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Protocol Signature Page

This protocol has been reviewed and confirmed by the principal investigator and the sponsor. The content is authentic, scientifically sound and compliant. Approval is granted to conduct this clinical study in accordance with this protocol.

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1 Study Abstract

This is a single-arm, open-label, prospective interventional clinical study with a self-before-after controlled design and no concurrent parallel control group. All enrolled subjects will receive sequential normal-saline irrigation followed by diluted norepinephrine irrigation during lithotripsy using single-use flexible ureteroscope (su-fURS) combined with negative-pressure ureteral access sheath (NPUAS). Each subject's normal-saline irrigation phase serves as their own baseline control. The hemostatic efficacy and intraoperative safety of norepinephrine-containing irrigation fluid will be evaluated. Four concentration gradients will be compared between groups to identify the optimal clinical irrigation concentration.

The study consists of two phases. **Phase 1** will enroll 15 subjects to verify the hemostatic efficacy and safety of norepinephrine irrigation fluid at 4 mg/3 L. **Phase 2** will include four concentration-gradient groups with 10 subjects per group (40 subjects in total). Dose-effect relationships of 2 mg/3 L, 4 mg/3 L, 6 mg/3 L and 8 mg/3 L will be explored. The optimal concentration will be determined by balancing hemostatic performance and safety. The study will be performed in full compliance with GCP and ethical requirements. All subjects will provide voluntary written informed consent.

Study Design: Single-arm, open-label, self-before-after controlled, prospective, single-center.

Study Population: Patients with upper-urinary-tract stones meeting inclusion-exclusion criteria.

Intervention: Intra-renal-pelvis perfusion of norepinephrine-diluted irrigation fluid at different concentrations intraoperatively.

Primary End-points: Hemoglobin concentration in irrigation fluid, systolic blood pressure (SBP), mean arterial pressure (MAP), heart rate (HR).

Secondary End-points: Safety-related discontinuation proportion (SRD), concomitant medications (CMs), incidence of adverse events (IAEs), Stone clearance rate (SCR).

Total Planned Sample Size: 55 subjects

2 Study Background and Rationale

2.1 Disease Background and Unmet Clinical Need

Urolithiasis is a common urological disorder in China, with a population prevalence of 1.5%-18% and an annual incidence of 150-200 per 100 000 persons; 25 % of

affected patients require hospital admission [1]. Upper-urinary-tract stones carry the most severe complications, including pain, urinary-tract infection and renal insufficiency, and may progress to renal failure in severe cases. The advent of flexible ureteroscopy has transformed the diagnosis and management of urolithiasis [2]. Single-use flexible ureteroscopes (su-fURS) offer superior maximum deflection angles, higher stone-free rates, lower procurement- and maintenance costs, improved pathogen-control profiles, and reduced physical and mental burden on surgeons [3-5]. Meanwhile, the negative-pressure ureteral access sheath (NPUAS) lowers intrarenal-pelvic pressure, evacuates stone fragments and laser-generated heat, improves procedural safety and stone-free rates, and reduces complications such as infection and renal injury related to prolonged operative time [6-8].

su-fURS combined with NPUAS represents a mainstream minimally-invasive procedure for upper-urinary-tract stones. This combination effectively reduces intrarenal-pelvic pressure and improves stone-removal efficiency, and has been recommended in domestic expert consensus, with indications extended to stones ≤3 cm [9]. Nevertheless, this technique has notable clinical limitations. Mucosal injury of the renal pelvis may occur during sheath placement, negative-pressure aspiration and sheath manipulation; laser lithotripsy further aggravates mucosal bleeding, resulting in poor intraoperative visualization. In addition, single-use flexible ureteroscopes have relatively limited image resolution [10]. Intraoperative bleeding substantially reduces stone-removal efficiency, prolongs operative time, and increases risks of infection and residual stones. Safe, simple and effective local hemostatic measures for this setting are currently lacking in clinical practice.

2.2 Pre-clinical and Preliminary Evidence for the Investigational Intervention

Norepinephrine is a potent α-adrenergic agonist that constricts systemic arterioles and venules and enhances platelet adhesion and secretion, thereby exerting local hemostatic effects [11]. Previous clinical studies have demonstrated favorable hemostatic efficacy and low adverse-event rates for diluted norepinephrine-saline irrigation in arthroscopic surgery [12].

Preliminary in-house pilot data indicate minimal systemic absorption of conventional normal-saline irrigation fluid during su-fURS + NPUAS lithotripsy. It is hypothesized that diluted norepinephrine irrigation fluid acts predominantly on local pelvic mucosa with negligible systemic absorption, yielding a manageable impact on systemic hemodynamics and supporting its intraoperative safety profile. To date, no published studies have evaluated the efficacy and safety of norepinephrine-containing irrigation fluid during flexible-ureteroscope lithotripsy; evidence-based guidance for this off-label application is absent.

2.3 Rationale for Single-Arm Self-Controlled Design

This intraoperative exploratory local-intervention study focuses on preliminary assessment of hemostatic efficacy and safety. A self-before-after control eliminates

inter-individual baseline variability and allows reliable estimation of intervention effects with modest sample sizes, offering high efficiency and low-cost performance.

Each subject receives conventional irrigation followed by investigational-drug irrigation within a single operative session. Confounders including surgical manipulation, anesthetic status, stone burden and operative duration remain identical within-subject; within-subject comparability is superior to parallel-group designs.

A concurrent parallel control arm would expose additional patients to surgical trauma and medical risks, conflicting with ethical principles. Self-controlled design avoids expanding sample size and minimizes subject-related burdens and ethical risks.

Single-arm self-before-after controlled designs are widely adopted in analogous domestic exploratory intraoperative-intervention studies; the present design conforms to common industry and ethical practice.

2.4 Domestic and International Research Status

Existing literature supports the clinical value of negative-pressure-sheath-assisted flexible ureteroscopy for lithotripsy. A small number of clinical reports mention norepinephrine-containing irrigation fluid for improving intraoperative hemostasis, yet no systematic studies have been performed in flexible-ureteroscopy settings to assess efficacy, safety or optimal concentration. This study addresses an unmet knowledge gap and may generate standardized, generalizable evidence for local hemostasis during flexible-ureteroscope lithotripsy.

3 Study Objectives and Hypotheses

3.1 Primary Objectives

- To evaluate the hemostatic efficacy of norepinephrine-containing irrigation fluid and characterize its intraoperative hemodynamic safety profile during su-fURS + NPUAS lithotripsy.
- To identify the optimal clinical concentration of norepinephrine-containing irrigation fluid by concentration-gradient comparison, balancing hemostatic performance and hemodynamic safety.

3.2 Secondary Objectives

- To investigate the proportion of participants whose study intervention is prematurely terminated because of safety-related adverse events or safety concerns.
- To quantify the rate of concomitant medication use.
- To calculate intraoperative and postoperative adverse-event rates for comprehensive safety assessment.
- To investigate the effect of norepinephrine-containing irrigation fluid on stone-free rate.

3.3 Study Hypotheses

- **Null Hypothesis (H_0)**: After norepinephrine irrigation, irrigation-fluid hemoglobin concentration shows no statistically significant difference versus normal-saline baseline, and hemodynamic indices change by more than 5 %.
- **Alternative Hypothesis (H_1)**: After norepinephrine irrigation, irrigation-fluid hemoglobin concentration is significantly lower than normal-saline baseline, and hemodynamic indices change by ≤5 %, supporting clinical hemostatic value and acceptable safety.

4 Study Design and Overall Framework

4.1 Core Design Attributes

- **Study Type**: Interventional clinical study
- **Study Design**: Single-arm, open-label, self-before-after controlled, prospective, single-center
- **Study Phase**: Phase I+II
- **Control**: Within-subject baseline control (normal-saline irrigation phase); inter-group parallel comparison for concentration-gradient investigation
- **Study Center**: Department of Urology, Geriatric Hospital of Nanjing Medical University

4.2 Study Phases

- **Screening Phase** (1day pre-operation): Inclusion-exclusion verification and informed-consent acquisition.
- **Intra-operative Baseline Phase**: After surgical initiation, lithotripsy is performed with conventional normal-saline irrigation. Baseline irrigation-fluid samples are collected 3 minutes after surgery commences.
- **Intra-operative Intervention Phase**: Switch to norepinephrine-containing irrigation fluid of target concentration. Surgical manipulation and irrigation flow-rate are kept identical to baseline. Post-intervention irrigation-fluid samples are collected after 3-minute intervention; continuous vital-sign monitoring is performed throughout.
- **Post-operative Follow-up Phase**: Vital-sign monitoring continues within 8 hours post-operation. Final safety assessment is performed before discharge; follow-up concludes if no abnormalities are identified.

5 Study Population, Inclusion and Exclusion Criteria

5.1 Inclusion Criteria (All must be satisfied for enrolment)

- Age 18–75 years of either sex.
- Clinically and radiologically confirmed renal or upper-ureteral stone with operative indication for super flexible ureteroscopic lithotripsy combined with negative pressure ultrasound lithotripsy (su-fURS + NPUAS).
- Subjects with definite surgical indication for upper urinary tract stones, tolerate general anesthesia, and agree to receive the targeted operative procedure.

5.2 Exclusion Criteria (Any single criterion leads to exclusion)

- Diagnosis of non-upper urinary tract stones.
- Intolerance to flexible ureteroscopic surgery.
- Poorly-controlled hypertension with blood pressure greater than 160/100 mmHg.
- History of coronary artery disease.

5.3 Subject Withdrawal and Drop-out Criteria

- Subject voluntarily withdraws informed consent and opts out of the study.
- Significant intraoperative hemodynamic abnormality occurs, prompting investigator-judged termination of study intervention.
- Intraoperative technical failure precludes adequate irrigation and specimen collection.
- Major protocol violation with critical missing data precluding efficacy-safety evaluation.

6 Study Intervention and Operational Specifications

6.1 Investigational Irrigation-Fluid Information

- **Investigational Drug**: Norepinephrine Bitartrate Injection
- **Diluent**: 0.9 % Sodium Chloride Injection (Normal Saline)
- **Concentration Gradients**: 2 mg/3 L, 4 mg/3 L, 6 mg/3 L, 8 mg/3 L
- **Route of Administration**: Intra-renal-pelvic perfusion intraoperatively
- **Mode of Use**: Continuous irrigation through the working channel of the flexible ureteroscope; irrigation flow-rate matches routine clinical practice.

6.2 Standardized Operating Procedures

All subjects receive general anesthesia. After stable anesthesia, ureteral access sheath and flexible ureteroscope are placed to establish operative access.

- **Baseline Phase**: Lithotripsy proceeds with normal-saline irrigation. Irrigation-fluid baseline specimens are collected 3 minutes after surgery starts; vital-signs are concurrently recorded.
- **Intervention Phase**: Switch to norepinephrine-containing irrigation fluid (4 mg/3 L for Phase 1). Surgical maneuvers and irrigation parameters remain identical to baseline. Postintervention specimens are collected after 3-minute intervention; vital-signs are documented.
-**Concentration-gradient Phase**: Subjects are randomized to respective concentration groups and undergo identical above-mentioned procedures.

Emergency Management: If systolic blood pressure increases by＞20% relative to baseline or significant hemodynamic instability emerges requiring pharmacotherapy, the study intervention must be immediately discontinued, and irrigation switched back to normal saline. Anesthesiologists provide symptomatic management.

6.3 Concomitant-medication Rules

- Routine peri-operative baseline medications and intraoperative anesthetic agents may be administered as standard-of-care; drug name, dose and time of administration shall be fully documented.
- Vasodilators, antihypertensives and other symptomatic agents given for intervention-related adverse reactions shall be thoroughly documented for indication, dosage and therapeutic response.
- Additional hemostatic agents are prohibited intraoperatively to avoid confounding efficacy assessment.

7 Study End-points and Evaluation Criteria

7.1 Primary End-points

- **Hemostatic-efficacy outcome**: Hemoglobin concentration in irrigation fluid (quantified as optical-density value at 405 nm wavelength). Differences between pre- and post-intervention are compared.
- **Hemodynamic-safety outcomes**: Changes in systolic blood pressure (SBP), mean arterial pressure (MAP) and heart rate (HR) before-versus-after intervention. A change ≤5 % is defined as not clinically-significant hemodynamic impact.

7.2 Secondary End-points

- Safety-related discontinuation proportion (SRD)
- Proportion of subjects receiving intraoperative concomitant medications (CMs)
- Stone clearance rate (SCR) (Post-operative-day 1)
- Intraoperative and postoperative incidence of adverse events（IAEs）

7.3 Assessment Methods

- **Hemoglobin assay**: Beyotime hemoglobin assay kit (Catalog No. P0381S). Assays are performed strictly by manufacturer instructions; optical density is measured at 405 nm and converted to hemoglobin concentration.
- **AE Grading**: Adverse events are graded 1-5 using Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE 5.0).
- **AE Causality Assessment**: Causality is categorized as definitely unrelated, possibly unrelated, possibly related, probably related, related. Causality is adjudicated comprehensively by investigators.

8 Study Flow, Visits and Schedule of Assessments

Study Phase	Time-point	Assessments and Procedures
Screening Phase	1-day pre-operation	1. Obtain informed consent 2. Medical-history taking and physical examination 3. Laboratory tests: complete blood count,

		liver-renal function, coagulation profile, electrolytes 4. Urinary-tract imaging (CT / Ultrasound) 5. Vital-sign measurement 6. Inclusion-exclusion criterion adjudication
Intra-operative Baseline Phase	0-6 min after surgical start	1. Routine surgery with normal-saline irrigation 2. Collect irrigation-fluid specimens at 3-6 min 3. Continuous SBP / MAP / HR monitoring for ~20 min
Intra-operative Intervention Phase	0-6 min after switching irrigation fluid	1. Maintain identical surgical maneuvers with norepinephrine-containing irrigation fluid 2. Collect irrigation-fluid specimens at 3-6 min 3. Continuous SBP / MAP / HR monitoring for ~20 min 4. Document subjects with safety-driven intervention termination, intraoperative concomitant medications and adverse drug reactions
Post-operative Follow-up	Within 8 h post-operation	1. Vital-sign monitoring every 2 hours 2. Record adverse events
End-of-study Visit	Post-operative Day 1	1. Remeasure vital signs 2. Imaging assessment for stone-free rate 3. Record adverse events, confirm resolution/status of adverse events 4. Adjudicate study completion

9 Sample-size Justification and Calculation

9.1 Phase 1 (Efficacy-validation Phase)

This phase adopts self-before-after controlled design for the primary endpoint of within-subject difference in irrigation-fluid hemoglobin concentration. Paired-t-test sample-size formula is applied：

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 * \sigma^2}{\delta^2}$$

Parameter settings: two-sided α=0.05 ($Z_{\alpha/2}$=1.96); power=90 % (Z_{β}=1.28); clinically-meaningful difference δ=1; standard deviation of differences σ =0.75. The theoretical sample-size is ~13 subjects. Accounting for a 10 % drop-out rate, 15 subjects are planned for Phase 1.

9.2 Phase 2 (Concentration-gradient Optimization Phase)

Four parallel concentration-gradient groups are set; each group uses independent self-before-after comparison. Following conventions for dose-exploratory studies and considering local patient-recruitment capacity, 10 subjects per group (40 total for four groups) are planned, which enables dose-effect-curve plotting and inter-group statistical comparison.

9.3 Total Sample-size

A total of 55 subjects will be enrolled across two phases. A 10 % drop-out margin is reserved to guarantee evaluable sample-size satisfying statistical-analysis requirements.

10 Statistical Analysis Plan

10.1 Definition of Analysis-sets

- **Full-Analysis-Set (FAS)**: All enrolled subjects receiving at least one study intervention. Used for primary efficacy and safety analyses.
- **Per-Protocol-Set (PPS)**: Subjects complying strictly with the protocol without major protocol violations and with complete data. Used for sensitivity analyses.
- **Safety-Analysis-Set (SAS)**: All subjects receiving ≥1 study intervention with available safety data. Applied to all safety-related analyses.

10.2 Efficacy Analysis

- Continuous variables are described as mean ± standard-deviation, median and inter-quartile range. Within-subject pre-post comparisons employ paired t-test; Wilcoxon signed-rank test is used for non-normally-distributed data.
- Categorical variables are presented as counts and percentages. Inter-group comparisons adopt Chi-square test or Fisher’s exact test as appropriate.
- Concentration-hemostasis-effect curves and concentration-hemodynamic-impact curves will be plotted. Optimal concentration will be determined by synthesizing both outcomes.

10.3 Safety Analysis

- Calculate incidence, frequency, severity, causality and outcome of all adverse events and serious adverse events.
- Characterize trends in vital-signs and laboratory parameters; report incidence of clinically-significant abnormal findings.
- Summarize proportion of interventions terminated due to adverse reactions and rate of symptomatic medication use.

10.4 Missing-data Handling

Last-Observation-Carried-Forward (LOCF) will be applied for missing primary-endpoint data. Sensitivity analysis with complete-case analysis will be performed to assess robustness of results.

11 Data Management and Quality Control

- Standardized Case-Report-Forms (CRFs) are completed by uniformly-trained research personnel to ensure truthful, accurate and complete documentation.
- Source documents (operative notes, anesthesia records, laboratory reports, CRFs) are traceable and cross-referenced.

Double is implemented for database construction. Data queries and resolution are completed before database lock for statistical analysis.

- Study-lead personnel conduct periodic monitoring to verify protocol- and GCP-compliance.
- The Ethics Committee performs scheduled continuing review and on-site inspection as required.

12 Ethical Principles and Subject Protection

This study strictly follows the Declaration of Helsinki, Measures for Ethical Review of Research Involving Human Biospecimens and Biomedical Research, and GCP 2020, adhering to the core principles of voluntariness, non-maleficence, justice and confidentiality.

- All subjects provide voluntary informed consent after adequate study-related disclosure. Subjects may withdraw unconditionally at any time without compromising routine clinical care.
- The study protocol and informed-consent documents have obtained approval from the Ethics-Review-Committee of Jiangsu Provincial Government-Run Hospital. Any protocol amendments must receive renewed ethical approval.
- Subjects' personal identifiers and medical records are kept strictly confidential; access is limited to authorized investigators, ethics-committee members and research-administrative authorities. No personal identifiable information will be disclosed in study publications.
- Medical treatment and corresponding compensation will be provided for study-related harm in accordance with national regulations.

13 Safety Monitoring, Adverse Events and SAE Management

13.1 Definition of Adverse Event (AE)

Any untoward medical occurrence experienced by a study subject throughout study participation, regardless of causal relationship to study intervention, must be fully

documented.

13.2 Definition of Serious Adverse Event (SAE)

An event is classified as SAE if any one of the following occurs:
- Subject death.
- Immediate life-threatening condition.
- Hospitalization required or prolongation of existing hospital stay.
- Permanent disability or loss of organ function.
- Other clinically-significant adverse events are approved by investigators.

13.3 Reporting and Management Workflow

- Intraoperative continuous vital-sign monitoring and scheduled post-operative monitoring are performed. Upon AE detection, investigators document the event and assess severity and causality.
- Once an SAE occurs, investigators deliver immediate rescue measures to secure subject safety, and report to the Ethics-Review-Committee and project-management department within 24 hours of SAE awareness.
- All adverse events are followed-up until resolution, clinical stabilization, or until investigators judge no further safety risk exists.

13.4 Key Risk Emergency Management

If subject systolic blood pressure rises ＞ 20% above baseline, norepinephrine irrigation must be halted immediately; irrigation reverts to normal saline. The anesthesiologist administers vasoactive symptomatic therapy according to vital-sign status. Resumption of surgery and study intervention is only considered after hemodynamic stabilization.

14 Risk-Benefit Assessment

14.1 Potential Risks

- Minimal systemic absorption of norepinephrine may induce transient blood-pressure elevation and heart-rate fluctuation.
- Rare local mucosal irritation reactions may occur.

These risks are mostly mild and transient. Continuous professional intraoperative anesthetic monitoring enables timely intervention; overall risks are manageable.

14.2 Potential Benefits

- Subjects may benefit from improved intraoperative hemostasis and surgical visualization, enhanced stone-removal efficiency, and reduced risks of residual stones and repeat surgery.
- Study findings may establish standardized local-hemostasis protocols for flexible-ureteroscope lithotripsy and provide new safe therapeutic options for similar patients, conferring clinical-practice and societal value.

15 Rules for Study Suspension, Termination and Early Completion

The study may be suspended or terminated if any of the following conditions apply:
- Unanticipated serious safety risks emerge such that study benefits are outweighed by potential harm.
- Interim analysis demonstrates lack of efficacy of the investigational intervention; further enrolment lacks scientific rationale.
- Suspension or termination is mandated by the Ethics-Review-Committee or higher-level research-administrative authorities.
- Severe subject-recruitment difficulty prevents achievement of pre-planned sample-size.
- Investigators determine study termination is warranted based on clinical-scientific judgment.

Upon suspension or termination, investigators shall promptly submit a Study Suspension/Termination Report to the ethics committee with rationale and arrange appropriate follow-up care for already-enrolled subjects.

16 Informed-Consent Specifications

- Investigators fully disclose study objectives, procedural workflow, potential risks, expected clinical benefits, alternative-treatment options and subject rights during screening, ensuring full subject comprehension.
- Ethics-committee-approved informed-consent form (Version 2.0, Date 04 March 2025) shall be used. Subjects sign and date the consent document personally.
- Study-specific procedures may only commence after informed-consent signature.
- Major protocol amendments trigger updated informed-consent documents and reconsent from subjects.

17 References

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18 Appendices

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