Comparative Study of Heparin Lock Concentrations and Thrombosis Risk Following PICC Placement in Oncology Patients: Protocol for A Randomized Controlled Study

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Background: *Cancer patients who undergo peripherally inserted central catheter (PICC) placement are predisposed to venous thromboembolism. Variations in the concentration of heparin used for catheter sealing may influence the rate of thrombosis, yet evidence from large randomized controlled trials remains limited. This study aims to compare the incidence of upper-extremity deep venous thrombosis (DVT) among cancer patients receiving three different sealing solutions—physiological saline, 10 U/mL heparin, and 50 U/mL heparin—after PICC insertion.*

Methods: *This is a single-center, single-blind, three-arm randomized controlled trial. A total of 639 adult patients with malignant tumors will be enrolled over a 12-month recruitment period and followed for six months. Participants will be randomly assigned (1:1:1) to receive one of the three sealing liquids through centralized allocation concealment. The primary outcome is the incidence of upper-extremity venous thrombosis. Secondary outcomes include the time to thrombosis onset and the severity of thrombus formation (graded in three levels). Statistical analyses will be performed on an intention-to-treat basis using chi-square tests for incidence comparison, Kaplan–Meier survival analysis with log-rank tests for time-to-event data, and Cox regression modeling to estimate adjusted hazard ratios for significant clinical variables.*

Discussion: *The trial is designed to clarify whether different concentrations of heparin sealing solutions affect the risk of PICC-related thrombosis in patients with cancer. The findings will help inform clinical guidelines regarding optimal catheter maintenance protocols and may contribute to reducing the incidence of catheter-associated thrombotic events in oncology care.*

BACKGROUND

Peripherally inserted central catheters (PICCs) are vascular access devices inserted through peripheral veins such as the basilic, cephalic, or median cubital veins, with the catheter tip positioned in the superior vena cava[1]. Since their introduction to China in the late 1990s, PICCs have been widely utilized for long-term intravenous therapies, including chemotherapy, total parenteral nutrition (TPN), and administration of medications in both adults and preterm infants[2–5]. Compared with other central venous access devices, PICCs are relatively safe; however, their placement still carries the risk of complications such as phlebitis, infection, catheter occlusion, and venous thrombosis[6,7]. PICC-related venous thrombosis is one of the most severe complications, resulting from endothelial injury during catheter insertion, prolonged indwelling time, or the hypercoagulable state of patients, especially those with malignancies[8,9]. The reported incidence of PICC-related deep venous thrombosis (DVT) varies across studies due to differences in

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patient populations, catheter types, and diagnostic methods. Notably, pulmonary embolism secondary to upper extremity DVT occurs in approximately 35% of cases, and the risk among cancer patients is more than twice that observed in the general population, reaching up to 51.4%[10–12]. Major risk factors include patient-specific characteristics, procedural variables, and catheter-related factors[11,13].

Preventing PICC-related thrombosis is therefore a key concern in clinical nursing and vascular access management. Catheter sealing is a critical procedure to maintain catheter patency and prevent occlusion. According to the Intravenous Therapy Technical Practices (China, 2014), catheter maintenance requires regular sealing with either normal saline or heparinized saline, with a volume twice the combined volume of the catheter and extension tube, applied under positive pressure[14]. The recommended heparin concentration ranges from 0 to 10 U/mL for PICC and central venous catheters (CVCs).

Since 2014, our center has used 0.9% normal saline as the sealing solution for patients with cancer and indwelling three-way membrane PICCs, and 10 U/mL heparin saline for patients with open-end PICCs. The incidence of catheter-related thrombosis was found to be as high as 29.17%, leading to prolonged hospitalization and increased treatment costs[15]. Meta-analyses comparing heparinized saline and normal saline have shown that heparin solutions are generally more effective in reducing catheter occlusion and thrombosis[16]; however, the optimal heparin concentration remains uncertain.

Previous studies have suggested that higher concentrations of heparin may provide better thrombosis prevention without significantly increasing bleeding risk. For instance[17] found that sealing with a high-concentration heparin solution (50 mg heparin in 4 mL saline) effectively prevented femoral vein catheter-related DVT without raising hemorrhagic complications. Since cancer patients are in a hypercoagulable state, they are at particularly high risk for thrombosis, yet evidence in this population remains limited.

The current guidelines of the Infusion Nurses Society (INS, 2011) and the Chinese Intravenous Therapy Technical Practice Code (2014) recommend sealing catheters with either 0.9% saline or heparin saline at 10 U/mL[14,18]. However, there is no global consensus, and clinical practice varies widely. Normal saline is considered safe and is often preferred for patients with coagulopathies, liver dysfunction, or bleeding tendencies. Nevertheless, saline lacks intrinsic anticoagulant properties, which may increase the likelihood of thrombus formation[19]. In contrast, heparin possesses potent anticoagulant effects through its interaction with antithrombin III, inhibiting several activated clotting factors and thereby preventing fibrin formation[20]. Despite its benefits, excessive or prolonged heparin use can cause adverse effects such as bleeding or heparin-induced thrombocytopenia (HIT)[21].

Several studies have examined the impact of heparin concentration on catheter patency and thrombosis prevention. Zhang et al. [22] compared three concentrations of heparin (50, 125, 250 U/mL) for sealing in non-cancer patients and observed blockage rates of 70%, 40%, and 15%, respectively. Yu et al. [23] found that a 50 U/mL heparin solution was most effective for maintaining intravenous indwelling needle patency. Xiao et al. [24] compared normal saline and 20 U/mL heparin solution in patients with nasopharyngeal carcinoma, reporting significantly lower thrombosis rates in the heparin group (11.4% vs 48.6%). Zeng et al. [25] conducted a systematic review and confirmed that heparin sealing (10–125 U/mL) was superior to saline in preventing PICC occlusion and thrombosis.

However, findings from Cochrane systematic reviews and other randomized controlled trials have shown conflicting results. Some studies reported no significant differences in infection, patency, or mortality rates between patients using heparinized and non-heparinized saline solutions during CVC maintenance[26–28].

In summary, evidence remains inconsistent across populations and clinical settings, and large-scale randomized controlled trials are lacking, particularly among cancer patients in China. The present study aims to compare the effects of different concentrations of heparinized sealing solutions (0 U/mL, 10 U/mL, and 50 U/mL) on the incidence of PICC-related upper extremity DVT in tumor patients. This randomized, single-blind, controlled trial seeks to provide scientific evidence

for optimizing catheter maintenance and reducing thrombotic complications in oncology care.

MATERIALS AND METHODS

Trial Design

This investigation is a prospective, single-center, single-blinded, randomized, parallel-controlled trial with a 1:1:1 allocation ratio. The objective is to compare the incidence of upper-extremity venous thrombosis among tumor patients receiving PICC catheterization when sealed with three different solutions: 0.9% saline, 10 U/mL heparin saline, and 50 U/mL heparin saline.
The trial protocol adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines and follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) framework. A schematic representation of the study process, including participant enrollment, intervention, and follow-up, is provided in Figure 1 and Supplementary File 1.

Study Hypotheses

The study is designed to test three primary hypotheses:

1. The incidence of thrombosis differs significantly between patients sealed with normal saline and those sealed with 10 U/mL heparin solution.
2. The incidence of thrombosis differs significantly between patients sealed with normal saline and those sealed with 50 U/mL heparin solution.
3. The incidence of thrombosis differs significantly between patients sealed with 10 U/mL and 50 U/mL heparin solutions.

Setting and Participants

The trial will be conducted in the Department of Oncology at Guangzhou First People's Hospital, where 639 cancer patients requiring PICC insertion will be enrolled between July 2017 and June 2018. Participants will be randomized equally into one of the three study groups. Eligible subjects must meet predefined inclusion and exclusion criteria (see Table 1).

Patients who experience serious adverse events or require unplanned catheter removal will be withdrawn. All participants will sign an informed consent form before enrollment, and they retain the right to withdraw at any time.

Ethical Considerations

Written informed consent will be obtained from all participants before inclusion. The study protocol was approved by the Ethics Committee of Guangzhou First People's Hospital and will be conducted in accordance with the Declaration of Helsinki and relevant clinical research regulations.

Outcome Measures

Primary Outcome

The primary endpoint is the incidence of upper-extremity venous thrombosis (UEVT), expressed as a percentage of patients developing thrombosis after PICC placement during the observation period.

- Numerator: Number of confirmed UEVT cases per unit time.
- Denominator: Total number of patients with PICC placement per unit time.

Diagnosis will be confirmed using color Doppler ultrasonography.

Secondary Outcomes

1. Time to Thrombosis: Defined as the interval between PICC insertion and the ultrasound-confirmed diagnosis of thrombosis.
2. Severity of Thrombosis: Classified into three grades according to ultrasonographic findings:
   - Grade I: Small, localized mural or pericatheter thrombus with <30% lumen narrowing and normal blood flow.
   - Grade II: Partial luminal obstruction (31–50%) with moderate echogenic thrombus and reduced flow on Doppler imaging.
   - Grade III: Complete or near-complete venous occlusion (>50%), characterized by extensive thrombus and absent or minimal blood flow on Doppler.

Table 1: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Patients aged over 18 years who voluntarily agreed to participate in the study.	• Patients with severe cognitive impairment unable to cooperate.
• Patients with a histopathological diagnosis of malignancy and scheduled for intravenous chemotherapy.	• Patients who did not provide informed consent.
• Peripherally inserted central catheter (PICC) placement performed by certified intravenous therapy nurses at the First People's Hospital of Guangzhou.	• Patients with severe complications or other serious chronic illnesses.
• Patients who received treatment in the hospital and underwent PICC maintenance in the hospital's catheterization clinic during treatment intervals.	• Patients not followed up in our hospital or lost to follow-up.
	• Patients who developed thrombosis immediately after catheter insertion.
	• Patients with hypercoagulable conditions or those using open-ended PICC catheters.

PICC – Peripherally Inserted Central Catheter

Figure 1:

	Preoperative Eva-			*Postinterention*
Enrollment	T0	T1	T2	T3
Eligibilit y screen	X			
Informed consent *a* 14*s*		X		
10 U/ml heparin solution group			X	
Assessments*			X	
Demographic data		X		
Medical history data		X		X
Laboratory testing		X		X
Image testing		X		X

Timeline for enrollment, interventions, and assesments.
Abbreviations: TO, variables at baseline; T1, Preoperative evaluations; T2, allocation: T3, post-intervention evaluation.
*For detailed information, see the 'data collection and management' section of this protocol.

Adverse Events

Adverse reactions—primarily bleeding and coagulation abnormalities—will be recorded and analyzed across groups. Coagulation indices, including aPTT, PT, Fbg, and TT, will be monitored to assess hemostatic status. Any serious adverse event will be promptly reported to the hospital's ethics committee.

Recruitment, Randomization, and Blinding

A dedicated research nurse will screen eligible patients during routine working hours. Following informed consent, participants will receive a unique study code generated through the SAS randomization module. Allocation will be concealed in sealed, sequentially numbered envelopes managed by the study randomizer.
Participants will be randomly assigned to one of three arms:

1. Group A: Saline sealing (0 U/mL heparin)
2. Group B: 10 U/mL heparin sealing
3. Group C: 50 U/mL heparin sealing

The trial is single-blind—participants will not know which sealing solution they receive. Due to procedural requirements, the research nurses will be aware of the intervention, but the statistical analysts will remain blinded throughout the data analysis phase.

Study Procedure

The trial consists of four consecutive phases:

1. Pre-screening: Identification of eligible cancer patients scheduled for PICC placement.
2. Screening: Verification of inclusion criteria and signing of informed consent (≤ 2 weeks).
3. Intervention: Random assignment to one of the sealing regimens; patients receive weekly or post-infusion sealing as per protocol.
4. Follow-up: Weekly vascular ultrasound for the first month, followed by monthly assessments until catheter removal or study completion.

Final ultrasonography will be conducted one day prior to catheter removal to detect any late thrombus formation.

Interventions

Sealing Procedure

All interventions follow standardized catheter maintenance protocols, differing only in sealing fluid concentration.

- Sealing Frequency: After each infusion and once weekly during intervals.
- Volume of Sealing Solution: Twice the combined volume of the catheter and extension tubing.
- Technique: "Push-stop-push" pulsed flush using 10–20 mL saline to generate turbulence, followed by 5 mL sealing solution under positive pressure (while maintaining 0.5–1 mL residual fluid before syringe withdrawal).

Group-Specific Protocols

- Group A: SAS sequence (Saline–Administer–Saline)
- Group B: SASH sequence (Saline–Administer–Saline–Heparin 10 U/mL)
- Group C: SASH sequence (Saline–Administer–Saline–Heparin 50 U/mL)

PICC Placement and Maintenance

All patients will undergo pre-procedure arm circumference measurement 10 cm above the elbow, and vascular assessment via color Doppler ultrasound.

Catheter insertion will be performed either through the traditional blind method or ultrasound-guided Seldinger technique, using 4 Fr single-lumen three-way valve PICCs or high-pressure single-lumen PICCs (Bard, USA).

Following insertion, catheter tip position will be confirmed by chest radiography. Maintenance includes weekly dressing changes, flushing, and positive-pressure sealing.

Equipment

- Ultrasound Guidance: Sonosite L25 portable Doppler system (5–10 MHz probe).
- Thrombosis Confirmation: Philips IE33 color Doppler ultrasound (10L probe).
- Puncture Kits: MST puncture kit (Bard, USA).

Data Collection and Management

Data will be collected using standardized Case Report Forms (CRFs) and recorded in a secure EpiData database managed by a trained data administrator.

Baseline information includes:

- Demographics: Age, gender, education, occupation, lifestyle, and insurance type.
- Medical History: Diagnosis, comorbidities, thrombosis or surgery history, smoking, radiotherapy/chemotherapy details, and prior central catheterization.
- Laboratory Parameters: WBC, RBC, HGB, PLT, PT, aPTT, FDP, Fbg, D-dimer, glucose, cholesterol, triglycerides, and liver function tests.
- Catheter Data: Puncture site, number of attempts, vessel type, and catheter tip

location.
Follow-up data include ultrasound findings, symptoms, thrombus grade, and catheter dwell time.

Follow-Up Schedule

Participants will be monitored from PICC insertion until removal. The follow-up duration ranges from 6 months to 1.5 years.

- Ultrasound Monitoring: Weekly during the first month, then every four weeks.
- Clinical Assessment: Weekly evaluation of thrombosis symptoms (pain, swelling, erythema, increased arm circumference).

Any patient-reported symptoms will prompt immediate clinical evaluation.

Sample Size Calculation

Based on previous data [11, 15], the estimated incidence of thrombosis is 30–40% in the saline group, 25% in the 10 U/mL group, and 15% in the 50 U/mL group. Assuming an α level of 0.017 (Bonferroni correction) and 80% power, 639 participants (213 per group) are required. This accounts for a 5% dropout rate. The planned sample size provides ≥ 99% power for Hypothesis 2 and 72% for Hypothesis 3. No interim analysis will be performed.

Statistical Analysis

All analyses will follow the intention-to-treat (ITT) principle. Descriptive statistics will summarize baseline variables using mean ± SD or median (IQR) for continuous data and counts (%) for categorical data.

- Between-group comparisons: ANOVA or Kruskal–Wallis tests for continuous variables; Chi-square or Fisher's exact test for categorical data.
- Ordinal data: Kruskal–Wallis and Wilcoxon rank-sum tests.
- Primary endpoint: Incidence of UEVT analyzed by Chi-square test.
- Time-to-event analysis: Kaplan–Meier curves with log-rank tests; Cox regression to estimate hazard ratios adjusted for clinical covariates.

Missing data will not be imputed. No subgroup or interim analyses are planned. A p-value < 0.05 will be considered statistically significant. The statistician performing data analysis will remain blinded to treatment allocation.

DISCUSSION

Peripherally inserted central catheter (PICC) placement has become an essential procedure in oncology for the administration of chemotherapy, parenteral nutrition, and other long-term intravenous therapies. Despite its clinical advantages, catheter-related venous thrombosis remains a major complication that can compromise vascular access, delay treatment, and increase morbidity. Therefore, preventing thrombosis is a central concern in PICC management, particularly in tumor patients who already possess a hypercoagulable state.

Proper catheter sealing is a key nursing intervention to maintain catheter patency and prevent thrombotic occlusion. Previous studies have suggested that the concentration of heparin in the sealing solution might influence thrombus formation; however, clinical practice remains inconsistent, especially in China, where there is no unified guideline regarding optimal heparin concentration. The present randomized controlled trial aims to provide evidence comparing the effects of different heparin concentrations in PICC sealing fluids on thrombosis incidence in cancer patients. Findings from this study are expected to guide clinical decision-making and improve the standardization of PICC maintenance protocols.

This trial is designed to reduce uncertainty in current practice and determine whether higher concentrations of heparin offer additional protection against thrombosis compared with lower concentrations or saline alone. The results will have practical implications for both clinical nursing and hospital infection-control protocols, as optimizing catheter sealing solutions could effectively reduce PICC-related venous complications and improve

patient outcomes.

However, certain limitations must be acknowledged. First, although the sample size is relatively large and sufficient to test the primary hypotheses, the statistical power for detecting differences between the 10 U/mL and 50 U/mL heparin groups was only 72%. A larger multicenter study would be needed to confirm these findings and enhance generalizability. Second, due to the operational nature of the intervention, this trial was conducted as a single-blind study. The nursing staff could not be blinded because of the practical aspects of solution preparation and administration. To minimize potential bias, all research nurses underwent standardized training on PICC maintenance procedures, including flushing, sealing, dressing replacement, and infusion techniques. Each nurse was required to pass competency assessments before participating in the study, ensuring consistent protocol adherence.

Moreover, all procedures were implemented in accordance with the Centers for Disease Control and Prevention (CDC) Guidelines for the Prevention of Intravascular Catheter-Related Infections, ensuring high-quality catheter care throughout the study. Finally, as this is a single-center study, the findings may not fully represent other clinical settings or populations. Future multicenter, large-scale randomized trials are recommended to validate these results and further refine evidence-based standards for PICC maintenance in oncology patients.

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