Clinical Research Protocol

Efficacy and safety study of uradil alone or in combination with esmolol in the treatment of acute hypertensive cerebral haemorrhage: a prospective, observational, observational multicentre study

Study Phases:	Investigator-Initiated Clinical Research
Drug Name:	Urapidil Injection, Esmolol Injection
Clinical Research Institution:	The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital)
Version Number:	V1.6
Version Date:	June 24, 2024

Principal Investigator's Protocol Signature Page

I will diligently fulfill my duties as an investigator in accordance with the regulations of the Chinese GCP. I will personally participate in or directly supervise this clinical research. I am aware of the clinical application and research status of the investigational drug and the research protocol for this clinical study. I agree to perform the relevant duties in compliance with Chinese law, Declaration of Helsinki, Chinese GCP, and this research protocol. Modifications to the protocol will only be made when necessary to protect the safety, rights, and welfare of the research participants, and only after approval by the Ethics Committee. I will be responsible for making clinical medical decisions, ensuring that research participants receive appropriate treatment in a timely manner in the event of adverse events, and recording and reporting these adverse events in accordance with national regulations. I guarantee that the data will be recorded truthfully, accurately, completely, and in a timely manner. I will accept inspections by drug regulatory authorities to ensure the quality of the clinical research. I pledge to keep the personal information of research participants and related matters confidential. I agree to prohibit commercial or economic activities related to this trial. I consent to the publication of the research results. I will provide a copy of the principal investigator's CV to the Ethics Committee before the study begins.

Research Institution: The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital)

Confidentiality Statement

The information contained in this document is confidential and is the property of The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital). This protocol provides relevant information for the purpose of conducting a clinical study by The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital). Researchers may disclose the contents of this protocol to trial participants, institutional review boards, ethics committees, or pharmacy and therapeutics committees for the same purpose, provided that the following conditions are met. The contents of this protocol shall not be used in other clinical studies or disclosed to any other individual or organization without prior written permission from The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital). Although this condition does not apply to disclosures required by law or regulation, researchers must promptly notify The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital) of such disclosures. Additionally, any supplemental information to this protocol is also confidential and the property of The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital). The principles of confidentiality for supplemental information are the same as those for the contents of the protocol and may only be used for purposes authorized by The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital). Disclosure to any other person without prior written permission is prohibited. If you possess this protocol without prior authorization, please

contact The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital) promptly and return the protocol and all copies to the hospital.

Research Institution: The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital)

Principal Investigator's Name / Date:

Compliance Statement

This trial will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and the National Medical Products Administration (NMPA) GCP guidelines for clinical research quality management in China.

The investigators, as well as the staff members of the research institutions responsible for conducting, managing, and supervising the clinical study, must have completed training on the protection of human research participants and GCP.

The study protocol, informed consent forms, recruitment materials, and all related documents will be submitted to the Ethics Committee (EC) for review and approval. Approval of the protocol and informed consent forms must be obtained prior to the enrollment of any research participants. All protocol amendments must be reviewed and approved by the EC before implementation. Furthermore, all changes to the informed consent forms also require EC approval, and it should be determined whether research participants who have signed previously approved versions of the informed consent form need to sign the new version again.

Ethical Statement

1.Compliance with Documents

This trial must be conducted in accordance with the standard operating procedures of each participating hospital and in compliance with the research protocol. The design of the research protocol follows the following documents:

(1)"Measures for the Ethical Review of Human Life-Related Medical Research" (2023)

(2)"Measures for the Ethical Review of Biomedical Research Involving Human Beings" (2016)

(3)WMA's "Declaration of Helsinki" (2013) (Note: Please specify the full title or document number if known)

(4)CIOMS's "International Ethical Guidelines for Biomedical Research Involving Human Subjects" (2002)

(5)Ethical Principles of GCP

(6)"Drug Administration Law of the People's Republic of China"

(7)"Good Clinical Practice Guidelines for Drug Clinical Research"

2.Ethics Committee

Prior to the start of the trial, the investigators must submit the research protocol, informed consent forms, approval documents from relevant authorities, drug inspection reports, and any advertisements for recruiting research participants to the Ethics Committee or an

organization with equivalent authority for review and approval. The written approval should be submitted by the investigators to The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital).

3.Informed Consent Forms

The informed consent forms must be submitted to the relevant Ethics Committee for approval, and each form must include all relevant content.

Before any potential research participant and/or their guardian participates in any activities related to the trial, the benefits and risks of the trial must be fully explained to them. After explaining the basic content of the trial and ensuring that the investigators are confident that each research participant and/or their guardian understands the purpose of the trial, each research participant and/or their guardian should be required to sign and date the informed consent form. The investigators must provide a copy of the signed informed consent form to the research participant and/or their guardian.

Abbreviations

Abbreviations	Full English Names
HICH	Hypertensive intracerebral hemorrhage
HRV	Heart Rate Variability
URA	Urapidil
ANS	Autonomic nervous system
HRS	Heart Rate Variability
ECG	Electrocardiogram
pk	pharmacokinetics
ADR	Adverse drug reaction
CRF	Case report form
CV%	Coefficient of variation
DRQ	Concentrator data ready queue
EC	Ethics committee
GCP	Good clinical practice
h	Hour
IRB	Institutional review board
kg	Kilogram
AE	Adverse event
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspect Severe adverse reaction

Abbreviations	Full English Names
TEAE	Treatment-emergent adverse event

Protocol Summary

1.Overview

Study Title	A Prospective, Open-Label, Observational Multicenter Study on the Efficacy and Safety of Urapidil Alone or in Combination with Esmolol for the Treatment of Acute Hypertensive Intracerebral Hemorrhage
Version Number	Version 1.6, June 24, 2024
Leading Institution	The First Affiliated Hospital of Shandong First Medical University (Shandong Qianfoshan Hospital)
Principal Investigators	
Study Type	Investigator-Initiated Clinical Study
Study Design	Observational Study
Study Drugs	Urapidil, Esmolol
Group Allocation	Urapidil Group Urapidil Combined with Esmolol Group
Route of Administration	Intravenous Infusion via Pump
Objectives	The purpose of this study is to explore the optimal blood pressure management strategy for patients with acute hypertensive intracerebral hemorrhage through a prospective, open-label, observational, multicenter clinical study. We aim to assess the impact of two different blood

	pressure control strategies on patient outcomes and provide scientific evidence to guide clinicians in formulating reasonable treatment plans.
Sample Size	300 patients in each group, totaling 600 patients
Gender	Both male and female participants are eligible
Interventions	None (observational study)
Duration of Treatment	7 days
Follow-up Period	3 months of routine clinical follow-up
Inclusion Criteria	(1) Participants aged 18 to 80 years with acute hypertensive intracerebral hemorrhage; (2) Participants with acute cerebral hemorrhage (basal ganglia hemorrhage < 50ml) confirmed by imaging within 6 hours of onset; (3) Participants with systolic blood pressure > 140 mmHg at admission; (4) Participants who have signed the informed consent form.
Exclusion Criteria	(1) Participants with cerebral hemorrhage who refuse to have their disease management information collected and/or who refuse to undergo follow-up assessments; (2) Participants with allergies to the study drugs; (3) Participants with secondary cerebral hemorrhage due to

	tumors, vascular malformations, aneurysms, trauma, thrombolytic therapy, or cerebral arteriovenous thrombosis; (4) Participants undergoing anticoagulant therapy or with coagulation disorders; (5) Pregnant women; (6) Participants with multiple organ failure; (7) Participants deemed unsuitable for enrollment by the investigators due to other factors.
Primary Endpoint	The rate of poor outcomes on the modified Rankin Scale (mRS) score at 3 months after onset among study participants, to assess whether blood pressure management with urapidil combined with esmolol benefits the participants (poor outcome: scores 4-6).
Secondary Endpoints	Changes in intracerebral hematoma volume among study participants, Heart rate variability, Time taken for blood pressure to reach the target level after administering antihypertensive drugs, mRS score at discharge, In-hospital mortality rate, Mortality rate within 3 months of onset, Adverse events during hospitalization, Incidence of seizures,Relevant complications,Length of hospital stay.

2.Study Flowchart

Screening Period	Treatment and Follow-up Period			
V0 (Informed Consent)	V1 (Treatment Period)	V2 (At Discharge)	V3 (1 Month Follow-up)	V4 (3 Months Follow-up)
Obtain signed informed consent, demographic information, and vital signs, Record concomitant medications taken within the past 2 weeks, Measure height and weight, Inquire about medical history, including past illnesses and treatment history, Document medication diagnosis, Assess	Collect information on medication administration and concomitant medications, Record the time taken from the start of medication administration to the achievement of target blood pressure, Re-evaluate	Prognosis of Participants with Cerebral Hemorrhage (assessed by the Modified Rankin Scale (mRS) Score), Review and assessment of adverse events; If routine laboratory tests such as complete blood count, biochemistry tests (liver and kidney function, blood glucose, blood lipids) are	Prognosis of Participants with Cerebral Hemorrhage (assessed by the Modified Rankin Scale (mRS) Score), Review and assessment of adverse events; If routine laboratory tests such as complete blood count, biochemistry tests (liver and kidney function, blood	Prognosis of Participants with Cerebral Hemorrhage (assessed by the Modified Rankin Scale (mRS) Score), Review and assessment of adverse events; If routine laboratory tests such as complete blood count, biochemistry tests (liver and kidney function, blood

Glasgow Coma Scale (GCS) score, blood pressure, heart rate, and initial CT hematoma size upon admission, Collect information related to surgical procedures, if any, If routine laboratory tests such as complete blood count, biochemistry tests (liver and kidney function, blood glucose, blood lipids), procalcitonin, CRP, and etiological tests are performed clinically, gather relevant information,	intracranial hematoma size, heart rate variability, monitor blood pressure, and assess the incidence of seizures and related complications within 24 hours of admission, Review and evaluate adverse events, Fill out the case report form accordingly.	performed clinically, gather relevant information, Fill out the case report form.	glucose, blood lipids) are performed clinically, gather relevant information, Fill out the case report form.	glucose, blood lipids) are performed clinically, gather relevant information, Fill out the case report form.

Fill out the case report form and other necessary documents.				

3.Study Schedule

Protocol	V0	V1	V2	V3	V4
Informed Consent Form	X				
Demographic	X				
Height	X				
Weight	X				
Medical History	X				
Medication Diagnosis	X				
Complete Blood Count	X		X	X	X
Biochemical Examination	X		X	X	X
Procalcitonin	X		X		
Cranial CT	X	X	X	X	X
Blood Pressure	X	X	X	X	X
Heart Rate Variability	X	X			
Outcome of Intracerebral		X	X	X	X
Concomitant Medication	X	X	X	X	X
Adverse Event Review and	X	X	X	X	X
Case Report Form (CRF)	X	X	X	X	X

*If there are routine clinical tests, collect them.

Main Body of the Proposal

1. Introduction

Hypertensive intracerebral hemorrhage (HICH) is a common and serious condition that poses significant challenges to the medical community due to its complexity and the severity of its outcomes. Over the past few decades, there has been considerable debate regarding blood pressure management strategies for patients with acute hypertensive intracerebral hemorrhage. Both hypertension and hypotension following intracerebral hemorrhage are associated with poor outcomes. Several trials aimed at reducing blood pressure in acute intracerebral hemorrhage patients have demonstrated a correlation between reduced blood pressure and decreased hematoma expansion in patients recruited within 6 hours of symptom onset. Current international guidelines, including those from the European Stroke Organization, the American Heart Association (AHA)/American Stroke Association, and the Canadian Stroke Best Practice Recommendations, advocate for lowering systolic blood pressure (SBP) to 140 mmHg as soon as possible after symptom onset, with a target of maintaining SBP between 130 and 150 mmHg. However, for certain patients, such as those with extremely high post-ICH blood pressure (SBP > 220 mmHg), a more individualized approach is necessary. Notably, patients with extremely high blood pressure (SBP > 220 mmHg) were not included in these trials, and lowering SBP to 140

mmHg in this population may be harmful, with an increased incidence of neurological deterioration and adverse renal events.

Elevated blood pressure (BP) is common in patients with acute spontaneous intracerebral hemorrhage (ICH) and is closely associated with hematoma growth, a significant independent predictor of clinical deterioration and outcomes in ICH patients. Previous studies have shown that hematoma growth predominantly occurs within the first 6 hours following spontaneous intracerebral hemorrhage. Therefore, early blood pressure reduction may help prevent hematoma growth. Research has indicated that ICH patients who achieve target BP sooner after onset are less likely to experience hematoma growth. Specifically, ICH patients who reach the target SBP of <140 mmHg within the first hour after randomization exhibit a lower absolute rate of hematoma enlargement. These findings support the benefit of reducing the time to reach target BP in ICH patients, with hematoma growth primarily attributed to ongoing bleeding and secondary vascular rupture. Hematoma growth predominantly occurs within the first 6 hours following ICH onset, particularly within the initial 2-3 hours, and the frequency of hematoma growth decreases as time progresses.

Autonomic nervous system (ANS) changes have been observed in patients with acute stroke, characterized by impaired cardiovascular regulation and a shift in the balance between sympathetic and parasympathetic activity. Clinically, ANS dysfunction has been associated with poor prognosis, increased mortality, and sudden death following stroke.

Heart rate variability (HRV) and baroreceptor sensitivity (HRS) changes are traditionally considered surrogate markers of cardiovascular ANS regulation. Previous studies on HRV in acute brain injury have primarily focused on ischemic stroke or traumatic brain injury (TBI). In TBI and ischemic stroke, HRV parameters have been shown to be independently associated with outcomes.

Urapidil (URA) is a selective α1-adrenoceptor antagonist and a central nervous system 5-HT1A receptor agonist, with dual peripheral and central antihypertensive effects. The antihypertensive effect of URA is dose-dependent and exhibits individual variability. URA has a self-limiting hypotensive effect, and even at higher doses, severe hypotension does not occur. URA reduces both pre- and afterload on the heart, decreases myocardial oxygen consumption, and increases cardiac output without causing reflex tachycardia or affecting heart rate. Additionally, URA does not increase intracranial pressure or affect cerebral artery hemodynamics, thereby helping to maintain cerebral perfusion pressure. URA also increases renal blood flow, reduces renal vascular resistance, and does not increase pulmonary blood shunt or decrease arterial oxygen partial pressure.

Esmolol is an ultra-short-acting, highly selective β1-adrenoceptor blocker that primarily antagonizes β1 receptors in myocardial cells. By blocking the activity of adrenaline and norepinephrine, it exerts its pharmacological effects. At higher doses, it also blocks β2 receptors in bronchial and vascular smooth muscle. Esmolol lacks intrinsic sympathomimetic activity or membrane-stabilizing effects at therapeutic doses. When

administered intravenously, it takes effect within 60 seconds, and its pharmacological action dissipates within 10-30 minutes after infusion cessation. Electrophysiological studies suggest that esmolol exhibits typical β1 receptor blockade effects, such as reducing heart rate, prolonging the sinus cycle, extending sinus node recovery time, and prolonging the AH interval and anterograde Wenckebach cycle. It also slows conduction in the atrial and ventricular myocardium and cardiac conduction system, extending the refractory period. By blocking sympathetic nerve excitation, esmolol lowers the ventricular fibrillation (VF) threshold.

Participants in studies on acute hypertensive intracerebral hemorrhage often experience increased heart rates and difficulty in controlling blood pressure. Previous studies have indicated that the time taken to lower blood pressure to normal levels and heart rate variability are associated with poor outcomes in study participants. This study aims to evaluate the efficacy of treatment strategies involving urapidil alone and in combination with esmolol for blood pressure reduction and heart rate control in participants with acute intracerebral hemorrhage.

2. Trial Design

2.1 Objectives of the Study

The primary aim of this study is to investigate the efficacy and safety of urapidil monotherapy versus esmolol combination therapy in managing acute hypertensive

intracerebral hemorrhage (HICH) through a prospective, open-label, observational, multicenter clinical trial. The findings will provide guidance for clinicians in developing optimal treatment protocols.

2.2 Endpoint Metrics

2.2.1 Primary Endpoint

The primary endpoint is the unfavorable modified Rankin Scale (mRS) score (≥4) at 3 months post-onset, assessing the benefit of blood pressure control with urapidil and esmolol combination therapy for study participants.

2.2.2 Secondary Endpoints

Changes in intracerebral hematoma volume during the acute phase,Heart rate variability,Time to achieve target blood pressure after initiating antihypertensive medication,mRS score at discharge,In-hospital mortality,Mortality within 3 months post-onset,Adverse events during hospitalization,Incidence of seizures,Related complications,Length of hospital stay

3. Study Design

3.1 Overall Design

1.This study employs a prospective, open-label, observational, multicenter clinical trial design. Participating centers must meet the following criteria:

2.Annual admission of over 100 HICH patients.

3.Availability of an intensive care unit (ICU, NICU not mandatory).

4.Dedicated researchers (with associate professor or higher title) and research coordinators/graduate students for the study.

5.Completion of pre-study training by all participating personnel.

6.Agreement to strictly adhere to the study protocol, collect data during hospitalization, and sign a contractual agreement prior to participant enrollment.

Data collection will occur at the following timepoints: admission, during hospitalization, pre-discharge, 1 month, and 3 months post-onset. If feasible, follow-ups at 6 and 12 months will be requested with participant consent.

3.2 Participating Centers and Principal Investigators

Lead Center:

The First Affiliated Hospital of Shandong First Medical University (Qianfoshan Hospital of Shandong Province)

Sub-centers:

Heze Hospital of Shandong Provincial Hospital, Xiajin County People's Hospital, Shanxian Central Hospital, Caoxian County People's Hospital, Liaocheng Brain Hospital, Liaocheng Second People's Hospital, Linyi People's Hospital, Shandong Provincial Third Hospital, Jining First People's Hospital, Affiliated Hospital of Jining Medical University, Pingyin County People's Hospital, Zhangqiu District People's Hospital, Jinan People's Hospital, Tai'an Central Hospital, The Second Affiliated Hospital of Shandong First Medical University, Zibo Central Hospital, Weifang People's Hospital, Affiliated Hospital of Binzhou Medical

University, Qingdao Municipal Hospital, Yantai Yuhuangding Hospital, Weihai Municipal Hospital, Yiyuan Traditional Chinese Medicine Hospital, Ningyang Traditional Chinese Medicine Hospital, Qingyun County People's Hospital, Dezhou Seventh People's Hospital, Hantai County People's Hospital, Pingyin County Traditional Chinese Medicine Hospital, Yiyuan County People's Hospital

3.3 Roles and Responsibilities in a Multicenter Study

Lead Center:

(1).Initiates study planning, designs the protocol and research flow, incorporating feedback from sub-center PIs to ensure advancement, rationality, and feasibility.

(2).Selects eligible sub-centers, ensuring rigorous selection based on regional representation, number of required centers, and eligibility criteria. Assists in ethics submission and approval.

(3).Executes designated research tasks per the protocol.

(4).Oversees quality control throughout the study, ensuring compliance and data authenticity.

(5).Establishes a data platform for timely data uploads and participant confidentiality.

(6).Analyzes and summarizes study results post-completion.

Sub-centers:

(1).Collaborates with the lead center's PI, offering input on the study design.

(2).Submits and obtains ethics approval with the lead center's assistance.

(3).Conducts designated research tasks per the protocol, adhering to compliance and data authenticity.

(4).Accepts oversight and suggestions from the lead center.

(5).Regularly uploads data as required, maintaining participant confidentiality

3.4 Multicenter Training and Quality Control

Prior to the study's commencement, an initial meeting is conducted to provide uniform training to investigators from all centers, encompassing the study protocol, informed consent procedures, and case report form (CRF) completion. During the study's progression, quality controllers from the lead center regularly conduct quality assurance checks on enrollment progress, medical records, informed consent forms, and CRFs across centers. Upon study completion, data quality controllers review the data, ensuring its accuracy and completeness before submitting it to statistical analysts for analysis as per the study requirements.

3.5 Sample Size Calculation

This study employs a prospective, open-label, observational design, with the primary endpoint being the unfavorable mRS score (≥4) at 3 months post-treatment. Based on guidelines [4] and relevant literature [24], we assume a 38% unfavorable mRS rate for the urapidil and esmolol combination group and a 55% rate for the urapidil monotherapy group. Using PASS software, with the Tests for Two Proportion module, we calculate the required sample size with a one-sided α of 0.05, a power of 0.9, and an anticipated

dropout rate of 20%. The initial sample size calculation yields 183 participants; however, to account for potential losses due to propensity score matching (PSM), the final sample size is determined as 300 participants per group.

3.6 Study Medications and Treatment Protocol

The study medications, urapidil injection and esmolol injection, are routine hospital drugs. Urapidil Injection (Shijiazhuang No. 4 Pharmaceutical Co., Ltd., National Medical Products Administration Approval No. H20233626): An initial bolus of 10 mg is administered intravenously over a slow injection, followed by a 5-minute observation period. The infusion rate is then adjusted based on the patient's blood pressure, generally not exceeding 2 mg/min.

Esmolol Injection (Qilu Pharmaceutical Co., Ltd., National Medical Products Administration Approval No. H19991058): A bolus of 1 mg/kg is administered intravenously within 30 seconds, followed by a maintenance infusion rate adjusted based on blood pressure, not exceeding 300 μg/kg/min.

3.7 Basic Treatment

Standard basic treatments for cerebral hemorrhage include blood pressure management, cerebral edema and intracranial pressure control, hemostasis, sedation and analgesia, respiratory support, maintenance of electrolyte and fluid balance, nutritional support, prevention of complications (such as deep vein thrombosis, lung infections, pressure ulcers), and rehabilitation therapy.

4. Study Population

The recruitment of participants for this study on hypertensive intracerebral hemorrhage will be completed between August 2024 and August 2025.

Recruitment Sites:

The First Affiliated Hospital of Shandong First Medical University (Qianfoshan Hospital of Shandong Province) and its participating sub-centers.

4.1 Inclusion Criteria

Participants eligible for this clinical study must meet all of the following criteria:

(1).Age between 18 and 80 years, with acute hypertensive intracerebral hemorrhage.

(2).Confirmed acute cerebral hemorrhage (basal ganglia hemorrhage < 50 ml) within 6 hours of onset, based on imaging.

(3).Systolic blood pressure > 140 mmHg at admission.

(4).Signed informed consent form.

4.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

(1).Refusal to allow the use of their medical information for research or follow-up.

(2).Allergy to the study medications.

(3).Secondary cerebral hemorrhage due to tumors, vascular malformations, aneurysms, trauma, thrombolytic therapy, or cerebral venous thrombosis.

(4).Current anticoagulation therapy or impaired coagulation function.

(5).Pregnancy.

(6).Multi-organ failure.

(7).Any other factors deemed unsuitable for inclusion by the research team.

5.Study Procedures

Group Allocation: Patients are categorized into two groups based on their actual clinical medication: the Urapidil group and the combined Urapidil and Esmolol group. Propensity score matching (PSM) is applied to adjust for confounding factors such as age and gender, thereby eliminating their potential influence between the two groups. Recruitment and observation of study participants are conducted by designated research doctors and nurses within the project team. Each group is further subdivided into two based on the volume of bleeding (<30ml group, >30ml group).

Treatment Protocol for Abnormal Physiological Indicators: When participants exhibit abnormal physiological indicators, the treatment team formulates the optimal plan based on their expertise, guidelines, and the latest literature. The following objectives serve as guidelines for rapid correction (within 1 hour) and maintenance for 7 days or until early discharge (or death within 7 days).

(1).Blood Pressure Management: Maintain systolic blood pressure at 130-140mmHg for 7 days using Urapidil or a combination of Urapidil and Esmolol.

(2).Intracranial Pressure Reduction: Reduce intracranial pressure through dehydrating therapies like mannitol, strategic positioning, and if necessary, surgical interventions like decompressive craniectomy to prevent cerebral hernia.

(3).Temperature Control: Aim for a body temperature of ≤37.5°C.

(4).Anticoagulation Reversal: Target an INR level of <1.5, corrected through the administration of Vitamin K, Prothrombin Complex Concentrate (PCC), or Fresh Frozen Plasma (FFP).

(5).Blood Sugar Regulation: For non-diabetic participants, maintain blood sugar levels at 6.1-7.8mmol/L; for diabetic participants, 7.8-10.0mmol/L.

5.1 Visit V0 (Screening Phase)

Informed Consent: Participants and their families must voluntarily sign a written informed consent form prior to screening. Only those who meet all inclusion criteria and none of the exclusion criteria are eligible to participate.

Data Collection: Collect demographic information (age, gender, ethnicity), height, weight, medical history, medication history (including prior 2 weeks), GCS score at admission, blood pressure, heart rate, initial CT hematoma size, surgical details, routine laboratory tests (if available: blood count, liver/kidney function, blood sugar, lipids, procalcitonin, CRP, pathogens), and fill out the case report form.

5.2 Visit V1 (Treatment Phase)

Medication Information: Collect data on antihypertensive and concomitant medications, time taken to achieve target blood pressure, and 24-hour post-admission CT scan results for hematoma size.

Heart Rate Variability (HRV) Analysis: Post-target blood pressure achievement, assess HRV using ECG or telemetry, focusing on R-R intervals. Analyze HRV using time-domain and frequency-domain methods to quantify cardiac autonomic activity.

Time-Domain Analysis: Includes metrics like average heart rate (AVHR), standard deviation of NN intervals (SDNN), root mean square of successive differences (RMSSD), percentage of NN intervals differing by >x ms (pNN20/pNN50), and standard deviation of the average NN intervals for each segment (SDANN). Values <100ms indicate reduced HRV, and <50ms significantly reduced, potentially predictive of ventricular arrhythmias.

Frequency-Domain Analysis: Comprises ultra-low, very-low, low, and high-frequency power components, with low frequency related to baroreflex sensitivity and high frequency linked to vagal efferent activity.

Blood Pressure Monitoring: Use automated or manual sphygmomanometers with appropriately sized cuffs on the non-paretic arm. Record blood pressure every 15 minutes for the first hour, then every 6 hours until 24 hours. Continue this every 6 hours until day 7 or discharge.

Complication Monitoring: Record the incidence of seizures and other related complications, review and assess adverse events, and update the case report form.

5.3 Visit V2 (Discharge)

Assess vital signs, prognosis using the modified Rankin Scale (mRS), medication use, adverse events, routine laboratory tests, and update the case report form.

5.4 Visit V3 (1-Month Follow-up)

Repeat assessments of vital signs (including height, weight, blood pressure, heart rate), prognosis (mRS), medication use, adverse events, routine laboratory tests, and update the case report form.

5.5 Visit V4 (3-Month Follow-up)

Three months after treatment, participants will undergo a follow-up visit encompassing the following:

Vital signs assessment (height, weight, blood pressure, heart rate);

Prognosis evaluation of cerebral hemorrhage participants using the modified Rankin Scale (mRS) score;

Collection of medication information;

Review and assessment of adverse events;

Routine laboratory tests, including blood count, liver/kidney function, blood sugar, lipids, procalcitonin, CRP, and pathogen tests (if applicable), with relevant information recorded;

Completion of the case report form.

6. Biological Sample Collection

All routine clinical samples (blood count, liver/kidney function, blood sugar, lipids, procalcitonin, CRP, pathogen tests, etc.) will be collected by clinical physicians or nurses. To minimize pain and discomfort, the source of samples will be determined by the medical team and researchers based on the participants' specific clinical conditions. The sampling protocol will be tailored by clinical staff according to the participants' individual conditions and corresponding treatment plans. Sampling timing can be scheduled and adjusted as per clinical needs.

7. Study Intervention Suspension and Participant Withdrawal/Discontinuation

7.1 Study Intervention Suspension

Should circumstances arise where study members are unable to continue the research, they must notify the principal investigator and the ethics committee, with reasons stated.

7.2 Participant Withdrawal/Discontinuation from the Study

7.2.1 Criteria for Suspension of Trial:

(1).If the investigator determines that continuing the trial would be detrimental to the participant.

(2).If the participant expresses unwillingness to continue the clinical study, requests withdrawal from the study, and withdraws the informed consent.

7.2.2 Criteria for Ending Clinical Study:

(1).Serious safety issues arise during the study, necessitating immediate termination.

(2).The ethics committee requires trial termination following its review.

(3).The health administrative department orders the termination of clinical research for any reason.

(4).The clinical therapeutic effect is found to be inadequate, lacking clinical value.

(5).Significant deviations occur in the study design or implementation, making it difficult to evaluate the therapeutic effect.

8. Study Evaluation

8.1 Efficacy Assessment

8.1.1 Demographic Data Collection

Includes age, weight, height, and ethnicity.

8.1.2 Efficacy Evaluation

The therapeutic effect is assessed based on the change in mRS scores before and after treatment.

8.1.3 Other Clinically Significant Changes from Screening

Monitor and record clinically relevant laboratory indicators such as red blood cell count, hemoglobin, and coagulation during participant follow-ups to assess other significant changes.

8.2 Safety Assessment

From enrollment to 3 months post-treatment, any adverse reactions experienced by participants should be promptly recorded.

9. Adverse Events, Serious Adverse Events, and Safety Risk Management

9.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward and unintended medical occurrence in a patient or clinical study participant administered a medicinal product during a clinical study, which does not necessarily have a causal relationship with the treatment. AEs include clinically significant abnormalities in laboratory test results that may indicate a disease or organ dysfunction. All observed AEs or those voluntarily reported by participants should be recorded in both the source documents and the CRF.

9.1.1 Collection of Adverse Events (AEs)

AEs in clinical studies are collected from the time of the first drug administration to the participants until three months post-treatment. For each AE, details such as the time of occurrence, severity, duration, management measures, and outcome must be described. Furthermore, an assessment of the causal relationship with the study drug and whether it meets the criteria for a serious adverse event (SAE) is conducted. If an SAE criterion is met, it must be recorded and reported following the SAE reporting process.

9.1.2 Criteria for Severity of Adverse Events

When completing the AE form, investigators will use the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to evaluate the intensity of AEs. The grading of event severity is standardized as follows:

Grade 1: Mild; asymptomatic or mild symptoms; only clinical or diagnostic observations; no treatment required.

Grade 2: Moderate; requiring minimal, local, or non-invasive intervention; limitation in age-appropriate instrumental activities of daily living (e.g., cooking, shopping, using the telephone, managing finances).

Grade 3: Severe or medically significant but not immediately life-threatening; resulting in hospitalization or prolongation of hospitalization; disabling; limitation in self-care activities of daily living (e.g., bathing, dressing, eating, toileting, taking medications), not bedridden.

Grade 4: Life-threatening; requiring urgent intervention.

Grade 5: Death related to the AE.

9.1.3 Criteria for Assessing the Relationship Between Adverse Events and Study Drugs

Investigators must assess the potential association between AEs and the study drug or concomitant medications using a five-point scale:

(1).Definitely related: The reaction occurs in a reasonable temporal sequence to drug administration, matches a known reaction type of the suspected drug, resolves upon drug discontinuation, and cannot be explained by the participant's clinical state or other reasons.

(2).Probably related: The reaction occurs in a reasonable temporal sequence, matches a known reaction type, significantly improves upon drug discontinuation, and cannot be explained by the participant's clinical state or other reasons.

(3).Possibly related: The reaction occurs in a reasonable temporal sequence, matches a known reaction type, may improve upon drug discontinuation, but could also be explained by the participant's clinical state or other reasons.

(4).Unlikely related: The reaction's temporal sequence or type does not match well with the suspected drug, does not improve upon drug discontinuation, and could be explained by the participant's clinical state or other reasons that improve with time or resolution.

(5).Definitely unrelated: The reaction's temporal sequence or type does not match the suspected drug, and can be explained by the participant's clinical state or other reasons that improve with time or resolution.

The first three categories are considered adverse reactions to the trial drug, and the incidence of adverse reactions is calculated accordingly.

9.1.4 Follow-up of Adverse Events

1.Treatment-related AEs of any grade should be followed up until:

(1).Resolution or improvement to baseline levels.

(2).Reassessment of the relationship with the study drug determines it to be unrelated, and the investigator confirms no further improvement is expected.

2.Treatment-unrelated AEs should be followed up until:

(1).The investigator confirms no further improvement is expected.

(2).The study database is closed, and no further safety data is collected.

3.Outcomes of AEs:

(1).Resolved without sequelae: Full recovery from the AE with no lasting effects.

(2).Resolved with sequelae: Recovery from the AE with residual effects.

(3).Not resolved: The AE persists.

(4).Death: The participant dies due to the AE. If possible, an autopsy report should be attached to the Case Report Form (CRF).

(5).When further information is unlikely to be obtained (e.g., patient or healthcare provider refuses to provide more information, or evidence suggests maximum efforts have been made but the patient is lost to follow-up).

Note: The end date and final outcome of all AEs must be recorded in the CRF.

4.Treatment Interventions and Measures Related to the Study Drug:

Any interventions for AEs must be recorded in the concomitant therapy section of the CRF, specifying whether they are pharmacological or non-pharmacological.

Record measures taken related to the study drug:

(1).None: No measures related to the study drug were taken.

(2).Interrupt/Adjust: Temporary discontinuation of the study drug, with possible re-initiation upon symptom resolution.

(3).Stop: Permanent discontinuation of the study drug.

9.2 Definition of Serious Adverse Events (SAEs)

Serious Adverse Event (SAE): An adverse event that meets any of the following criteria:

(1).Results in death of the study participant.

(2).Is life-threatening to the study participant.

(3).Requires hospitalization or prolongation of existing hospitalization.

(4).Results in persistent or significant disability/incapacity.

(5).Constitutes a congenital anomaly/birth defect, or is a medical event deemed serious by the investigator.

All SAEs occurring during clinical research must be documented in SAE reporting forms.

9.2.1 Reporting of SAEs

The investigator must complete an SAE report form whenever a study drug-related SAE occurs.

9.2.2 Follow-up of SAEs

1.For SAEs unrelated to treatment: Follow-up should continue until:

(1).Resolution or improvement to baseline levels.

(2).The investigator confirms no further improvement or stability of the SAE.

2.For SAEs related to treatment: Follow-up should continue until:

(1).Resolution or improvement to baseline levels.

(2).The investigator confirms no further improvement or stability of the SAE.

9.2.3 Investigator's Responsibilities in SAE Management

1.Implement necessary and reasonable medical measures to ensure the safety of study participants.

2.Determine the relevance of the SAE to the trial or trial medication.

3.Maintain accurate records and follow-up of SAEs.

4.Report promptly to relevant authorities as required by GCP.

9.3 Definition of Significant Medical Events

Significant medical events are those that, based on appropriate medical and scientific judgment, may not immediately threaten life or result in death or hospitalization but have the potential to harm study participants or require intervention (e.g., medical or surgical) to prevent an SAE.

9.4 Definition of Adverse Reactions (ARs)

Adverse Reaction (AR): A harmful and unintended response to a medicinal product occurring at doses normally used for the prophylaxis, diagnosis, or treatment of a disease, or a manifestation of such a response. It excludes reactions caused by drug abuse, overdose, misuse, or quality issues.

9.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SAEs are subject to review by clinicians. For each death case, a determination must be made whether it is natural or caused by drug-related/non-drug-related SAEs. Drug-related SAEs not included in the trial protocol or product characteristic summary are classified as SUSARs.

9.6 Emergency Response Plan for Cerebral Hemorrhage

(1).Immediate Assessment: The medical team conducts a rapid assessment, including vital signs, neurological signs, and imaging studies (e.g., CT scan if necessary).

(2).Stabilization: Measures are taken to stabilize vital signs, ensure airway patency, administer oxygen therapy or mechanical ventilation, and maintain blood pressure and circulation through intravenous fluids.

(3).Emergency Surgery: If significant cerebral hemorrhage or severe intracranial hypertension occurs, immediate assessment for neurosurgical intervention (e.g., hematoma evacuation, decompressive craniectomy) is conducted.

(4).Postoperative Monitoring: Patients are transferred to the Intensive Care Unit (ICU) for close monitoring and symptomatic treatment.

Section 10. Statistical Methods

10.1 Analysis Sets

(1).Safety Analysis Set (SS): Includes all study participants who were enrolled, received the study drug, and had safety data recorded.

(2).Efficacy Analysis Set (ES): Comprises all study participants who were enrolled, received the study drug, and had pre- and post-treatment efficacy evaluation data.

10.2 General Analysis

Data analysis is performed using SPSS 26.0. Continuous data are summarized using mean, standard deviation, median, minimum, and maximum values. Categorical data are summarized using frequencies and percentages.

(1).For normally distributed continuous variables, the t-test is used to compare groups.

(2).For non-normally distributed variables, the Mann-Whitney U test is applied.

(3).For categorical outcomes, Chi-square or Fisher's exact test is used.

(4).A one-sided α of 0.05 is adopted.

(5).Repeated measures are analyzed using repeated measures ANOVA or generalized estimating equations.

(6).Missing or illogical data can be deleted from analysis.

10.3 Safety Analysis

Safety parameters are summarized and analyzed based on the SS. Adverse events are coded using MedDRA, and summarized by System Organ Class (SOC) and Preferred Term (PT), including incidence rates, drug-related event rates, and SAE rates.

10.4 Efficacy Analysis

The summary and analysis of efficacy parameters will be based on the Efficacy Analysis Set (ES).

11. Data Management

11.1 Data Recording

This study will utilize Case Report Forms (CRFs) for timely, accurate, and complete data collection and management.

11.2 CRF Completion and Modification

(1).Completion: CRF data originates from source documents such as original records and laboratory test reports, and must be consistent with these documents. All observations and

test results specified in the trial protocol must be recorded in the CRF promptly, accurately, completely, clearly, and truthfully, without unauthorized alterations.

(2).Modification: If necessary, corrections to CRF data must be made in accordance with system prompts, detailing the reason for the modification. The EDC system's logical verification process will check the entered data for logical consistency and flag questionable data for review or explanation by the Principal Investigator (PI) or data entry personnel.

11.3 Data Entry

Investigators or dedicated data entry personnel will enter data into a computer system for storage as per the protocol requirements. Data entry personnel will perform checks for completeness and logical consistency of the entered clinical research data.

11.4 Data Cleaning

Quality control personnel will review the data. A final quality control check will be conducted by sampling a portion of the database data. The data quality in the database is considered acceptable if the error rate falls below the specified threshold.

11.5 Data Processing

After data inspection and cleaning, the data will be submitted to statistical analysts for analysis as required.

11.6 Retention of Study Records

In accordance with GCP principles, investigators must retain all detailed source documents

of study participants and record relevant information in the CRF regarding trial progress, medication administration, laboratory test data, safety data, and efficacy assessments. Recorded data must be complete, timely, and clear. Source documents, medical records, etc., should be clear, detailed, and easily identifiable by personnel involved in the clinical study.

11.7 Use of Stored Samples and Data

Data collected during this clinical study will be analyzed and stored by the project leader. Obtaining permission from the project leader to transmit data will be part of the informed consent process. With the consent of the study participant's guardian and approval from the local institutional ethics review committee, biological samples without personal identifiers will be stored with the project leader for the same purposes as the collected data. While maintaining the anonymity of study participant information, code-linked information between stored biological samples and phenotypic data of their source study participants will be provided to the project leader. During the study, study participants may withdraw their informed consent for the storage of their biological samples for other research, but the informed consent for the storage of biological samples cannot be withdrawn after the study's completion.

If the project leader, investigators, or medical institutions intend to publish literature or papers related to this study, they must obtain the consent of the other two parties before publication.

12. Supporting Documents and Operational Considerations

12.1 Regulatory Basis

This clinical study must comply with Good Clinical Practice (GCP), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP), and applicable laws, regulations, and ethical review opinions within the territory of the People's Republic of China.

12.2 Ethics

12.2.1 Ethics Committee Review

The conduct of this trial follows GCP, relevant regulations, and ethical review opinions. Before the trial commences, investigators must submit the trial protocol, informed consent form, study participant recruitment procedures, and other written materials to the ethics committee for review and approval. The project leader can only proceed with the clinical study after receiving the ethics committee's approval. During the trial, any new amendments to the trial protocol, informed consent form, etc., must be reviewed and approved in writing again as per regulations. The completion or early termination of the clinical study must also be reported to the ethics committee.

12.2.2 Informed Consent

Before a study participant enrolls in the clinical study, the investigator or their designated representative will explain the study background, pharmacological characteristics of the investigational product, trial protocol, potential benefits and risks (including known and

foreseeable risks and possible adverse events) to each study participant or their legal guardian. The legal guardian and the study physician must sign and date the informed consent form before the study participant enters the trial (before screening exams).

12.2.3 Confidentiality of Study Participants

The collection and collation of data from study participants involved in this clinical research are limited to the investigation of the pharmacokinetics, tolerability, short-term safety, and usage of the drug. Adequate measures will be taken during the collection and processing of these data to ensure confidentiality and compliance with existing laws and regulations on privacy protection. It is the researcher's responsibility to maintain the anonymity of study participants. Study participants can only be identified in CRFs or other documents using uppercase letters, numbers, and/or codes, not their names. Researchers must record participant codes, names, and home addresses but must keep documents revealing participant identities strictly confidential.

12.3 Study Termination

12.3.1 Investigator-Initiated Trial Termination

The investigator may request to discontinue the trial due to certain circumstances. The investigator must notify study participants, the project leader, and the ethics committee of the termination and provide justification.

12.3.2 Project Leader-Initiated Trial Termination

Reasons for the project leader to request trial termination or suspension at a particular site may include, but are not limited to:

(1).Financial reasons

Administrative reasons

(2).Failure of the investigator to follow the protocol, GCP, etc.

(3).Inability of the investigator to recruit sufficient study participants

(4).Safety concerns

The project leader must notify investigators and the ethics committee in writing and provide justification before terminating the clinical study.

12.4 Quality Control and Assurance

To ensure the quality of the trial, the project leader (First Affiliated Hospital of Shandong First Medical University) and key project researchers will develop the clinical study protocol, relevant contingency plans, and SOPs before the official start of the trial. Relevant researchers participating in the trial will undergo training related to drug clinical research.

13. Confidentiality and Privacy

Researchers, medical institutions, and their personnel must maintain strict confidentiality of any information/data related to the clinical study provided by the project leader and any knowledge/data obtained by medical institutions during the conduct of the clinical study. Without the written permission of the project leader, no research materials or data can be

disclosed to unauthorized third parties. Study participant contact information will be securely stored at each clinical research center for internal use during the study period.

14. Publication of Research Outcomes

It is planned to publish 1-4 academic papers based on the findings of this study.