Clinical Study of the Efficacy and Safety of Analgesia-First Minimal Sedation As an Early Antihypertensive Treatment for Spontaneous Intracerebral Hemorrhage: A Multicenter, Prospective, Randomized, Single-Blinded, Positive Reference Drug-Controlled, Superiority Test Clinical Trial

Protocol No.: N/A

Sponsor: **The Third Affiliated Hospital of Southern Medical University**

Statistics Unit: **Department of Biostatistics, Southern Medical University**

Statistical Analysis Plan

Version No.: 0.1

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Confidentiality Statement

The information contained in this statistical analysis plan is confidential and proprietary to the Third Affiliated Hospital of Southern Medical University. Without the permission of the Third Affiliated Hospital of Southern Medical University, it shall not be revealed, published, or otherwise disclosed.

Version information

Version	Date	Prepared by	Comments/Major Modifications
V0.1	Sep. 30, 2021	Xu Xiaohan	Initial release

SIGNATURE PAGE OF STATISTICS UNIT

I now sign to confirm that I have read this statistical analysis plan (version No. and version date: V0.1/Sep. 30, 2021) in detail and that this statistical analysis plan accurately describes the statistical analysis contents of the clinical trial data. By signing here, I agree to perform statistical analysis following this statistical analysis plan.

Protocol Title	Clinical study of the efficacy and safety of analgesia-first minimal sedation as an early antihypertensive treatment for spontaneous intracerebral hemorrhage
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviations	Full Name
BIS	Bispectral index
CI	Confidence interval
DBP	Diastolic blood pressure
ICP	Intracranial pressure
MAP	Mean arterial pressure
SBP	Systolic blood pressure

1 INTRODUCTION

This statistical analysis plan is jointly developed by the statisticians, the clinical principal investigator, and the sponsor according to the study protocol "Clinical study of the efficacy and safety of analgesia-first minimal sedation as an early antihypertensive treatment for spontaneous intracerebral hemorrhage" (protocol No.: N/A, protocol version No.: V2.0, version date: Jun. 30, 2020), "Case Report Form" (version date: Jun. 30, 2020), "Good Clinical Practice" issued by the National Medical Products Administration of the People's Republic of China, "Guidelines for Plan and Report of Data Management and Statistical Analysis in Drug Clinical Trials" and "Biostatistics Guidelines for Drug Clinical Trials". It specifies the contents and form of the statistical analysis report and will be finalized and approved before the database lock of study data.

2 STUDY OBJECTIVES

2.1 Primary Objective

To validate the efficacy and safety of analgesia-first minimal sedation as an early, rapid, and stable antihypertensive treatment for intracerebral hemorrhage.

2.2 Secondary Objectives

(1) To evaluate the efficacy of analgesia-first minimal sedation to diminish the early hematoma expansion of intracerebral hemorrhage patients and its improvement on the short-term prognosis of hemorrhagic stroke.

(2) To evaluate the effects of analgesia-first minimal sedation on the inflammation level, neurological deterioration, adverse reaction reduction, and maintenance of stable vital signs in patients with intracerebral hemorrhage.

3 STUDY DESIGN

3.1 Overall Design

A multicenter, randomized, single-blinded, positive reference drug-controlled and superiority test design is adopted for the trial.

The subjects will be followed up till day 90 after treatment initiation at the following time points: Before treatment; hourly within 24 h after treatment; and then, once daily till day 7 and at the day when the subject is transferred out of intensive care unit (ICU) if the subject stays in ICU for more than 7 days, or once daily till the subject is transferred out of ICU if the subject stays in ICU for less than 7 days; and on days 28 and 90 after treatment initiation for all subjects. The study design and study flow are shown in Figure 3.1.1 below.

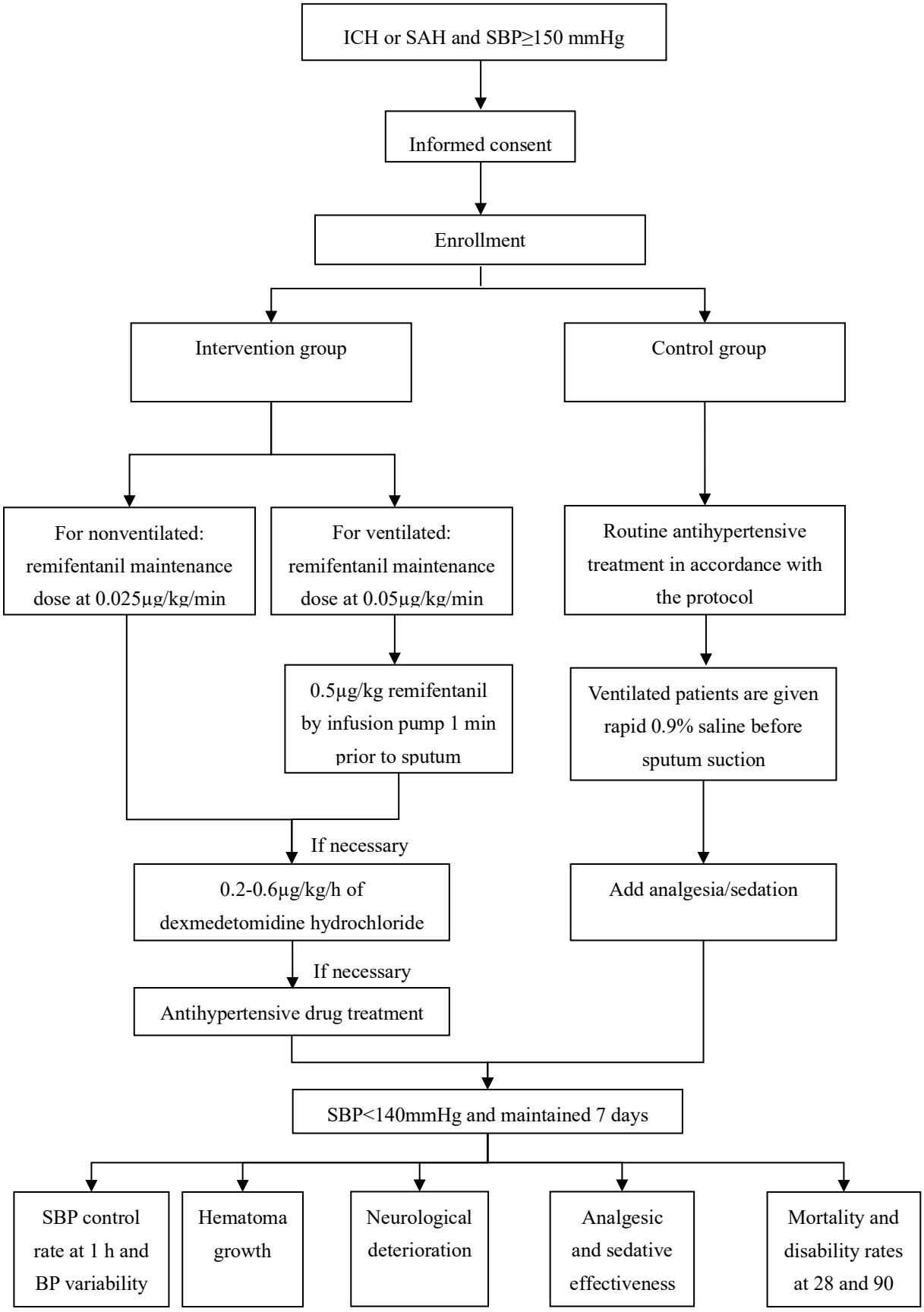

Figure 3.1.1. Schematic diagram of study design

3.2 Grouping and Intervention Plan

The overall objective of antihypertensive treatment is to reduce systolic blood pressure (SBP) to 110 mmHg–140 mmHg within 1 h after treatment initiation and maintain this SBP level for 7 days (or till the subject is discharged from ICU within <7 days).

Analgesia-first minimal sedation group (experimental group): Standard analgesia-first minimal sedation treatment by intravenous infusion; remifentanil + dexmedetomidine (if necessary) + antihypertensive drugs (if necessary); Remifentanil by rapid pump infusion will be given to mechanically ventilated patients before sputum aspiration and rapid analgesic pretreatment is performed for patients with operational pain;

Antihypertensive drug treatment group (control group): Antihypertensive treatment will be intravenously given to subjects with reference to the recommendations in "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage" (2015 edition) and in accordance with their actual conditions, and the antihypertensive drugs, dosing regimens, and dosages are decided by the responsible clinicians; additional analgesic/sedative treatment will be given to the subjects with pain and agitation, and rapid pump infusion pretreatment with normal saline will be performed for mechanically ventilated subjects before sputum aspiration.

The dosing criteria are detailed in section 2.7 of the protocol.

3.3 Statistical Hypothesis

A superiority test is performed in the study using a 1 h blood pressure control rate as the primary assessment indicator. If the experimental group has a statistically higher 1 h blood pressure control rate than the control group, it could be inferred that the experimental group is superior to the control group with regard to early, rapid and stable antihypertensive effect in patients with intracerebral hemorrhage. The statistical hypotheses are as follows:

Null hypothesis (H_0): $\pi_T - \pi_C = 0$ (overall 1 h blood pressure control rates are the same in the two groups);

Alternative hypothesis (H_1): $\pi_T - \pi_C \neq 0$ (overall 1 h blood pressure control rates are different in the two groups).

In which, π_T and π_C represent the 1 h blood pressure control rates in the experimental group and control group, respectively.

3.4 Randomization and Blinding

Randomization: Subjects are randomly grouped using a centralized randomization method. Factors that need to be considered for centralized randomization include: (1) Emergency surgical intervention expected within 24 h (yes, no); (2) Recent use of antiplatelet or anticoagulant drugs (yes, no); (3) Mechanical ventilation in patient at the time of enrollment (yes, no). Centralized randomization of all subjects shall be completed within 2 h after subject inclusion into the study. Centralized randomization is performed using the central randomization system provided by the Department of Biostatistics, Southern Medical University. Investigators log into the system (or call the central randomization voice response system) to apply for treatment for eligible subjects in sequence of the time of eligibility for screening.

Blinding: The study uses a single-blinded design in which only the investigators other than the subjects know the intervention method.

3.5 Study Flow

The study flowchart is detailed in Appendix 1.

4 ASSESSMENT INDICATORS

4.1 Efficacy Assessment Indicators

4.1.1 Primary efficacy measure

1 h SBP control rate. At least two SBP measurements (at an interval of ≥2 minutes) of < 140 mmHg can be diagnosed as SBP control. The SBP control rate is calculated as below:

$$\text{1 h SBP control rate} = \frac{\text{Number of subjects with SBP control within 1 h}}{\text{Number of all subjects}} \times 100\%$$

4.1.2 Secondary efficacy measures

(1) Incidence rate of early (at 24 ± 6 h after treatment) hematoma expansion

Definition of hematoma expansion: Hematoma expansion is defined as (hemorrhage volume after treatment – baseline hemorrhage volume before treatment)/baseline hemorrhage volume before treatment >33%.

(2) Nervous system functional assessment

Nervous system functional assessment methods include the National Institutes of Health Stroke Scale, Glasgow Coma Scale score, Nonverbal Adult Pain Assessment Scale, Richmond Agitation-Sedation Scale, and Reaction Level Scale.

(3) Length of ICU stay

The subject's length of stay in ICU or stroke ward is recorded in hours, and the time less than 1 hour is recorded as 1 hour. At the same time, a summary analysis of indicators in days is provided.

(5) Duration of mechanical ventilation

The subject's duration of mechanical ventilation in ICU or stroke ward is recorded in hours, and the time less than 1 hour is recorded as 1 hour. At the same time, a summary analysis of indicators in days is provided.

(6) Mortality rate within 28 days and 90 days

(7) Modified Rankin scale score

(9) BP variability

Based on the blood pressure measurements of each subject (excluding those before and after sputum aspiration), the mean and standard deviation of SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP) of each subject are calculated. Then the coefficient of variation of each indicator is calculated as standard deviation/mean × 100%, *i.e.*, the variability of blood pressure indicators of each subject.

(10) Variability of BP before and after sputum aspiration

The mean and standard deviation of SBP, DBP, and MAP before and after sputum aspiration of each subject are calculated based on the blood pressure measurements before and after sputum aspiration of each subject. Then the coefficient of variation is calculated as standard deviation/mean × 100%, *i.e.*.

4.2 Safety Indicators

In the study, the safety endpoints include the following:

(1) Adverse event

- Adverse Event: In the study, aside from the expected natural disease exacerbation caused by intracerebral hemorrhage progression (such as organ failure or other complications), as judged by the investigator, any medically diagnosed new disease, exacerbation of pre-existing comorbidity, and other unpredictable medical event after intervention should be considered as an adverse event.

- Serious Adverse Event: It refers to any adverse medical event at any dose that meets one or multiple of the following criteria: 1) Results in death; (2) Is life-threatening (note: the term "life-threatening" is defined as that in the view of the investigator, the patient is at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death); 3) Requires hospitalization or prolongation of existing hospitalization; 4) Results in persistent or significant disability or incapacity; 5) Results in congenital anomaly or birth defect; and 6) Important medical event (an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require medical or surgical intervention as judged by the investigator to prevent one of the outcomes listed above).
- The correlation between an adverse event and the trial intervention will be analyzed following the corresponding judgment criteria, which include 5 categories: "certainly related, highly related, possibly related, possibly related, certainly unrelated". The adverse events judged as "certainly related, highly related, and possibly related" are regarded as related to the trial intervention.
- Adverse events and Serious adverse events are classified as mild, moderate, and severe in terms of severity.

(2) Routine physical examination: Heart rate, blood pressure, body temperature, blood oxygen saturation, respiratory rate

(3) Laboratory examinations

- Hematology: Red blood cells, hemoglobin, white blood cells, hematocrit, and platelets
- Coagulation function: Prothrombin time, activated partial thromboplastin time, D-dimer, and fibrinogen
- Creatinine, serum albumin, and troponin
- Blood biochemistry: Serum urea nitrogen, alanine aminotransferase, aspartate aminotransferase, total bilirubin, N-terminal pro-brain natriuretic peptide, serum creatinine, and blood glucose
- Infection indicator: Procalcitonin and C-reactive protein

5 SAMPLE SIZE

Blood pressure control rate within 1 h after treatment initiation is the primary assessment indicator (qualitative data) of this trial. According to the results of the large-scale clinical study INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial 2 completed in 2013, the 1 h SBP control rate after intensive treatment with antihypertensive drugs was 33.4%. Analgesia and sedation help rapidly lower blood pressure and reduce blood pressure fluctuations, control sympathetic storming, decrease overall stress level, maintain cerebral oxygen balance, lower intracranial pressure (ICP), and alleviate cerebral edema, thereby achieving cerebral protection for intracerebral hemorrhage patients. However, there is a lack of authoritative studies on the correlation between antihypertensive treatment of intracerebral hemorrhage and post-brain injury stress level, cerebral oxygen metabolism and ICP level. Based on past clinical experiences, the 1 h SBP control rate is expected to be 34% and 51% in intracerebral hemorrhage patients who receive antihypertensive drugs and analgesia-first minimal sedation, respectively. A parallel design and two-sided tests with a significance level of 0.05 and a test power of 80% are used in this trial. The sample size is estimated to be 132 subjects in each group using the sample size estimation software nQuery Advisor + nTerim 8.0. Considering a dropout rate of ≤20%, the final confirmed sample size is 165 subjects in each group and 330 subjects in total.

6 INTERIM AND FINAL ANALYSES

Only a final analysis rather than an interim analysis is performed in the study.

7 ANALYSIS DATA SET

(1) **Intent-to-treat Set**: It refers to all patients expressing the intention to receive treatment and signing the informed consent form.

(2) **Modified Intent-to-treat Set**: It is equivalent to the Full Analysis Set and includes all remaining patients after a minimal and reasonable removal procedure from patients that have signed the informed consent, received at least 1 intervention, and had a record of the corresponding efficacy measures. Baseline data analysis is based on Full analysis set, and efficacy analysis is based on the results from Full analysis set analysis.

(3) **Per-protocol Set**: It refers to patients who meet the inclusion criteria, do not meet the exclusion criteria, and have completed the treatment regimen with good adherence. Per-protocol analysis is performed to examine its consistency with the Full analysis set analysis to determine result stability.

(4) **Safety Set**: It refers to all patients who have been randomized, received at least 1 dose of the study drug, and had at least 1 safety assessment record.

Note: The data set names in this statistical analysis plan are adjusted, but their definitions correspond to those in the protocol.

8 STATISTICAL ANALYSIS

8.1 General Principles

8.1.1 General considerations

In the study, statistical analysis is performed using the statistical software SAS 9.4.

The primary study conclusion is based on the intent-to-treat analysis. Demographic and baseline data are analyzed using the Full analysis set. Unless otherwise specified, the analysis of primary and secondary efficacy measures is based on Full analysis set. Safety analysis is based on the Safety analysis set.

Unless otherwise specified, all statistical inferences are performed using the two-sided test, and the test level with statistical significance is set at 0.05. Parametric methods should be used whenever possible. When the data do not meet the requirements of parametric methods, data transformation methods can be applied to make them compliant with the requirements. If they still fail to meet the conditions, non-parametric methods may be considered. P-values for all statistical tests will be rounded up to three decimal places. P-values less than 0.001 are expressed as "<0.001".

For continuous variables, descriptive statistics will include the mean, median, standard deviation, maximum, and minimum; unless otherwise specified, the mean and median will be rounded to 1 more decimal place than what the raw data have, and the standard deviation will be rounded to 1 more decimal place than what the mean has. But all statistics will be rounded to not more than 3 decimal places. For categorical variables, descriptive statistics will include the number of subjects, percentage (rounded to 1 decimal place), and/or number of events. Percentage is not calculated if the number of subject or event is 0. Unless otherwise specified, the denominator for percentage calculation is the total number of subjects in the corresponding group being analyzed.

8.1.2 Multi-center effect

In the study, randomized grouping is performed using the centralized randomization method, and each center enrolls subjects taking two drugs. As the subjects are widely distributed in many centers, the center effect is not considered in statistical modeling.

8.1.3 Covariate considerations

In the multivariate analysis, the following randomization stratification factors are considered to be included in the model: Emergency hematoma removal or neurosurgical intervention is expected within 24 h (yes, no); use of antiplatelet or anticoagulant drugs within the past week (yes, no); mechanical ventilation in patient at the time of enrollment (yes, no).

8.1.4 Multiplicity problem

In the study, there is only one primary efficacy endpoint, i.e., the 1 h SBP control rate, and no multiplicity problem is involved. For the 1 h SBP control rate, a two-sided test at a significance level of 0.05 is performed. For supportive analyses of other endpoints, a two-sided test at a nominal significance level of 0.05 is applied.

8.1.5 Handling of missing data

To facilitate statistical analysis, the missing data may be handled according to the following rules when necessary:

(1) If applicable, laboratory test values will be handled according to the following rules

- Laboratory test values that are recorded as less than (or equal to) or greater than (or equal to) the detection limit (e.g., $<x$, $\leq x$, $>x$ and $\geq x$) will be processed as equal to the detection limit (i.e., $=x$) in the summary of descriptive statistics.
- If the test result is "x1–x2", it will be recorded as the mean of x1 and x2 in the descriptive statistical analysis.
- In case of other special circumstances, for example, "+/-" and "3+" are present, the specific treatment methods will be given in the footnotes.

(2) Missing efficacy and safety data will not be inputted.

8.1.6 Statistical result output

The information on treatment groups in the statistical analysis figures and tables will be displayed based on the description below.

Treatment groups	Information on treatment groups in figures and tables
Experimental group	Experimental group
Control group	Control group

All statistical results are directly outputted from SAS. Templates for figures, tables, and lists can be found in an independent document "Figure and Table Templates". The output templates serve as criteria for standardizing the work of the programmers. There is no need for modification, review and approval of the non-substantial or modifying adjustments to the output templates that do not interfere with the statistical analysis plan.

8.2 Relevant Definitions

8.2.1 Definition of baseline

Definition of baseline for efficacy and safety: Unless otherwise stated, the baseline data are the last non-null measurements before treatment.

8.2.2 Derived data

(1) Age (year) = (date of signing informed consent form - birth date + 1)/365.25, rounded to an integer.

(2) BMI (kg/m^2) = weight/height^2. Where the weight is in kilogram (kg), and the height is in meter (m).

(3) MAP = DBP + 1/3 (systolic blood pressure - diastolic blood pressure).

(4) Coefficient of variation = standard deviation/mean × 100%.

(5) Change in blood pressure before and after sputum aspiration = Blood pressure after sputum aspiration - blood pressure before sputum aspiration.

(6) Change from baseline value = post-treatment measurement - baseline value. If the baseline value is missing and the change from baseline value cannot be calculated, it shall be recorded as missing data.

(7) Percentage of change from baseline value = (post-treatment measurement - baseline value)/baseline value. If the baseline value is missing and the change from baseline value cannot be calculated, it shall be recorded as missing data.

8.3 Demographic and Baseline Characteristics

The analyses of demographic and baseline characteristics is based on Full analysis set, and these characteristics will be summarized by the experimental group, control group, and total.

For continuous variables, the descriptive statistics will include mean, standard deviation, median, P25, P75, maximum, and minimum; for continuous variables, if the quantitative data are in a normal distribution, the two-sample t-test will be used for the inter-group comparison; otherwise, the Wilcoxon rank-sum test based on the t approximation will be applied.

For categorical variables, the descriptive statistics will include the number and percentage of subjects. The categorical data are compared between groups using the Pearson's chi-squared test (χ^2 test) or Fisher's exact test.

8.3.1 Subject disposition

The disposition of all subjects is summarized and analyzed, and the enrollment and randomization, screen failure and its reason, withdrawal from the trial, and trial completion of the subjects are separately summarized. Subjects who withdraw from the trial are summarized according to the primary reasons of their withdrawal from the trial. Meanwhile, the number and percentage of subjects in each analysis population are summarized by the group, and the percentage of subjects is calculated based on the number of cases actually enrolled in each group.

8.3.2 Demographics

The statistical description and inter-group comparison are carried out on the demographics, which includes: Age (year), gender (male, female), ethnicity, height (cm), weight (kg), body mass index (kg/m^2), education level, smoking, and drinking history.

8.3.3 Medical history

The statistical description and inter-group comparison are conducted on the medical history, which includes: History of allergies, previous history of central nervous system disorders, previous history of underlying diseases (intracerebral hemorrhage, ischemic stroke, acute coronary syndrome, and other), concurrent central nervous system disorders, and other concurrent medical conditions [hypertension, diabetes (type I or type II), dyslipidemia, and other).

8.3.4 Pre-treatment head computed tomography examination and other general information

The statistical description and inter-group comparison are performed on pre-treatment head computed tomography examination and other general information, which include: Location of hemorrhage (basal ganglia region, thalamus, cerebral lobe, cerebral ventricular, cerebellum, brainstem, and other), baseline hemorrhage volume (mL), presence or absence of intraventricular hemorrhage, surgical intervention expected within 24 h (yes vs. no), emergency hematoma removal or neurosurgical intervention expected within 24 h (yes vs. no), use of antiplatelet or anticoagulant drugs within the past week (yes vs. no), and mechanical ventilation in patient at the time of enrollment (yes vs. no).

8.3.5 Use of analgesic and sedative antihypertensive drugs

The percentage of patients receiving each drug in two groups, as well as the total amount (mg) of major drugs and duration of medication (h) are summarized by the visit.

The drugs summarized from the experimental group include remifentanil, dexmedetomidine, urapidil, nicardipine, sodium nitroprusside, and oral drugs (amlodipine, benazepril, irbesartan, fosinopril, carvedilol, lercanidipine, losartan, nitrendipine, valsartan, and enalapril). The drugs summarized from the control group include urapidil, nicardipine, sodium nitroprusside, nitroglycerin, propofol, butorphanol, dezocine, fentanyl, midazolam, pentazocine, sufentanil, and oral drugs.

8.4 Efficacy Analyses

The efficacy analysis is based on the Full analysis set, and for the primary efficacy measure, the analysis result is also based on the Per-protocol set analysis.

The statistical significance level is two-sided 0.05.

8.4.1 Primary efficacy measure analysis

8.4.1.1 Primary Analysis

Blood pressure values and their changes from baseline values within 24 h post treatment and on days 2 to 7 in the two groups are summarized by the visit, and the change profiles of blood pressure values and their changes from baseline values are provided.

The primary efficacy measure is the 1 h SBP control rate. The number of cases with 1 h SBP control and the control rate in the experimental group and control group are separately calculated, and their 95% confidence intervals (CIs) are estimated by the Clopper-Pearson method.

The logistic regression analysis is applied for inter-group comparison, taking the reaching of target SBP at 1 h post-treatment initiation as the dependent variable, the groups as the independent variables, and the randomization stratification factors [Emergency hematoma removal or neurosurgical intervention expected within 24 h (yes, no); use of antiplatelet or anticoagulant drugs within the past week (yes, no); mechanical ventilation in patient at the time of enrollment (yes, no)] as covariates for correction. The rate difference between the two groups (experimental group - control group, the same below) is calculated based on the model, and its 95% CI is calculated by the Delta method.

8.4.1.2 Sensitivity analysis

To evaluate the result robustness, the following sensitivity analyses of the 1 h SBP control rate (primary endpoint) will be made:

- **Sensitivity analysis 1:** The Per-protocol set based primary analysis as described in 8.4.1.1, which is repeated to assess the effects of different analysis populations on the results.
- **Sensitivity analysis 2:** The analysis that takes no correction factors into account. The 95% CI of rate difference between the two groups is calculated based on the Newcombe score, and the inter-group comparison is conducted using the Fisher's exact test.

8.4.1.3 Subgroup analysis

To investigate the efficacy consistency of treatments in different subgroup populations, the following subgroup analyses of the 1 h SBP control rate will be performed based on the Full analysis set. It should be noted that the subgroup analysis is exploratory as the statistical power of subgroup populations is not considered in the study design. In addition, considering that the results calculated based on the small subgroups may be unstable and are even likely to cause misinterpretation, if the total number of subjects in a subgroup is < 15 or the number of events is ≤ 3 during the subgroup analysis, the subgroup concerned will not be analyzed.

The following subgroup analyses take no correction factors into consideration. The 95% CI of rate difference between the two groups is calculated based on the Newcombe score, and the inter-group comparison is performed using the Fisher's exact test.

- Age: < 65 years old vs. ≥ 65 years old;
- Baseline systolic blood pressure: ≥ 180 mmHg vs. < 180 mmHg;
- History of hypertension: Yes vs. no;
- Baseline hemorrhage volume: ≥ 30 mL vs. <30 mL;
- Baseline Glasgow Coma Scale score: ≤ 8 points vs. > 8 points;
- Intraventricular hemorrhage at baseline: Yes vs. no;
- Location of hemorrhage: Basal ganglia region, thalamus, cerebral lobe, cerebral ventricular, cerebellum, brainstem, and other.

8.4.2 Secondary efficacy measure analysis

8.4.2.1 24 h blood pressure control rate

The number of cases with 24 h blood pressure control and the control rate in the experimental group and control group are separately calculated, and their 95% CIs are estimated by the Clopper-Pearson method.

The logistic regression analysis is applied for inter-group comparison, taking the reaching of target blood pressure at 24 h post-treatment initiation as the dependent variable, the groups as the independent variables, and the randomization stratification factors [Emergency hematoma removal or neurosurgical intervention expected within 24 h (yes, no); use of antiplatelet or anticoagulant drugs within the past week (yes, no); mechanical ventilation in patient at the time of enrollment (yes, no)] as covariates for correction. The rate difference between the two groups (experimental group - control group, the same below) is calculated based on the model, and its 95% CI is calculated by the Delta method.

The following subgroup analyses are conducted on the 24 h blood pressure control rate without considering the correction factors. The 95% CI of rate difference between the two groups is calculated based on the Newcombe score, and the inter-group comparison is performed using the Fisher's exact test.

- Emergency hematoma removal or neurosurgical intervention expected within 24 h: Yes vs. no;
- Use of antiplatelet or anticoagulant drugs within the past week: Yes vs. no;
- Mechanical ventilation in patient at the time of enrollment: Yes vs. no.

8.4.2.2 Incidence rate of early hematoma expansion

The hemorrhage volume before treatment and at 24 h post treatment, and the changes in hemorrhage volume from baseline within 24 h post treatment are summarized and compared between the two groups.

The number of cases with early hematoma expansion and its incidence rate in the experimental and control groups are separately calculated, and their 95% CIs are estimated by the Clopper-Pearson method. The 95% CI of rate difference between the two groups is calculated based on the Newcombe score, and the inter-group comparison is conducted using the Fisher's exact test.

8.4.2.3 Nervous system functional assessment

The assessment data of nervous system functions are summarized and compared between the two groups by the visit.

Change profiles are provided for National Institute of Health Stroke Scale, Glasgow Coma Scale, Reaction Level Scale, Nonverbal Adult Pain Assessment Scale and Richmond Agitation-Sedation Scale scores.

8.4.2.4 Length of ICU stay

The length of ICU stay (h/day) is summarized and compared between the two groups.

8.4.2.5 Duration of mechanical ventilation

The duration of mechanical ventilation (h/day) is summarized and compared between the two groups.

8.4.2.6 Mortality rates of subjects at 28 and 90 days after hospitalization

Mortality rates of subjects at 28 and 90 days after hospitalization in the experimental group and control group are separately calculated, and their 95% CIs are estimated by the Clopper-Pearson method. The 95% CI of rate difference between the two groups is calculated based on the Newcombe score, and the inter-group comparison is conducted using the Fisher's exact test.

8.4.2.7 Modified Rankin scale score

The modified Rankin Scale scores of the subjects at baseline and 28 and 90 days after hospitalization are summarized and compared between the two groups.

8.4.2.8 BP variability

The SBP variability, DBP variability, and MAP variability are separately summarized and compared between the two groups by the visit.

8.4.2.9 Variability of BP before and after sputum aspiration

The changes in SBP, DBP, and MAP before and after sputum aspiration are separately summarized and compared between the two groups by the visit.

The variabilities of changes in SBP, DBP, and MAP before and after sputum aspiration are separately summarized and compared between the two groups by the visit.

Change profiles are provided for the mean changes of blood pressure before and after the sputum aspiration.

8.5 Safety Analysis

Safety analysis includes adverse events, routine physical examinations, and laboratory examinations. The safety analysis will be based on the Safety analysis set.

8.5.1 Adverse events and serious adverse events

The total number of cases, occurrences and incidence rates of adverse events will be separately summarized by the experimental group and control group.

Drug-related adverse events are defined as adverse event that are "certainly", "highly" and "possibly" related to the study drug as determined by the investigator. If the correlation of an adverse event to the study drug is not determined, the adverse event will be counted as related to the study drug.

The incidence rates of adverse events and serious adverse events in the two groups are compared by the Pearson χ^2 test.

Adverse events will be summarized according to the following categories:

- All adverse events
- Adverse events related to the study drug
- Serious adverse events
- Serious adverse events related to the study drug
- Adverse events leading to withdrawal
- Adverse events leading to withdrawal and related to the study drug
- Severe Adverse events
- Adverse events that are severe and related to the study drug
- Adverse events leading to death
- Adverse events leading to death and related to the study drug

When summarizing adverse events according to correlation, the patients who experienced the same adverse event for more than once but with varying degrees of correlation to the study drug are counted only once in the frequency table, and the maximal correlation of the adverse event is applied.

8.5.2 Routine physical examination

The descriptive statistics are used to summarize the baseline data of routine physical examinations (heart rate, blood pressure, body temperature, blood oxygen saturation, respiratory rate) and the measurement data of all visits after the use of study drug.

8.5.3 Laboratory examinations

The following laboratory examination parameters will be collected:

- Hematology: Red blood cells, hemoglobin, white blood cells, hematocrit, and platelets
- Coagulation function: Prothrombin time, activated partial thromboplastin time, D-dimer, and fibrinogen
- Creatinine, serum albumin, and troponin
- Blood biochemistry: Serum urea nitrogen, alanine aminotransferase, aspartate aminotransferase, total bilirubin, N-terminal pro-brain natriuretic peptide, serum creatinine, and blood glucose
- Infection indicator: Procalcitonin and C-reactive protein

The descriptive statistics are used to summarize the baseline data of laboratory examinations and the measurement data of all visits after the use of study drug, and the cross-classification table is employed to summarize normal/abnormal changes before and after the administration.

9 INSTRUCTIONS FOR STATISTICAL ANALYSIS IN THE PROTOCOL

Not applicable.

10 QUALITY CONTROL

To ensure that the results in the Tables, Figures, and Lists delivered every time are of high standard, the quality control process of the TFL will be defined in the *Quality Control Plan* in detail.

11 APPENDIX

11.1 Appendix 1 Study Flowchart

Stage	Screening Period	Intervention Period				Follow-up Period	
Visits	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time points	Day 0	At 24±6 h	Day2	Day 3	Day4 or later	Day 28	Day 90
Collection of general medical history							
Signing of Informed Consent Form	●						
Medical history	●						
Demographics	●						
Physical examination	●	●					
Qualification of inclusion and exclusion criteria	●	●					
Efficacy observation							
Duration of reaching target SBP		●	●	●	●		
Blood pressure value		●	●	●	●		
Early hematoma expansion		●					
Neurologic assessment		●	●	●	●		
Duration of mechanical ventilation					●		
Length of ICU stay					●		
Monitoring of regional cerebral oxygen saturation		●	●	●	●		
BIS monitoring		●	●	●	●		
Mortality and disability rates at 28 days						●	
Mortality/disability rates at 90 days							●

Stage	Screening Period	Intervention Period				Follow-up Period	
Visits	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time points	Day 0	At 24±6 h	Day2	Day 3	Day4 or later	Day 28	Day 90
Safety observation							
Physical examination		●	●	●	●		
Brain natriuretic peptide (pg/mL)		●	●	●	●		
C-reactive protein (mg/L)		●	●	●	●		
White blood cell count (×10^9/L)		●	●	●	●		
D-dimer (μg/L)		●	●	●	●		
Fibrinogen (g/L)		●	●	●	●		
Total bilirubin (μmol/L)		●	●	●	●		
Alanine transaminase (U/L)		●	●	●	●		
Aspartate aminotransferase (U/L)		●	●	●	●		
Blood urea nitrogen (mmol/L)		●	●	●	●		
Creatinine (μmol/L)		●	●	●	●		
Blood glucose (mmol/L)		●	●	●	●		
Documentation of Adverse event							
Drugs side effects		●	●	●	●		
Procedure related side effects		●	●	●	●		
Complications during ICU stay		●	●	●	●		
Causes of ICU death		●	●	●	●		
Other work							
Concomitant medication		●	●	●	●		

Stage	Screening Period	Intervention Period				Follow-up Period	
Visits	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time points	Day 0	At 24±6 h	Day2	Day 3	Day4 or later	Day 28	Day 90
Daily drug use		●	●	●	●		
Total drug use		●	●	●	●		