, surgeons, postoperative assessors, and statisticians until database lock or in case of a medical emergency requiring unblinding.

7.0 OUTCOME MEASURES AND ASSESSMENTS

7.1 Primary Outcome Measures:

1. Intraoperative Pain Scores: Assessed using a 10-point Visual Analog Scale (0=no pain, 10=worst pain imaginable) at the end of the procedure.
2. Operative Time: Duration from skin incision to wound closure (minutes).
3. Need for Supplemental Anesthesia: Requirement for additional anesthetic doses due to patient-reported intolerable pain after initial infiltration (Yes/No).
4. Postoperative Pain Scores: Assessed using a 10-point VAS at 24 hours postoperatively.
5. Incidence of Postoperative Vasospasm: Development of arteriovenous fistula tremor reduction or absence within 48 hours postoperatively.

7.2 Secondary Outcome Measures:

6. Surgical Success Rate: Successful creation of a functional arteriovenous fistula (Yes/No).

7. Postoperative Complications: Incidence of hematoma or hemorrhage within 24 hours after surgery.
8. Fistula Maturation at 8 Weeks: Clinical maturation (easily palpable vein with straight segment >10 cm, adequate diameter, and well-palpable thrill) OR ultrasonographic maturation (outflow vein diameter >6 mm, depth <6 mm, and blood flow >500 mL/min).
9. Primary Unassisted Patency at 1 Year: Interval from access creation until first access occlusion or any intervention to maintain or restore patency.
10. Primary Unassisted Patency at 5 Years: Interval from access creation until first access occlusion or any intervention to maintain or restore patency.
7.3 Schedule of Assessments:

Assessment	Baseline	Intra-op	Post-op 24h	Post-op 48h	8 Weeks	1 Year	5 Years
Demographics	✓						
Intra-op VAS		✓					
Operative Time		✓					
Supplemental Anesthesia		✓					
Post-op VAS (24h)			✓				
Vasospasm				✓			
Surgical Success		✓					
Complications (24h)			✓				
Fistula Maturation					✓		
1-Year Patency						✓	

Assessment	Baseline	Intra-op	Post-op 24h	Post-op 48h	8 Weeks	1 Year	5 Years
5-Year Patency							✓

8.0 SAMPLE SIZE CALCULATION

- Parameters: Based on pilot data and literature, the mean intraoperative VAS score in the Lidocaine group is assumed to be 4.0. We anticipate a reduction to 2.5 in the Ropivacaine group (standard deviation 1.5). With a two-sided alpha of 0.05 and power (1-beta) of 80%.
- Formula: Sample size formula for comparing two independent means.
- Calculation: 18 participants per group are required. Accounting for a 10% dropout rate, the total planned sample size is 40 participants.

9.0 RANDOMIZATION AND BLINDING

9.1 Randomization: A computer-generated random number sequence will be used for 1:1 allocation. Block randomization (block size of 4) will be employed to ensure group balance.

9.2 Blinding: Double-blinding will be implemented. The allocation sequence will be concealed. All study solutions will be identical in appearance.

10.0 DATA MANAGEMENT AND QUALITY CONTROL

- Data will be collected using designed electronic Case Report Forms (eCRFs).
- Data entry will be performed independently by two persons, followed by logical checks and consistency verification.
- Standard Operating Procedures (SOPs) will be established and followed. All study personnel will receive uniform protocol training.
- Regular data review meetings will be held.

11.0 STATISTICAL ANALYSIS PLAN

11.1 Analysis Sets:

- Full Analysis Set (FAS): Will include all randomized participants who received at least one dose of the study intervention and have at least one post-baseline efficacy

assessment, analyzed according to the intention-to-treat (ITT) principle.

- Per-Protocol Set (PPS): Participants who complete the study without major protocol deviations.
- Safety Set (SS): All participants who receive at least one dose of the study intervention, used for safety analysis.

11.2 Statistical Methods:

- Descriptive Statistics: Continuous variables will be described as mean ± standard deviation or median (interquartile range). Categorical variables will be described as frequency (percentage).
- Between-Group Comparisons:

  - Continuous variables (e.g., VAS scores, operative time): Independent samples t-test if normally distributed with equal variance; otherwise, Mann-Whitney U test.
  - Categorical variables (e.g., supplemental anesthesia rate, complication rate, patency rate): Chi-square test or Fisher's exact test.

- Survival Analysis: Kaplan-Meier curves will be plotted for 1-year and 5-year patency rates, and groups will be compared using the Log-rank test.
- All statistical analyses will be performed using SPSS Statistics version 26.0. A two-sided p-value < 0.05 will be considered statistically significant.

12.0 ETHICS AND REGULATION

- This study protocol and informed consent form have been submitted to and approved by the Institutional Review Board of Lianyungang First People's Hospital (Approval Number: LW-20241021002-01).
- The study will be conducted in full conformity with the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP).
- Any protocol amendments will be submitted to the IRB for approval.