# 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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**Privacy Statement:**

The information contained in this study protocol is provided only for the review of the project investigator, the ethics committee, and relevant agencies. disclosure of any information to third parties unrelated to the study is strictly prohibited without the approval of the Principal Investigator.

**Study protocol abstract**

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| **Title** | Clinical study of the efficacy and safety of analgesia-first minimal sedation as an early antihypertensive treatment for spontaneous intracerebral hemorrhage |
| **Sponsor** | Hong Yang |
| **Primary research institution** | The Third Affiliated Hospital of Southern Medical University |
| **Research center** | Seventeen national hospitals are involved in this study: The Third Affiliated Hospital of Southern Medical University, Xuanwu Hospital Capital Medical University, Qilu Hospital of Shandong University, First Affiliated Hospital of Kuming Medical University, The First Affiliated Hospital of Xinjiang Medical University, Xinqiao Hospital of Army Medical University, Henan Provincial People's Hospital, The Second Hospital University of South China, The Second People's Hospital of Shenzhen, The People's Hospital of Guangxi Zhuang Autonomous Region, Zhongshan People's Hospital, The First Hospital of Lanzhou University, The First Affiliated Hospital of HuNan University of Medicine, Guangdong 999 Brain Hospital, MaoMing People's Hospital, The Fifth Affiliated Hospital of Southern Medical University, The Fifth Affiliated Hospital Sun-yet sen University. |
| **Study objectives** | (1) **Primary study objective:** To validate the efficacy and safety of analgesia-first minimal sedation as an early and rapid antihypertensive treatment for intracerebral hemorrhage patients compared with conventional antihypertensive treatment.<br>(2) **Secondary study objective:** 1) To evaluate the efficacy of analgesia-first minimal sedation in the control of early hematoma expansion in intracerebral hemorrhage and in the improvement of short-term prognosis of intracerebral hemorrhage patients compared with antihypertensive drugs; 2) To evaluate the superiority of analgesia-first minimal sedation in healthcare worker satisfaction. |
| **Study hypothesis** | (1) The analgesia-first minimal sedation strategy relies on the remifentanil-mediated alleviation of pain-induced stress response and the antisympathetic activity of dexmedetomidine to restore the elevated BP to normal level in patients with intracerebral hemorrhage. This |

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| | strategy allows rapid stabilization of blood pressure, and its use as a pre-treatment for patients on mechanical ventilation prior to painful procedures reduces blood pressure variability and thereby results in etiologic treatment. It is more effective in blood pressure control than conventional symptomatic antihypertensive treatment;<br>(2) 1) The analgesic and antisympathetic effects of the analgesia-first minimal sedation strategy effectively stablizes blood pressure, controls factors that affect early hematoma expansion, reduces the incidence of early hematoma expansion and improves prognosis; 2) Precise dose control of analgesic and sedative allows the patient to be awaken at any time and observations of pupil reflex and consciousness. This strategy significantly reduces the frequency of assessment and dose adjustment by healthcare workers, lowers their workload, increases patient adherence, and improves healthcare worker satisfaction. |
| **Study design** | A multicenter, prospective, randomized, single-blinded, positive reference drug-controlled, superiority clinical trial |
| **Subject population** | **Inclusion criteria:** (1) Definitive diagnosis of intracerebral hemorrhage induced acute brain injury by computed tomography; (2) Persistent increase in systolic blood pressure (Systolic blood pressure≥150 mmHg); (3) >18 years old; (4) Feasible for emergency antihypertensive treatment and real-time monitoring; (5) Time of disease onset and intensive care unit admission within 24 h.<br>**Exclusion criteria:** (1) Contraindications for intensified antihypertensive therapy (such as known serious carotid stenosis and uncontrolled heart failure); (2) Secondary intracranial tumors, abnormal coagulation or hemolytic intracerebral hemorrhage; (3) History of ischemic stroke within 30 days prior to onset; (4) Subject benefits little from any of the interventions in the study due to the presence of known disease or condition as determined by the chief physician (such as the presence of dementia or disability); (5) Allergy to opioids; (6) Comorbidity that interferes with trial results; (7) Presence of serious untreated arrhythmia; (8) Pregnant or lactating; (9) Currently participating in other drug study or clinical trial, or unwilling to provide informed consent. |

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| **Diagnostic criteria** | Diagnosis of intracerebral hemorrhage is performed based on the 2010 Diagnostic criteria for spontaneous intracerebral hemorrhage in adults. Diagnosis of early hematoma expansion in intracerebral hemorrhage is performed based on the diagnostic criteria of Kazui et al. |
| **Sample size** | Early blood pressure control rate is the primary efficacy measure of this trial. We expect that the 1h blood pressure control rate is 34% among intracerebral hemorrhage patients who receive antihypertensive drug, and 51% among those who receive analgesia-first antihypertensive therapy. Two-tailed tests with significance level of 0.05 and test power of 80% as well as a parallel design are used in this trial. Sample size is estimated to be 132 subjects per group using the nQuery Advisor + nTerim 4.0, with <20% drop out rate. The final confirmed sample size is 165 subjects per group, and 330 subjects in total. |
| **Randomization** | Subjects are randomly grouped using a centralized randomization method. Factors that need to be considered for centralized randomization include: (1) Emergency hematoma removal or neurosurgical intervention is expected within 24h (yes, no); (2) Use of antiplatelet or anticoagulant drugs within the past week (yes, no); (3) Mechanical ventilation in patient at time of enrollment (yes, no). |
| **Blinding** | This study uses a single-blinded design in which only the investigators and not the subjects know the method of intervention. |
| **Intervention** | The overall treatment goal is to reduce systolic blood pressure < 140 mmHg within 1h of treatment initiation and to maintain this systolic blood pressure level for 7 days.<br>**Intervention group:** all enrolled subjects are given standard analgesia-first minimal sedation treatment. Drugs are administered by intravenous infusion; Remifentanil + dexmedetomidine + antihypertensive drug (when necessary); Patients on mechanical ventilation are given remifentanil by infusion pump as rapid analgesia pre-treatment for operational pain prior to sputum aspiration;<br>**Control group:** all enrolled subjects are given the routine antihypertensive treatment. Antihypertensive drug, treatment protocol and dose are selected by the responsible clinician. |

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| **Efficacy measures** | (1) **Primary measures:** Blood pressure control rate at 1h post-treatment initiation. (2) **Secondary measures:** 1) Incidence rate of early (within 24 ± 6h of receiving treatment) hematoma expansion; 2) Blood pressure variability; 3) Neurologic function; 4) Length of intensive care unit stay; 5) Length of mechanical ventilation; 6) Mortality and disability rate at 28 and 90 days. |
| **Safety indicators** | (1) Routine physical examination and key vital sign examination;<br>(2) Laboratory examinations: inflammatory markers, other biomarkers, coagulation markers, liver and kidney functions, blood glucose, and blood oxygen saturation;<br>(3) Adverse events and serious adverse events. |
| **Follow-up** | Subjects were followed up until they were transferred out or discharged from intensive care unit (longest until day 28 in intensive care unit). Follow-up time points include before treatment, and 1d, 2d, 3d, 4d, 5d, 6d, 7d or later after treatment (until transferred out or discharged from intensive care unit). All subjects will be followed up 28 and 90 days after initiation of treatment. |
| **Superiority test** | A superiority test is performed in this study in which a significantly higher blood pressure control rate within 1 h of treatment in the experimental group than in the control group indicates superior treatment efficacy in the experimental group. |
| **Statistical methods** | **Statistical hypothesis:**<br>$H_0$: $\pi_T - \pi_C = 0$ (1h Blood pressure control rate is generally consistent between the two groups);<br>$H_1$: $\pi_T - \pi_C \neq 0$ (1h Blood pressure control rate is different between the two groups).<br>**Statistical analysis:** One-hour Blood pressure control rate is the primary efficacy measure in this study. Since it is a quantitative variable, the Pearson $\chi^2$ test is used for inter-group comparison. For secondary efficacy endpoints, qualitative variable is compared using the Pearson $\chi^2$ test, ordinal variable is compared using the Kruskall-Wallis test, and quantitative variable is compared using two sample t-test or the corresponding non-parametric tests. Logistic regression is used when considering other confounding factors; center effect is assessed by the |

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| | CMH test; subgroup analysis may also be performed on factors that affect outcome variables by comparing primary and secondary efficacy endpoints between subgroups. |
| **Expected progress** | 2017.12-2018.12 Completion and publication of study protocol;<br>2018.01-2021.01 Collection and registration of clinical cases at each research center, blood sample collection and testing, and participation in academic conference;<br>2021.02-2021.12 Data processing and statistical analysis, check and fill in missing data, mid-term summary of study;<br>2022.01-2022.06 Continued clinical subject collection and data processing;<br>2022.07-2022.12 Data processing and analysis, research report writing, and result verification meeting. |

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# 1. Research background and objectives

## 1.1 Research background

Hemorrhagic stroke is due to bleeding into the brain by the rupture of a blood vessel. Hemorrhagic stroke may be further subdivided into intracerebral hemorrhage and subarachnoid hemorrhage [1]. It has the characteristics of high incidence, high morbidity and high mortality, the incidence is around 12% to 15% of cases per 1,00,000 per year, higher in Asia and low-income and middle-income countries. The case fatality rate ranges from 25–48%, is relatively low in high-income countries [1, 2]. Cerebral amyloid angiopathy is a known cause of hemorrhage stroke, advanced age, male gender, Asian race, excessive alcohol consumption and smoking are well-accepted risk factors [1, 2]. Intracerebral hemorrhage accounts for 25-55% of brain stroke in Asian countries, and 10-15% of European and American countries. The 1-month mortality rate of intracerebral hemorrhage patients is as high as 35-62%, and about 80% of surviving intracerebral hemorrhage patients are still disabled after 6 months. Hemorrhagic stroke is one of the major causes of death and disability [3], and a serious medical and financial burden among Chinese residents [4]. Early hematoma expansion is a major cause of neurologic degeneration and poor clinical prognosis in intracerebral hemorrhage patients [5-7]. The incidence rate of hematoma expansion is 18-36% within 3h of intracerebral hemorrhage onset [5], and 13-32% within 6h of intracerebral hemorrhage onset [8]. Hematoma expansion occurs less frequently at 6-24 h, and rarely beyond 24 h after onset. Hematoma volume increase at the original sites is still present in some patients few days or even 2 weeks after disease onset. This is known as rehemorrhage [9, 10]. Increased blood pressure or "hypertension" has already been confirmed as a risk factor of intracerebral hemorrhage development and poor prognosis. Several large observational studies have demonstrated that blood pressure is positively correlated with intracerebral hemorrhage development, and hypertension results in higher risk of intracerebral hemorrhage than ischemic stroke [11, 12]. A systematic review has shown that a 10mmHg increment in systolic blood pressure (SBP) causes a 42% increase in the risk of intracerebral hemorrhage. In addition, blood pressure is also positively correlated with the risk of recurrent stroke [11]. About 90% intracerebral hemorrhage patients have increased blood pressure that usually occurs immediately after disease onset [13-15]. Although most patients display spontaneous decrease in blood pressure, a large proportion of patients still maintain an elevated blood pressure over time [13, 14]. A previous observational study showed that blood pressure

elevation in intracerebral hemorrhage is clearly associated with the prognosis of death or disability [16]. Blood pressure elevation in the acute phase of intracerebral hemorrhage is associated with poor prognosis, and its mechanism of action includes the local increase of initial hemorrhage and early hematoma expansion at hemorrhagic sites [17-22], and the increased risk of early recurrent hemorrhage, serious cerebral edema [23, 24], and recurrent stroke [25]. Blood pressure affects intracerebral hemorrhage prognosis the most within the few hours following disease onset because this is the time when hematoma expansion is most likely to occur [26, 27]. Antihypertensive treatment is equally as important during the subacute phase because the increase in brain tissue volume caused by intracerebral hemorrhage induced cerebral edema few days after onset increases the risk of early recurrent stroke [26, 27].

The dramatic increase in BP after intracerebral hemorrhage [28] is the major cause of hematoma expansion and the major factor that affects patient prognosis [29-32]. Past studies have demonstrated that antihypertensive treatment during the acute phase of intracerebral hemorrhage can lower the chance of nervous system disease exacerbation and hematoma expansion [33, 34], indicating that early antihypertensive treatment is necessary. The intracerebral hemorrhage Acutely Decreasing Arterial Pressure Trial [35] showed that perihematoma cerebral blood flow and oxygen supply are not affected by blood pressure, suggesting that intensified antihypertensive treatment in the acute phase of intracerebral hemorrhage has no effect on cerebral perfusion and perihematoma edema, and is thereby a safe treatment in the acute phase of intracerebral hemorrhage. The "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage" published in 2015 in Stroke [36] recommended early antihypertensive treatment and clearly stated that rapid decrease of blood pressure to 140 mmHg is safe in intracerebral hemorrhage patients with no obvious antihypertensive contraindications [36].

Although the necessity and safety of early antihypertensive treatment have been agreed upon among researchers, the significant differences between large clinical studies conducted in recent years have led to great controversy on the effect of early antihypertensive treatment in acute intracerebral hemorrhage and disease prognosis. The completed intensive blood pressure reduction in acute intracerebral hemorrhage trials [37] [26, 38] have demonstrated that early intensified antihypertensive treatment is beneficial for intracerebral hemorrhage patients. In contrast, the Antihypertensive Treatment of Acute Cerebral Hemorrhage [39, 40] revealed

that intensified antihypertensive treatment results in no significant improvement in the clinical prognosis of patients. A meta-analysis of early antihypertensive treatment for intracerebral hemorrhage, which includes the above studies, showed that differences in early blood pressure control rate and blood pressure increase variability, in addition to differences in inclusion criteria and complications, are also the major causes of inconsistency between these studies. There is currently no consensus on the best antihypertensive regimen as it is difficult to reach the optimal blood pressure level timely. Furthermore, some antihypertensives drugs can induce rebound hypertension and increased intracranial pressure (ICP) [41], causing huge problems in clinical decision and implementation processes for intracerebral hemorrhage patients.

Some studies have now shown that stress response, pain, ICP increase and pre-onset blood pressure elevation are factors that cause acute blood pressure increase in intracerebral hemorrhage patients [36]. In particular, restlessness and pain are the major factors that cause peripheral blood pressure and ICP increase and affect the efficacy of antihypertensive treatment in intracerebral hemorrhage patients. Adverse outcomes in intensive care unit (ICU), such as strong light and noise stimulation, various invasive life support treatments, disease-induced pain, stress due to intolerable pain and sleep deprivation, and dramatic blood pressure and ICP increases, can lead to secondary intracerebral hematoma expansion and subsequently cause neurologic degeneration and cerebral tissue damage [42, 43]. Therefore, the primary principles of intracerebral hemorrhage treatment are to keep quiet [3], restore blood pressure to normal level, stably reduce blood pressure, decrease blood pressure variability, lower the chance of recurrent hemorrhage, and thereby improve long-term prognosis [38, 44, 45]. Traditional antihypertensive treatment can only resolve the issue of BP elevation but not the root cause of disease.

Analgesia and sedation are critical components of and a global consensus in the clinical management of intracerebral hemorrhage patients [36, 46]. The basic objective of analgesia and sedation in intracerebral hemorrhage patients is to control anxiety, restlessness and pain, and to reduce harmful stimulation and stress response induced by medical procedures. On the other hand, analgesia and sedation can protect the brain by decreasing oxygen consumption and increasing ischemic tolerance in cerebral tissues [47]. Control of blood pressure and ICP elevation and reduction of blood pressure variability can lower the chance of hematoma

expansion and improve prognosis in the patients. The Lund concept proposed in 1990 is a consented analgesia and sedation strategy for severe craniocerebral injury. This concept promotes the use of benzodiazepines, including midazolam and propofol for deep sedation [48]. However, recommendations are lacking for the treatment of mild to moderate carniocerebral injury. It has been previously reported that maintenance sedation in patients with mild craniocerebral injury is associated with hypoxemia, low APACHE II score and shock, and can reduce cortisol level and induce adrenal insufficiency [49]. On the other hand, early hematoma expansion is highly likely in intracerebral hemorrhage patients after disease onset [50], and changes in intracranial condition are strongly correlated with the degree of impaired consciousness in the patients. Excessive use of analgesic and sedative depends on the patient's state of consciousness and thereby affects accurate evaluation of disease condition [51, 52]. Therefore, dynamic clinical observation has significant implications in the judgment of disease exacerbation and further surgical treatment in patients with moderate craniocerebral injury [53]. High-level evidence on the efficacy of analgesia and sedation in patients with craniocerebral injury is currently lacking due to the injury being listed as an exclusion criteria in several large-scale clinical studies. Therefore, many analgesia and sedation guidelines are unable to provide recommendations for issues related to analgesia and sedation in spontaneous intracerebral hemorrhage patients [54-56].

The key to acute intracerebral hemorrhage treatment is to balance the relationship between intracranial pressure, cerebral perfusion pressure and blood pressure fluctuation. Remifentanil is a fentanyl μ-type opioid receptor agonist with strong and fast-acting analgesic effects. The drug can rapidly establish blood-brain balance within 1min inside the body, and it is quickly metabolized by non-specific esterase in the plasma [57, 58]. In addition, remifentanil does not induce ICP elevation [47] and can alleviate pain induced by sputum aspiration, body turning and back clapping in severe patients [59]. A randomized trial on patients with craniocerebral injury has indicated that a remifentanil-based sedation strategy can significantly reduce the amount of sedative used and shorten the time of mechanical ventilation without affecting the functional assessment of the nervous system [60]. In terms of dosage, some researchers believe that a satisfactory analgesic and sedative effect can be achieved by using a low dose of remifentanil (0.05 to 0.075 μg/kg/min) [61, 62]. In regards to its safety, remifentanil (≤0.05 μg/kg/min) can help maintain critically ill patients who are on the spontaneous mode of

mechanical ventilation under a good sedation status while they are conscious [63]. For procedure-related pain, analgesic pre-treatment of 1 μg/kg remifentanil in mechanically ventilated patients prior to sputum aspiration can prevent procedure-induced dramatic blood pressure increase [64]. Dexmedetomidine is an α2-adrenergic agonist that inhibits sympathetic activity by activating the pre-synaptic α2-receptor in the locus coeruleus, which in turn reduces norepinephrine release. Dexmedetomidine is a non-γ-aminobutyric acid drug that only slightly affects consciousness and breathing and helps patients with craniocerebral injury stay conscious while under sedation, allowing real-time functional assessment of the nervous system. Past studies have shown that dexmedetomidine is safe to use in critically ill neurosurgical patients [65] and is beneficial for mechanical ventilation withdrawal in brain injury patients [66]. It can maintain a good level of sedation in neurocritically ill patients without inducing significant hemodynamic complications.

There are currently 27 "spontaneous intracerebral hemorrhage" related clinical trials that are registered on clinicaltrials.gov, and the area of study include "correlation between spontaneous intracerebral hemorrhage and blood pressure, body temperature management and factor VII a. However, studies related to "analgesia and sedation treatment and prognosis of spontaneous intracerebral hemorrhage" are still lacking. Based on the above background, we intend to carry out a nation-wide multicenter study to confirm that analgesia-first minimal sedation can rapidly stabilize blood pressure, reduce blood pressure variability, effectively minimize early hematoma expansion and improve prognosis of spontaneous intracerebral hemorrhage patients.

## 1.2 Study objectives

**Primary study objective**

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

**Secondary study objectives**

(1) To evaluate the efficacy of analgesia-first minimal sedation in the reduction of early hematoma expansion and the improvement of short-term prognosis of intracerebral hemorrhage patients.

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

### 1.3 Study hypothesis

(1) The analgesia-first minimal sedation strategy relies on the remifentanil-mediated alleviation of pain-induced stress response and the antisympathetic activity of dexmedetomidine to restore the elevated blood pressure to normal level in patients with intracerebral hemorrhage. This strategy allows rapid stabilization of blood pressure, and its use as a pre-treatment for patients on mechanical ventilation prior to painful procedures reduces blood pressure variability and thereby results in etiologic treatment. It is more effective in blood pressure control than conventional symptomatic antihypertensive treatment.

(2) 1) The analgesic and antisympathetic effects of the analgesia-first minimal sedation strategy effectively stabilized blood pressure, controls factors that affect early hematoma expansion, reduces the incidence of early hematoma expansion and improves prognosis; 2) Precise dose control of analgesic and sedative allows the patient to be awaken at any time and observations of pupil reflex and consciousness. This strategy significantly reduces the frequency of assessment and dose adjustment by healthcare workers, lowers their workload, increases patient adherence, and improves healthcare worker satisfaction.

## 2. Trial design

A multicenter, randomized, single-blinded, positive reference drug-controlled and superiority test design is used for this trial

### 2.1 Multicenter

The Third Affiliated Hospital of Southern Medical University, Xuanwu Hospital Capital Medical University, Qilu Hospital of Shandong University, First Affiliated Hospital of Kuming Medical University, The First Affiliated Hospital of Xinjiang Medical University, Xinqiao Hospital of Army Medical University, Henan Provincial People's Hospital, The Second Hospital University of South China, The Second People's Hospital of Shenzhen, The People's Hospital of Guangxi Zhuang Autonomous Region, Zhongshan People's Hospital, The First Hospital of Lanzhou University, The First Affiliated Hospital of HuNan University of Medicine, Guangdong 999 Brain Hospital, MaoMing People's Hospital, The Fifth Affiliated Hospital of Southern Medical University, The Fifth Affiliated Hospital Sun-yet sen University.

### 2.2 Study subject

### 2.2.1 Diagnostic criteria

(1) Diagnostic criteria for spontaneous intracerebral hemorrhage

Diagnostic criteria are based on the 2010 "Diagnostic Criteria for Spontaneous Intracerebral Hemorrhage in Adults" issued by the National Health and Family Planning Commission [67]: 1) Clinical manifestation: 1. Acute onset; 2. Symptoms: disease onset is generally presented as sudden headache, nausea, vomiting, one-sided limb weakness, sensory abnormality, slurred speech or inability to speak, incontinence, unconsciousness and neck stiffness, and most patients are accompanied by elevated blood pressure; some patients also have seizures; 3. Signs: hemiplegia, hemifacial sensory disorder, hemianopia, gaze palsy, dysarthria, aphasia, varying degrees of consciousness disturbance, positive pathological stimulation, and positive meningeal irritation; critically ill patients may have moderate to severe coma, unequal or needle-like pupils and unstable vital signs; 2) Imaging: head computed tomography examination is the preferred "gold standard" for intracerebral hemorrhage diagnosis; 3) Laboratory examinations: routine blood and urine tests, blood glucose, electrolyte, and liver and kidney function.

Clinical manifestations and imaging examinations can together provide definitive diagnosis of intracerebral hemorrhage. Diagnostic workflow is in strict compliance with the recommendations in the "AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage" by Hemphill et al. in 2015 [36, 43].

(2) Diagnostic criteria for hypertension and blood pressure compliance

Automated non-invasive blood pressure module of ICU or stroke unit monitoring will be used to measure blood pressure. A balloon cuff suitable for the size of the upper arm of the subject will be selected and fastened to the brachial artery of the non-affected upper limb with moderate tightness to monitor blood pressure. Hypertension was diagnosed with at least two SBP measurements ≥150 mmHg (interval ≥2 minutes); At least two SBP measurements <140 mmHg (≥2 minutes between two measurements) were diagnosed as blood pressure compliance.

(3) Diagnostic criteria for early hematoma expansion

Diagnostic criteria for early hematoma expansion in intracerebral hemorrhage are based on those used by Kazui et al.: hematoma expansion is diagnosed when $V_2$-$V_1$≥12.5 cm³ or ($V_2$-$V_1$)/$V_1$＞33% ($V_1$ and $V_2$ represent the hematoma volume from two computed

tomography scans, respectively) [22].

### 2.2.2 Inclusion criteria

(1) Definitive diagnosis of intracerebral hemorrhage induced acute brain injury by computed tomography [42];

(2) SBP ≥150 mmHg for at least twice (based on the brachial artery pressure from the upper arm; the two measurements are conducted ≥2 minutes apart);

(3) >18 years old;

(4) Feasible for emergency antihypertensive treatment and real-time blood pressure monitoring;

(5) Disease onset is within 24 h (if subject's time of onset is unknown, the last known time is selected);

(6) ICU or stroke unit admission within 24 h.

### 2.2.3 Exclusion criteria

(1) Subject has contraindications for emergency intensified antihypertensive treatment (such as severe carotid, vertebral or cerebral artery stenosis, known Moyamoya disease or multiple arteritis, and severe aortic stenosis or severe kidney failure);

(2) Intracranial hemorrhage secondary to intracranial tumor, recent trauma, cerebral infarction and thrombolytic therapy;

(3) History of ischemic stroke within 30 days before disease onset;

(4) Clinical or imaging examination reveals an expected high mortality in subject within the next 24h (Glasgow Coma Scale score 3-5, and hemorrhage-induced midline shift or sustained deep coma) (note: intracerebral hemorrhage patients often have secondary epilepsy, and given that the decline of consciousness after secondary epilepsy is not positively correlated with the severity of intracranial hemorrhage, these patients cannot only be assessed by consciousness);

(5) Presence of dementia or significant post-stroke disability (modified Rankin Scale ≥3 points [69]);

(6) Coagulation disorder caused by drugs or hematologic diseases (coagulation disorder is defined as <50×10^9/L blood platelet or ≥1.8 international normalized ratio);

(7) Allergy to opioids;

(8) Interference test result, assessment and follow-up of comorbidity (such as malignant tumor and respiratory diseases);

(9) Presence of sinus arrest, borderline rhythm, grade II and above atrioventricular block and malignant arrhythmia (individuals with bradycardia and arrhythmia who have good pulse from pace-marker are not excluded);

(10) Individual is pregnant or lactating;

(11) Currently participating in other drug studies or clinical trials;

(12) Subject or guardian is unwilling to provide his/her informed consent form, or subject is highly unable to persist with the study and follow-up;

(13) Subject's participation in the study will increase his/her study-related risk, and other reasons that make the subject unsuitable for the study as determined by the investigator.

### 2.2.4 Termination/withdrawal criteria

(1) Patient/close relative can request for the termination of study at any time, and the reason must be recorded;

(2) Withdrawal/termination decided by the investigator;

1) Investigator determines base on experience that the subject should withdraw from the clinical trial;

2) Subject experiences complications and special physiological changes during the trial and is no longer suitable to proceed with the trial;

3) Subject has poor adherence and affects efficacy and safety assessments;

4) If any serious adverse event is identified by the physician during intervention and termination or change of study-related treatment is required, the subject should be withdrawn from the study and the withdrawal should be recorded in detail.

(3) Criteria for complete termination of clinical trial

1) Serious safety issues identified during the trial;

2) Major error in the clinical trial protocol that makes evaluation of the efficacy of the trial product difficult; or major deviation in the implementation of a good protocol;

3) Sponsor requests termination of the trial due to funding and management reasons.

### 2.2.5 Rejection criteria

(1) Individual who is found to not meet the inclusion criteria or meet any one of the exclusion criteria after enrollment;

(2) ICF is not obtained within 24 h of onset;

(3) Individual with very incomplete follow-up data;

(4) Disease progression within 24 h that results in the need of any life-saving treatments;

(5) Other: rejection criteria include various conditions that affect efficacy or safety assessment of the subject, such as serious trial protocol violation and the inability to obtain data, and any case of rejection must be discussed among the primary investigators, data manager, statistician and sponsor before a decision is reached.

### 2.2.6 Subject screening

(1) Subject screening: all patients who meet the inclusion criteria must fill out a case screening form, and those who also do not meet any of the exclusion criteria are included in this study.

(2) Expected study duration: January 2017 - December 2022.

## 2.3 Sample size

BP control rate within 1h of treatment initiation is the primary efficacy measure (qualitative data) in this trial. The large-scale clinical trial INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial 2 completed in 2013 showed that blood pressure control rate was 33.4% in the patients within 1h of receiving intensified antihypertensive treatment [26]. Analgesia and sedation help rapidly lower blood pressure and reduce blood pressure fluctuations in intracerebral hemorrhage patients, control sympathetic storming, decrease overall stress level, maintain cerebral oxygen supply and consumption balance, lower ICP, alleviate cerebral edema and thereby protect the brain. However, authoritative studies on the correlation between antihypertensive treatment in intracerebral hemorrhage and post-brain injury stress level, cerebral oxygen metabolism and ICP level are currently lacking. Based on past clinical experiences, the 1h blood pressure control rate is expected to be 34% among intracerebral hemorrhage patients who receive antihypertensive drug, and 51% among those who receive analgesia-first sedation therapy. Two-tailed tests with significance level of 0.05 and test power of 80%, as well as a parallel design are used in this trial. Sample size is estimated to be 132 subjects per group using the nQuery Advisor + nTerim 4.0, with <20% drop out rate. The final confirmed sample size is 165 subjects per group, and 330 subjects in total.

## 2.4 Randomization

Subjects are randomly grouped using a centralized randomization method. Factors that need to be considered for centralized randomization include: (1) Emergency hematoma removal or neurosurgical intervention is expected within 24 h (yes, no); (2) Use of antiplatelet or anticoagulant drugs within the past week (yes, no); (3) Mechanical ventilation in patient at

time of enrollment (yes, no). All subjects are grouped by central randomization within 2h of selection into the study. Central randomization is conducted on the central randomization system provided by the Department of Biostatistics of Southern Medical University. Investigators log into the system (or call the central randomization voice response system) in sequence of the time of qualification to apply for treatment for the qualified subject.

**2.5 Blinding**

This study uses a single-blinded design in which only the investigators and not the subjects know the method of intervention.

**2.6 Superiority test**

Superiority test is performed in this study using early blood pressure control rate and blood pressure change rate as primary assessment indicators. Significantly higher early blood pressure control rate and lower blood pressure change rate in the experimental group than in the control group suggest that treatment in the experimental group has superior stabilizing and antihypertensive effects during early intracerebral hemorrhage than in the control group.

**2.7 Grouping and intervention**

Subjects are grouped into the intervention group or control group using the central randomization system upon enrollment. Intervention is performed on the subjects in accordance to the protocol of each group. The overall antihypertensive treatment goal is to reduce SBP $<$140 mmHg within 1h of treatment initiation and maintain this SBP level for 7 days until subject is discharged from ICU (also applies to subjects who are transferred out of ICU in 7 days).

**Intervention group:** Overall treatment principle: analgesia first, then sedation if necessary. 1) Remifentanil will be administered by IV infusion and maintained at a dose of 0.025 μg/kg/min in non-mechanically ventilated patients and a dose of 0.05 μg/kg/min in mechanically ventilated patients [61, 62]; 2) SBP is measured after 10 minutes of continuous infusion, if SBP is still ≥140 mmHg, then dexmedetomidine will be applied using an infusion pump at a dose of 0.2 μg/kg/h, BP is measured again after 15 minutes of continuous infusion; 3) If SBP is still ≥140 mmHg, the maintenance dose of dexmedetomidine will be increased 0.1 μg/kg/h; 4) Blood pressure is measured every 10 minutes during the infusion, and the maintenance dose of dexmedetomidine will be increased accordingly up to a maximum of 0.6 μg/kg/h; 5) If blood pressure is still not reduced by the concurrent use of dexmedetomidine at

its maximum dose, then the routine antihypertensive treatment of the respective center is applied, and IV antihypertensive treatment is recommended for rapid reduction of SBP to its target range; 6) Mechanically ventilated patients are given rapid remifentanil (0.5 μg/kg) infusion as an analgesic prior to sputum suction to reduce procedure-related pain; 7) Precautions: Subject must be treated if the following conditions occur during treatment: A. Acute agitation: loading dose of remifentanil (0.2 μg/kg for 1 minute) or low dose of propofol (0.3 mg/kg); B. Hypotension: the dose of remifentanil or dexmedetomidine can be lowered if SBP < 110 mmHg in order to maintain a blood pressure of 110-140 mmHg. If SBP < 90mmHg or diastolic blood pressure (DBP) < 50 mmHg, dexmedetomidine must be reduced or discontinued (remifentanil must be reduced if dexmedetomidine is not used) immediately, along with the addition of small dose of norepinephrine or dopamine to maintain blood pressure at 110-140 mmHg; C. Bradycardia (sinus rhythm <60 beats/min): If there is no clinical evidence of hypotension or hypoperfusion, then dexmedetomidine should be reduced and observation is continued; D. Severe bradycardia [heart rate (HR) <50 beats/min or new sinus arrest, borderline rhythm and grade II and above atrioventricular block]: dexmedetomidine is discontinued and subject is given prohypertensive drug and isoproterenol to maintain HR at 60 beats/min (1 mg dissolved in 50 ml normal saline and infused by micropump); E. Extreme agitation: defined as ineffective control of agitation after 3 administrations of remifentanil (loading dose) or propofol (low dose) after symptomatic treatment; treatment is adjusted to 6 h propofol sedation, with antipsychotics (haloperidol) when necessary; after 6 h of propofol, sedation is changed to dexmedetomidine; if this situation occurs 3 times, then treatment is changed to propofol maintenance sedation.

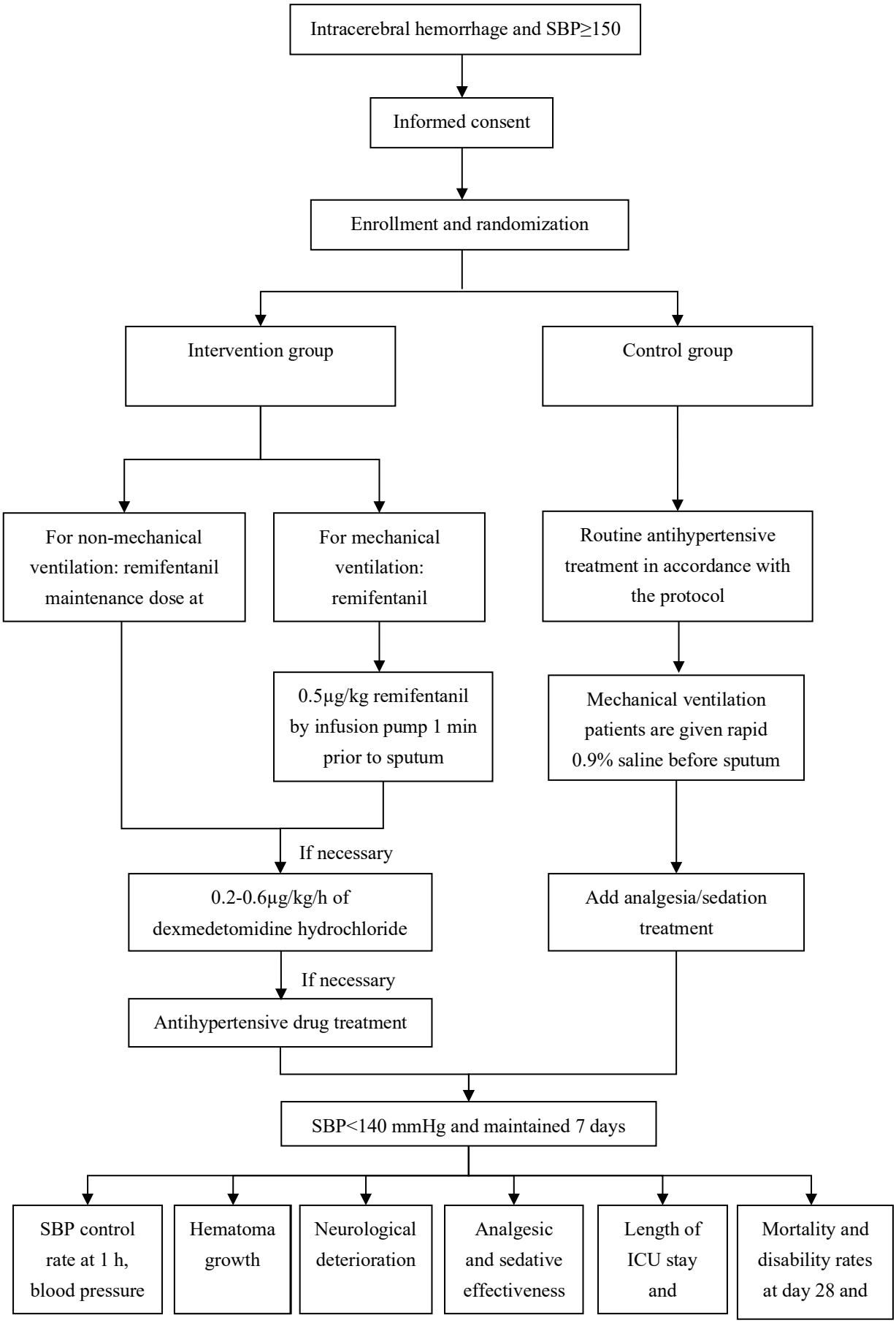
**Control group:** antihypertensive drug treatment group. Routine antihypertensive treatment is performed in accordance to the protocol of each respective research center. Urapidil, nicardipine, and labetalol will be used in this group. Urapidil will be used as follows: a slow IV injection of 10–15 mg and then IV pumping for maintenance at an initial rate of 2 mg/min, adjusted according to blood pressure to a maximum of 9 mg/min. Nicardipine will be used as follows: IV pumping at 0.5 μg/kg/min adjusted according to blood pressure to a maximum of 6 μg/kg/min. Labetalol will be used as follows: IV infusion for maintenance at 1–4 mg/min until the aim is reached. No previous study has explored whether intracerebral hemorrhage patients who retain the ability to cough up sputum during aspiration have a better prognosis.

Therefore, the mechanically ventilated patients in the control group will be administered a rapid physiological saline infusion as a controlled pretreatment.

### 2.8 Follow-up and time points

Follow-up is conducted until patient is transferred out or discharged from ICU (observation up to day 28 of ICU), and the follow-up time points include before treatment, 24 h, day 2, day 3, day 4, day 5, day 6 and day 7 after treatment, and at time of ICU discharge. All subjects will be followed up 28 days and 90 days after initiation of treatment.

## 2.9 Trial flowchart (see below)



## 3. Observation parameters and assessment

### 3.1 General information

(1) Demographics: gender, age, height, weight, ethnicity, occupation, marital status, smoking and drinking history.

(2) General clinical data: past medical history, course of disease, treatment history, comorbidity, medication use, and initial blood pressure.

(3) Head computed tomography parameters: hemorrhage volume, site of hemorrhage, presence or absence of intraventricular hemorrhage, and intraventricular hemorrhage volume determined by the physician.

### 3.2 Efficacy measure

**Primary efficacy measures:** SBP control rate.

Early SBP control rate: real-time blood pressure monitoring is performed following treatment initiation. Pressure cuff is placed and adjusted around the upper arm of the unaffected side, and blood pressure is monitored every 10 min. Time of blood pressure control, SBP, DBP and mean arterial pressure (MAP) at 1h post-treatment initiation will be recorded. The number of patients in whom SBP decreased to < 140 mmHg at 1 h post treatment initiation will be compared to the total number in each group of patients.

**Secondary efficacy measures:**

(1) Incidence rate of early (within 24 ± 6 h of treatment) hematoma expansion: Head computed tomography re-examination is required for the subjects after 24 h of treatment. For subjects who undergo emergency hematoma removal or neurosurgical intervention within 24 h, re-examination is defined as 24 h post-surgery. Results from the re-examination are used to evaluate hematoma expansion. If the first head computed tomography cannot be performed within 24 ± 6h after treatment, then hematoma expansion is assessed based on the last applicable head computed tomography results within 24 h or the first head computed tomography result after 30 h (the former is preferred). All subjects underwent non-contrast head computed tomography scanning at 5 mm thickness without gap, forming 18-20 layers of 512×512 matrix. Head computed tomography images of all subjects are stored in DICOM format on Compact Disc Read-Only Memory and are each named according to the subject's code. Intactness and pairing of subject information and image are confirmed by the responsible investigators. Hematoma volume and presence or absence of intraventricular hemorrhage are independently analyzed by two experienced neuropathologists without knowledge of the subjects' clinical data, treatment, image date and sequence of enrollment. Hematoma volume is calculated by ABC/2, namely hematoma volume = long axis of

hematoma × short axis of hematoma × number of hematoma layers × layer thickness [7, 70]. Hematoma expansion is defined as $V_2$-$V_1$≥12.5 cm³ or ($V_2$-$V_1$)/$V_1$＞33% ($V_1$ and $V_2$ represent the hematoma volume in the two computed tomography scans, respectively) based on the diagnostic criteria by Kauiz et al. [71].

(2) Blood pressure variability: SBP, DBP and MAP will also be recorded on days 1-7 of treatment. Blood pressure control rate and coefficient of variation are calculated from the mean and standard deviation (± s) of SBP, DBP and MAP [82]. Blood pressure control rate = (number of controlled blood pressure /number of effective blood pressure) × 100%, Coefficient of variation = (the standard deviation/the mean value) × 100%.

(3) Neurologic function: assessed once every morning using the National Institute of Health stroke scale [72, 73], Glasgow Coma Scale [68] scores and Reaction Level Scale;

(4) Duration of ICU stay;

(5) Duration of mechanical ventilation;

(6) Mortality and disability rates at 28 day and 90 days: Participants will be followed up at 28 day and 90 days after enrollment. Follow-up included survival and improved Modified Rankin Scale score.

**3.3 Safety indicators**

(1) General physical examination (height, weight, body temperature, blood pressure, HR, pulse, respiratory frequency, blood oxygen saturation in fingertip, bowel movement and bowel sound) and examination of key body signs (including other special clinical examinations, such as those of the nervous system).

(2) Laboratory examinations: biomarkers: B-type Natriuretic Peptide; inflammatory markers: Procalcitonin, C-reactive protein and Leukocyte; coagulation markers: D-dimer and fibrinogen; liver function: total bilirubin and liver enzyme; kidney function: urine nitrogen and serum creatinine; and blood glucose level.

(3) Side effects from the procedure: unexpected endotracheal intubation, unintentional extubation, pressure ulcers, deep vein thromboses, and ICU-acquired muscle weakness.

**3.4 Adherence measures**

(1) Drug use: daily and total amount of drug used are recorded.

(2) Duration of drug use: drug use begins from the patient's admission to ICU, and the duration of drug use is recorded.

## 3.5 Adverse event and serious adverse event

### 3.5.1 Adverse event

In this study, any new medically diagnosed disease, exacerbation of pre-existing comorbidity and other unpredictable medical events, aside from the expected natural disease exacerbation caused by intracerebral hemorrhage progression (such as organ failure or other complications), identified in the subject by the investigator after intervention in the clinical trial should be considered as an adverse event [75], including side effects from the study drug and the procedure.

(1) tachycardia: HR >100 beats/min, or HR >100 beats/min before treatment but shows 20% increase;

(2) bradycardia: HR <60 beats/min, or HR <60 beats/min before treatment but shows >10% reduction;

(3) appearance of previously non-existing arrhythmia (sinus arrest, borderline rhythm, grade II and above atrioventricular block, extrasystole, atrial fibrillation, supraventricular tachycardia and malignant arrhythmia) or syncope;

(4) hypotension: SBP <90 mmHg or DBP < 50 mmHg;

(5) respiratory inhibition: respiratory rate <12 times/min;

(6) hypoxemia: blood oxygen saturation <90% or 10% reduction from baseline;

(7) diarrhea: appearance of previously non-existing diarrhea that cannot be explained by intracranial lesion;

(8) elevated blood glucose: appearance of previously non-existing hyperglycemia >7.0 mmol/L;

(9) infusion site reactions: appearance of previously non-existing chills, fever, peripheral edema and injection pain;

(10) procedure related side effects: unplanned endotracheal intubation, unintentional extubation, deep vein thrombosis, pressure ulcer, ICU-acquired weakness;

(11) complications during ICU stay: sepsis, shock;

(12) causes of ICU death: the death of any cause in ICU.

If any of the above conditions is identified, the investigator must decide whether it is or not an adverse event. If adjustment of the study protocol is not required, then the study may proceed. If disease condition changes and treatment needs to be discontinued or modified, the subject

is withdrawn from the study and recorded in detail (see withdrawal criteria), and any subsequent clinical treatments are focused on saving the life and improving diagnosis of the subject; any event that is considered as an adverse event must be recorded in the adverse event report form and be reported.

### 3.5.2 Serious adverse event

Serious adverse event refers to any adverse medical events at any dose that meets one or multiple of the following criteria:

(1) Death-causing;

(2) Life-threatening (note: the terms "life-threatening" and "serious" are defined as events that lead to immediate death in the patients as determined by the investigator, and not the hypothesis that worsening of the event may result in death);

(3) Requires hospitalization or prolonged hospitalization;

(4) Causes permanent or obvious disability/function impairment;

(5) Causes deformity and congenital malformation;

(6) Important medical events (intervention measures are required based on the investigator's advice to prevent the above conditions or occurrence of life-threatening conditions in the subject, even if the event is not immediately life-threatening and does not cause immediate death or hospitalization).

In this study, possible SAEs may include (1), (2), (4) and (6). If these 4 serious adverse events are identified, they must be immediately reported. Report of all adverse events (whether they are serious or non-serious) is conducted from the time of enrollment until 90 days after study initiation. Adverse events and Serious adverse events that occur after completion of study should be collected and reported if the investigators believe that the events are caused by the study protocol. Serious adverse event must be recorded in the Serious adverse event report form.

### 3.5.3 Determination of severity

Severity of adverse event and serious adverse event is assessed based on the following criteria:

(1) Mild: absence of obvious symptoms or discomfort; daily activity and function is not affected; drug treatment is generally not required for symptom relief;

(2) Moderate: symptom causes obvious discomfort; daily activity and function are affected;

participation in study can be continued; requires intervention to relieve symptom;

(3) Severe: severe illness causes serious discomfort; symptom causes loss of function and significantly affects daily activity; severity may result in treatment discontinuation; requires symptomatic treatment and/or hospitalization.

### 3.5.4 Determination of causality

The correlation between adverse event and serious adverse event and intervention is assessed by the following criteria:

(1) Certainly related (must quality 5 criteria)

This type of adverse event is confirmed to be related to the trial intervention. An adverse event can be considered as "certainly related" if it meets the following criteria: 1) adverse event occurrence shows logical time correlation with the drug intervention; 2) adverse event cannot be logically explained by known disease conditions and environmental or toxic factors in the patients; 3) adverse event disappears or alleviates upon discontinuation of the intervention; 4) adverse event is consistent with the reaction to intervention; 5) External factors can be excluded;

(2) Highly related (must meet the first 3 criteria)

This type of adverse event is highly believed to be correlated with the trial intervention. An adverse event can be considered as "highly related" if it meets the following criteria: 1) adverse event occurrence shows logical time correlation with the drug intervention; 2) adverse event cannot be logically explained by known disease conditions and environmental or toxic factors in the patients; 3) adverse event disappears or alleviates upon discontinuation of the intervention; 4) adverse event is consistent with the reaction to intervention or is not a known adverse reaction to other intervention; 5) adverse event reappears when intervention is continued;

(3) Possibly related (must meet the first 2 criteria)

This type of adverse event is unlikely related to the intervention, but its correlation with the intervention cannot be definitely excluded. An adverse event can be considered as "possibly related" if it meets the following criteria: 1) adverse event occurrence shows logical time correlation with the drug intervention; 2) adverse event cannot be logically explained by known disease conditions and environmental or toxic factors in the patients; 3) adverse event is consistent with the reaction to trial intervention;

(4) Possibly unrelated (must meet the first 2 criteria)

This type of adverse event generally meets the following criteria: 1) adverse event occurrence has no logical time correlation with the trial intervention; 2) adverse event is clearly caused by the disease condition and environmental or toxic factors of the patient or the use of other concurrent treatment; 3) adverse event is inconsistent with the reaction to trial intervention; 4) adverse event is no longer present or exacerbated upon re-initiation of the intervention.

(5) Certainly unrelated

This type of adverse event is clearly determined to be induced by external factors (disease and environment) and does not meet the criteria for "possibly unrelated", "possibly related" or "highly related".

### 3.5.5 Follow-up and record of Adverse event and Serious adverse event

Adverse event and serious adverse event are evaluated based on the clinical condition of the subjects and recorded throughout their stay in ICU. Investigators are required to fill out the adverse event record form truthfully and record the name, start date and time, time interval and severity of adverse event, and whether or not measure is taken (if yes, the correlation (certainly related, highly related, possibly related, possibly unrelated and certainly unrelated) between concurrent medication and treatment and analgesia-first minimal sedation). All adverse events should be tracked until resolved or disease condition is stabilized. The outcome, date and time of adverse event, and whether the subject is withdrawn from the trial due to adverse event should be recorded. Note: continuation of a pre-existing adverse event is not recorded, but re-appearance of adverse event after recovery should be recorded.

### 3.5.6 Reporting of Serious adverse event

The safety of the subject should always be prioritized in the clinical study under any circumstance. Therefore, investigators should always be alert and try their best to monitor all potential adverse events. Once any serious adverse event occurs, it must be recorded and reported to and handled by the corresponding emergency unit.

### 3.5.7 Adverse event and treatment of Adverse event in this study

Once any adverse event is identified, immediate medical treatment or intervention (if necessary) should be provided to the subject. All clinical treatments should be based on saving the life and improving the prognosis of the subject. Any adverse event that occurs during intervention should be determined by the investigator. If treatment discontinuation or modification is required, the subject should be withdrawn from the study and the withdrawal should be recorded in detail (withdrawal criteria). Any adverse event that occurs after intervention should be appropriately handled by the clinician based on disease progression and recorded in detail, and the subject is not withdrawn from the study.

Processing (specific measures) and reporting of serious adverse events: 1) When serious adverse event is considered, the chief physician must inform the primary investigator or other physicians, and if disease exacerbates, salvage should be performed while notifying the project manager. The investigational drug should also be immediately discontinued if necessary; 2) If an event is determined as serious adverse event, corresponding treatment or salvage measure should be performed immediately based on the subject's clinical manifestation, and vital signs should be stabilized as much as possible. Diagnosis and treatment assistance can be requested from other related departments if necessary, and the "Emergency Plan for the Prevention and Management of Damages and Unexpected Events in Subjects during Treatment" is initiated; 3) When a serious adverse event is confirmed by the project manager, it must be reported in writing to the primary investigators, ethics committee of the drug clinical research institutions, sponsor and serious adverse event specialist of the research center within 24 h, and the research center then reports to the Food and Drug Administration and the provincial food and drug administration. Serious adverse event can be reported in a standard form provided by the sponsor or Food and Drug Administration. The part that is reported by the sponsor must be compliant with the reporting requirements of relevant laws and regulations. (see detailed Standardized operation of Serious adverse event Reporting)

Documentation: 1) Research physician should make good documentation of adverse events, including description, start and end time, severity and frequency of adverse events, whether or not treatment is required, and if so what treatment is given. 2) The occurrence, progression and treatment of serious adverse event should be recorded in as much detail as possible in the original case form and the Case Report Form. The serious adverse event should be tracked until it is resolved or the disease is stabilized. A final report should be submitted to the responsible primary investigator, ethics committee of drug clinical research institution, sponsor and Food and Drug Administration when the cause of serious adverse event is known (a written report should be submitted to relevant departments when necessary).

## 4. Concurrent medication/treatment and drug management

### 4.1 Concurrent medication

(1) All other analgesics except the investigational drug are prohibited during the trial, such as various non-opioid analgesics.

(2) Other medications (e.g. antihypertensive drug) that must be taken for other comorbidities at time of enrollment should be recorded in the "comorbidity and drug use" of the Case Report Form.

Physicians must request patients to bring all current medications to the hospital during

follow-up in order to determine the patients' concurrent medication use. The name, dose, frequency and time of use of drugs or other treatments that are required for comorbidity must be recorded in the Case Report Form for subsequent analysis and reporting.

**4.2 Concurrent treatment**

(1) Patients need to take concurrent treatments according to the guidelines and recommendation of the investigators during the trial.

(2) Intracranial hypertension must be controlled using active comprehensive measures [36, 76]: 1) Body position: lift head by 30°; 2) Hemodynamics monitoring via central venous pressure to avoid hypotension, low effective blood volume, perfusion-induced cerebral ischemia and subsequent ICP elevation; 3) Analgesia and sedation: analgesia and sedation is not required for the control group. Analgesia and sedation-based brain protection therapy is performed on the subjects based on the guidelines and drug use of the respective center; 4) Airway management: $PaCO_2$ is maintained at 30-35 mmHg, $PaO_2$＞80 mmHg and oxygen saturation ＞95% to avoid hypoxemia; 5) Body temperature is maintained at normal level or mild hypothermia, and hypothermia treatment can be performed when necessary; 6) Reasonable control of cerebrospinal fluid drainage and speed; 7) Permeability treatment targeted at 300-320 mOsm/L, and at 290-300 mOsm/L for elderly and renal insufficiency patients; 8) If ICP continues to increase after taking the above measures, head computed tomography must be re-examined and surgical intervention can be used if necessary.

(3) Management of abnormal coagulation: 1) Routine cogulation monitoring. Clotting factors or platelet replacement therapy can be given to patients with clotting factor deficiency and thrombocytopenia. Oral anticoagulant drugs such as warfarin should be discontinued in patients who develop intracerebral hemorrhage from these drugs, and the patients should be corrected to the International Normalized Ratio as soon as possible by vitamin K, fresh frozen plasma and prothrombin complex supplements. 2) Prevention of thromboembolism After exclusion of lower extremity venous embolism by vascular ultrasound, intermittent air compression device can be applied to paralyzed limbs, and may have certain protective effect against deep vein thrombosis during intracerebral hemorrhage.

(4) Volume management: central venous catheter should be placed into the subjects as soon as treatment initiates in order to monitor and maintain central venous pressure at 8-12mmHg.

(5) Body temperature management: cooling measures include anti-infective treatment, physical cooling and hypothermia treatment. The goal of cooling is to keep the body temperature under 38℃, but no lower than 35℃.

(6) Blood glucose management: blood glucose should be monitored to avoid hyperglycemia and hypoglycemia. Blood glucose should be maintained at 7.7-10.0 mmol/L.

(7) Other comprehensive treatment and management: reasonable nutritional support and

close monitoring of changes in electrolyte level, lungs, digestive tract and kidney functions.

(8) Concurrent delirium management: haloperidol is the drug of choice, but antipsychotic drugs such as clozapine or olanzapinecan be used for patients who are prohibited from or intolerable to haloperidol.

(9) Necessary treatments for other diseases or symptoms (unrelated to the indications in this study) are permitted for the patients. However, they must be recorded in detail on the Case Report Form.

**4.3 Drug management**

(1) Pre-trial management: investigational drug and reference drug are prepared by the sponsor prior to the trial.

(2) Trial period management: a management system for the investigational drug during the trial should be established. Each research institution is responsible for designating an investigational drug manager. The drugs are locked in a secure cabinet and stored at room temperature. A dedicated "Clinical Research Drug Use Record Form for Studying the Efficacy and Safety of Analgesia-First Minimal Sedation as an Early Antihypertensive Treatment for Spontaneous Intracerebral Hemorrhage " is constructed to record the release date and code number of the investigational drug, initial of the subject, amount of drug given and recovered, and signature of the drug manager.

(3) Post-trial management: the drug manager is responsible for collecting all remaining drugs and returning them to the sponsor.

## 5. Follow-up visit flowchart (see below)

**Follow-up visit 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 | | ● | ● | ● | ● | | |

| 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 |
| BIS monitoring | | ● | ● | ● | ● | | |
| Mortality and disability rates at 28 days | | | | | | ● | |
| Mortality/disability rates at 90 days | | | | | | | ● |
| **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) | | ● | ● | ● | ● | | |

| 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 |
| **Documentation of Adverse event** | | | | | | | |
| Drugs side effects | | ● | ● | ● | ● | | |
| Procedure related side effects | | ● | ● | ● | ● | | |
| Complications during ICU stay | | ● | ● | ● | ● | | |
| Causes of ICU death | | ● | ● | ● | ● | | |
| Other work | | | | | | | |
| Concomitant medication | | ● | ● | ● | ● | | |
| Daily drug use | | ● | ● | ● | ● | | |
| Total drug use | | ● | ● | ● | ● | | |

# 6. Data management

## 6.1 Data entry

### 6.1.1 Data source

Data in this study mainly include: demographics, general clinical information, blood pressure measurement, head computed tomography examination, laboratory examinations and patient prognosis data. Demographics and general clinical information can be obtained at baseline. Laboratory examinations are conducted at baseline, and also at each follow-up if needed. Patient prognosis data are obtained during follow-up.

### 6.1.2 Data entry

Data collection and management in this study are performed using the Electronic Data Capture system.

### 6.1.3 Staff training

The Electronic Data Capture system supplier is responsible for providing the primary investigator with the corresponding training prior to the official start of the study. If time allows, the primary investigator may also provide training to all users. Once Electronic Data Capture users are familiar with the operation of the system, they may register for their Electronic Data Capture user accounts.

### 6.1.4 Data entry

Data are entered by the trained Electronic Data Capture system users. Each participating research center is recommended to designate a research assistant (data entry clerk) responsible for work related to the data. The research assistant must assure that the data are true, complete and accurate at time of entry. All items in the data record form must be filled, and no blanks or missing items are allowed (diagonal line is drawn within the space with no data). The research assistant should try to ensure that all laboratory examination items are complete. Subject's data record is submitted and reviewed by the study director within 3 days of observation completion. Data are entered into the Electronic Data Capture system once they have been confirmed to be accurate.

## 6.2 Data review and cleaning

(1) The data manager and the investigator should develop a data range check and logical check together based on the range and interdependency of the values of the various indicators in the Case Report Form.

(2) The original Case Report Forms are archived and stored in order of the subject codes after completion of data entry and review, and the retrieval catalog is filled in for review later on.

(3) Data in the database are locked after they have been reviewed, assessed and confirmed to be correct. No changes are allowed for any locked data files. Issues that are identified after data locking can be amended in the statistical analysis after confirmation. Confirmation of issues should be recorded in detail.

### 6.3 Data review meeting and unblinding

Depending on the circumstance, the investigator may host a data review meeting to discuss any unresolved suspicious data identified during data management and divide the data sets.

### 6.4 Database locking

The data manager will lock the database once all data suspicions have been resolved and data set have been divided. Changes to the data are not allowed in principle after database locking, but may be done so by database unlocking. However, this should be done with extreme care to avoid frequent locking and unlocking of database.

## 7. Statistical analysis

### 7.1 Analysis data sets

(1) Intent-to-treat population: patients that have expressed willingness to receive treatment and signed the informed consent.

(2) Modified Intent-to-treat population: equivalent to the full analysis set, which includes all remaining patients after a minimal and reasonable removal procedure of 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 Modified Intent-to-treat population, and efficacy analysis is based on the results from Modified Intent-to-treat population analysis.

(3) Per-protocol population: patients who meet the inclusion criteria, do not meet the exclusion criteria, and have completed the treatment regimen with good adherence. Per-protocol population analysis is focused on examining the consistency with intent-to-treat population analysis to determine result stability.

(4) Safety assessment population: patients who have undergone randomized grouping, taken the drug at least once and have at least 1 safety assessment. Missing values for any safety measures are not estimated.

### 7.2 Statistical analysis plan

(1) Statistical software: statistical analyses are performed using the SAS 9.4 statistical software.

(2) Basic principle: all statistical inferences are tested using two-tailed tests, with a significance level of 0.05 and a confidence level of 95%. Parametric tests should be used whenever possible. If the data do not meet parametric requirements, data may be converted until they meet the requirements. If the requirements cannot be met after data conversion, then non-parametric tests may be considered.

(3) Missing data: any missing data for efficacy analysis can be filled in by the last observation carried forward method, namely the last observed data are used as the final results for patients who cannot complete the entire treatment. Missing data are not estimated for safety assessment.

(4) Drop out analysis: total drop out rate and drop out caused by adverse event in each group are compared using the $\chi^2$ test.

(5) Descriptive statistics: quantitative data are expressed as mean, standard deviation and confidence interval. Minimum value, maximum value, P25, median and P75 may also be shown when necessary. Non-parametric test results are expressed as median and mean rank. Ordinal data are expressed as frequency distribution and the corresponding percentages, as well as median and mean rank. Qualitative data are expressed as positive rate, number of positive and denominator.

(6) Baseline data analysis: baseline data (including demographics) are described and statistically inferred.

(7) Statistical hypothesis

Early hematoma expansion rate is the primary measure for efficacy assessment. The hypothesis for the comparison of hematoma expansion rate between the two groups is:

Null hypothesis $H_0$: $\pi_T - \pi_C = 0$ (1h SBP control rate is the same between the experimental group and control group, $\pi_T$ *and* $\pi_C$ represent early hematoma expansion rate in the experimental group and control group);

Alternative hypothesis $H_1$: $\pi_T - \pi_C \neq 0$, (1h SBP control rate is different between the experimental group and control group).

(8) Efficacy analysis:

Primary efficacy measure: 1h SBP control rate is the primary efficacy measure in this study. Given that it is a count data, it is compared using the Pearson $\chi^2$ test. Logistic regression analysis is used when other confounding factors are considered.

Secondary efficacy measures: qualitative variables are analyzed by the Pearson $\chi^2$ test; ordinal variables are analyzed by the Kruskall-Wallis test; quantitative variables are analyzed by one-way ANOVA (multiple groups), two-sample t-test (two groups), or corresponding

non-parametric tests.

(9) Center effect analysis: quantitative measures are analyzed by a general linear model, and qualitative measures are analyzed by the CMH test;

(10) Subgroup analysis: subgroup analysis may be performed on variables that may affect outcome by comparing the primary and secondary efficacy measures between the subgroups.

(11) Safety analysis: Adverse event incidence rate is compared between the two groups using the Pearson $\chi^2$ test, and all Adverse events that occur during the trial are listed and described. Intra-group and inter-group comparisons of quantitative measures are performed using the corresponding tests. Normal/abnormal changes in laboratory test results before and after the study are analyzed, and the relationship between these abnormal changes and the investigational drug is also examined.

(12) Mid-term analysis: mid-term analysis is not performed in this study.

More details regarding the above analysis methods are shown in the statistical analysis plan.

## 8. Ethical considerations

### 8.1 Ethical review

To ensure that this clinical study is compliant with the Declaration of Helsinki and the relevant regulations for clinical research in China. Investigators in mainland China will submit this trial protocol to the Ethics Committee. Each research location will receive approval of the trial protocol, informed consent and other relevant files prior to the start of the study.

All trial protocol amendments (excluding administrative changes and corrections that do not affect the subjects, data or trial execution) must be immediately submitted to the Ethics Committee for review and approval before being implemented. The investigator is responsible for making sure that all requirements for study approval have been met, and trial protocol amendments or serious adverse events are reported to the Ethics Committee (or other corresponding organizations) based on the requirements of the committee.

### 8.2 Informed consent

Each subject who is conscious and has normal comprehension capability has the chance to read through the entire informed consent prior to selection into the study. In addition, the investigator or authorized researcher will meet with the subject in a room or clinic and provide the subject with a complete and overall introduction to the research background, objectives, methods and process, types of examinations that will be performed, rights and obligations of the individual, nature of the protocol, possible risks, unpredictable and other

questions and choices that may be encountered, and the benefits of the study for the subject. Subjects will have sufficient time and opportunity to ask questions, and the research physician must provide subjects with simple, truthful, accurate and satisfactory answers. Subjects will have sufficient time to discuss with their family members before deciding on whether or not to participate in the study. Subjects must know that they can withdraw from the study at any time without any reasons. Subjects also must know that the research physician may ask them to withdraw from the study when an adverse event is identified or when the research physician believes that participation in the study no longer meets the best interest of the subjects. Subjects agree to the collection and use of data relevant to this study, and are willing to cooperate and complete all follow-up visits. Investigator must ask the subject at time of withdrawal if he/she agrees to the use of the collected data. Subjects should participate in this study on a voluntary basis and will be asked to sign the informed consent. Before the start of any study-related processes, the investigator or the appointed representative must obtain the signed informed consent from each subject. The investigator will retain the original informed consent of each subject, and each subject will also receive a copy of the informed consent.

It is expected that a great portion of subjects with relatively severe disease condition may not be able to sign the informed consent due to changes in consciousness and problems in communication. When necessary, the ability of the potential subject to sign the informed consent will be assessed by other physicians who are not part of the research team. If the subject is incapable of signing the informed consent and informed consent is unobtainable from the subject, then the subject's legal guardian must be informed of the above contents and provide an informed consent. Once the subject regains his/her capacity, informed consent should be obtained from the subject again immediately.

Intensive care and treatment should be performed as soon as intracerebral hemorrhage has been clearly diagnosed. Once the subject has been diagnosed with intracerebral hemorrhage, he/she must undergo examinations, resuscitation and treatments as indicated in the guidelines. In principle with the contents of the study, informed consent must be obtained within 2h and processed according to the trial protocol. If informed consent is not obtained within 2h, the ethics committee of the hospital will approve the study to be carried out before obtaining the informed consent from the family. If the family does not give their consent later in the study, the subject's case report will be marked as withdrawn. The informed consent should be

retained and archived as a clinical trial document for subsequent review.

### 8.3 Privacy protection

The patients' personal information will be kept strictly confidential and will not be disclosed unless required by relevant laws. Government departments, hospital ethics committee and other relevant researchers may access the patients' information as required. The results from this study may be published on medical journal under the understanding and assistance of the patients and their families, and all records related to the patients will be kept confidential as per the requirements of the law.

### 8.4 Research drugs and cost

Remifentanil and dexmedetomidine used during this study have indications for ICU application. Patients will not be required to cover any extra expenses of normal medical care during the study.

## 9. Quality control and quality assurance

### 9.1 Standard operating procedure

Standard operating procedures should be established for all procedures in the study. The sponsor and investigators should perform their respective duties, strictly follow the clinical trial protocol, and use Standard operating procedures to ensure the implementation of the quality control and quality assurance system of the clinical trial.

### 9.2 Laboratory quality control

Standard operating procedures and quality control procedures must be established for all laboratory measures in each center.

### 9.3 Clinical monitoring

An auditor is appointed by the sponsor to monitor the clinical trial and to instruct investigators to conduct the clinical trial according to the trial protocol and requirements.

### 9.4 Inspection

The sponsor is responsible for the inspection of this trial and for providing investigators with proof of inspection.

## 10. Organization and implementation (progress)

2017.12-2018.12 Completion and publication of study protocol;

2018.01-2021.01 Collection and registration of clinical cases at each research center, blood sample collection and testing, and participation in academic conference;

2021.02-2021.12 Data processing and statistical analysis, check and fill in missing data,

mid-term summary of study;

2022.01-2022.06 Continued clinical subject collection and data processing;

2022.07-2022.12 Data processing and analysis, research report writing, and result verification meeting.

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## 12 Supplementary

Glasgow Coma Scale

| Eye opening response | Verbal response | Motor response |
|---|---|---|
| 4 Eyes open spontaneously | 5 Oriented | 6 Obeys command |
| 3 Eyes open to speech | 4 Confused | 5 Moves to localized pain |
| 2 Eyes open to pain | 3 Inappropriate words | 4 Flex to withdraw from pain |
| 1 No eye opening | 2 Incomprehensible sounds | 3 Abnormal flexion |
| | 1 No verbal response | 2 Abnormal extension |
| | | 1 No motor response |

Note: minor: 13-15 points; moderate: 9-12 points; severe: 6-8 points; very severe: 3-5 points

The National Institutes of Health Stroke Scale

| | Test | Score |
|---|---|---|
| 1a | Level of Consciousness (LOC):<br>If comprehensive evaluation is not possible (such as tracheal intubation, speech impairment, tracheal trauma and bandaging), the examiner must select one of the responses. Patient with no response to harmful stimulation (not reflex) are scored 3. | 0 = Alert, very responsive<br>1 = Drowsy, minor stimulation can arouse patients to complete command, answer questions or show response<br>2 = Drowsy and slow response, requires strong and repeated stimulation or painful stimulation to have random response<br>3 = Only reflex or spontaneous response, or completely has no response or paralysis |
| 1b | LOC Questions: (score only the initial response, no hints from the examiner)<br>Ask month and age. Response must be correct and not generally correct. Patients with aphasia and coma who cannot comprehend the questions are scored 2. Patients who cannot speak due to tracheal intubation, tracheal trauma, severe dysarthria, speech impairment or other reasons (not caused by aphasia) are scored 1. | 0 = Both correct<br>1 = One correct<br>2 = Neither correct |
| 1c | LOC commands:<br>opens/closes eyes, grip and release non-paretic hand. If neither hands can be examined, use another command (stick tongue out).Score only the first attempt. Patients can be scored if they have made an attempt to complete the command. If the patient is unresponsive, the task should be demonstrated and then the patient can be scored. An appropriate command should be given to patients with trauma, amputation or other physiological defects. | 0 = Both correct<br>1 = One correct<br>2 = Neither correct |
| 2 | Gaze:<br>Test only horizontal eye movement. Score voluntary or reflexive (oculocephalic) eye movement. Patients with conjugate deviation of eyes that can be corrected by voluntary or reflexive activity are scored 1. Patients with isolated peripheral nerve paresis (III, IV and V) are scored 1. Gaze can be tested in aphasic patients. The examiner can choose one reflexive activity to test patients with ocular trauma, bandages, blindness or vision disorders. Establish eye contact and ask patient to move eyes from one side to the other. Gaze palsy may be observed occasionally. | 0 = Normal<br>1 = Partial gaze palsy (abnormal gazing in one or both eyes, but no passive gazing or total gaze paresis)<br>2 = Passive gaze or total gaze paresis (not overcome by oculocephalic maneuver). |
| 3 | Visual fields: | 0 = No visual loss |

| | Test | Score |
|---|---|---|
| | Use finger counting or visual threat to determine upper and lower quadrants of visual field. Patients who see fingers on the side can be scored as normal. If there is unilateral blindness or enucleation, score visual fields in the other eye. Patients with clear-cut assymetry (including quadrantanopia) are scored 1. Blind patients (due to any reason) are scored 3 and tested using double simultaneous stimulation. If there is extinction, score a 1 and use the results to answer question 11. | 1 = Partial hemianopia<br>2 = Complete hemianopia<br>3 = Bilateral hemianopia (blindness, including cortical blindness) |
| 4 | Facial palsy:<br>Ask patients to show teeth, raise eyebrows and close eyes using verbal commands or demonstrations. In poorly responsive or incomprehensible patients, score symmetry of grimace in response to noxious stimuli. If possible, remove facial bandages, orotracheal tube, tape or other physical barriers before testing. | 0 = Normal<br>1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)<br>2 = Partial paralysis (total or near total paralysis of lower face, central paralysis)<br>3 = Complete paralysis (paralysis in one or both sides of the face, loss of movement in upper and lower face, peripheral paralysis) |
| 5 | Arm motor:<br>Extend upper arm: 90º if sitting, 45º if supine. Hold position for 10s; If patient is aphasic, use voice and pantomime to encourage, and no harmful stimuli should be used. Examiner can lift patient's arm to the required position and encourage patient to hold the position. Score only the affected side. | 0 = No drift, arm remains in position for 10s<br>1 = Drift, arm can be lifted but drifts down before full 10s; does not hit bed or other support<br>2 = Some effort against gravity, arm cannot get to or maintain 90º (if sitting) or 45º (if supine), drifts down to bed relatively quickly<br>3 = No effort against gravity, arm rapidly falls<br>4 = No movement<br>9 = Amputation or joint fusion<br>5a Left arm<br>5b Right arm |
| 6 | Leg motor:<br>Extend leg by 30º; If patient is aphasic, use voice or pantomime to encourage, and no harmful stimuli should be used. Examiner can lift patient's arm to the required position and encourage patient to hold the position. Score only the affected side. | 0 = No drift, leg holds at position for 5s<br>1 = Drift, leg drifts down before full 5s, but does not hit bed<br>2 = Some effort against gravity, leg drifts down within 5s and hits bed relatively quickly<br>3 = No effort against gravity, leg drifts down rapidly<br>4 = No movement<br>9 = Amputation or joint fusion<br>6a Left leg<br>6b Right leg |

| | Test | Score |
|---|---|---|
| 7 | Limb ataxia:<br>The objective is to find signs of bilateral cerebellar lesions. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose and heel-shin tests are performed on both sides, and ataxia is scored if present out of proportion to weakness. Patient who cannot understand or is paralyzed is not scored. In case of blindness, test by having the patient touch nose from extended arm position. Only in the case of amputation or joint fusion, examiner should record the score as 9, and clearly write the explanation for this choice. | 0 = Absent<br>1 = Present in one limb<br>2 = Present in two limbs<br>If ataxia is present:<br>1 = Yes, 2 = No for left arm<br>9 = Amputation or joint fusion<br>1 = Yes, 2 = No for right arm<br>9 = Amputation or joint fusion<br>1 = Yes, 2 = No for left leg<br>9 = Amputation or joint fusion<br>1 = Yes, 2 = No for right leg<br>9 = Amputation or joint fusion |
| 8 | Sensory:<br>Test for sensation using pinprick. Sensation or grimace to pinprick or noxious stimulus in the obtunded or aphasic patient. Score sensory loss due to stroke only. Precise testing of many body parts, including arms (not hands), legs, trunk and face) in patients with unilateral sensory loss. Severe or complete sensory loss is scored 2. Stuporous and aphasic patients are scored 1 or 0. Patients with brainstem stroke and bilateral sensory loss are scored 2. Quadriplegic patients who do not respond are scored 2. Comatose patients (1a=3) are scored 2. | 0 = Normal, no sensory loss<br>1 = Mild to moderate sensory loss, patient feels pinprick is less sharp or is dull on the affected side, or is only aware of being touched<br>2 = Severe to total sensory loss, patient is not aware of being touched in the face, arm or leg. |
| 9 | Language:<br>Naming and reading tests. Ask the patient to name the items and read some sentences. Comprehension ability is determined by patient's response and response to command during routine nervous system exmamination. Patients with visual loss can be asked to identify objects placed in the hand, repeat and pronounce. Intubated patients should be asked to write their answers. Comatose patients (1a=3) are scored 3. The examiner must choose a score for stuporous or uncooperative patients. A score of 3 is only given if the patient is mute or unable to follow commands. | 0 = Normal, no aphasia<br>1 = Mild to moderate aphasia: some obvious loss of fluency or comprehension, but able to express their ideas without restraints<br>2 = Severe aphasia: patient communicates with broken language, examiner must infer, ask and guess, limited range of exchangeable information, examiner has difficulty communicating with patient<br>3 = Mute or global aphasia: unable to talk or understand |
| 10 | Dysarthria:<br>Do not tell patient why they are being tested. Ask the patient to read or repeat words on a list. Patients with severe aphasia can be scored based on the clarity of articulation of their spontaneous speech. Score 9 only for patients who are | 0 = Normal<br>1 = Mild to moderate dysarthria, some unclear articulation that is difficult but comprehensible<br>2 = Severe dysarthria, incomprehensible<br>9 = Intubated or other physical barrier |

| | Test | Score |
|---|---|---|
| | intubated or have other physical barriers to speech. Clearly record the reasons for this score. | |
| 11 | Extinction and inattention (neglect):<br>Score normal if the patient has a severe visual loss preventing visual double simultaneous stimulation, but the response to cutaneous stimuli is normal. Score normal if the patient has aphasia but does not appear to attend to both sides.<br>Neglect is determined by the patient's ability to distinguish simultaneous cutaneous and visual stimuli on both sides show patient the standard picture and ask patient to describe. Physician encourages patient to look closely at the picture and identify the characteristics of the left and right side. Patient's inability to recognize the contents of one side of the picture may be taken as evidence of abnormality. Physician asks patient to close eyes and test bilateral cutaneous sensation using pinprick in arm or leg. Presence of unilateral sensory neglect may be taken as evidence of abnormality. | 0 = No inattention<br>1 = Visual, tactile, auditory, spatial or personal inattention; or extinction to bilateral simultaneous stimulation in one of the sensory modalities.<br>2 = Profound hemi-inattention; hemi-attention to more than one modality; does not recognize own hand or orients to only one side of space. |

Remifentanil for injection (1mg:50mL) speed calculation table

| Weight (kg) | Loading pump speed (mL/h)* | Maintenance pump speed (mL/h) | | | | | Rapid pump dose (mL)# |
|---|---|---|---|---|---|---|---|
| | 0.2μg/kg pump dose | 0.01μg/kg/min | 0.02μg/kg/min | 0.03μg/kg/min | 0.04μg/kg/min | 0.05μg/kg/min | |
| 30 | 18 | 0.90 | 1.80 | 2.70 | 3.60 | 4.50 | 0.75 |
| 35 | 21 | 1.05 | 2.10 | 3.15 | 4.20 | 5.25 | 0.88 |
| 40 | 24 | 1.20 | 2.40 | 3.60 | 4.80 | 6.00 | 1.00 |
| 45 | 27 | 1.35 | 2.70 | 4.05 | 5.40 | 6.75 | 1.13 |
| 50 | 30 | 1.50 | 3.00 | 4.50 | 6.00 | 7.50 | 1.25 |
| 55 | 33 | 1.65 | 3.30 | 4.95 | 6.60 | 8.25 | 1.10 |
| 60 | 36 | 1.80 | 3.60 | 5.40 | 7.20 | 9.00 | 1.50 |
| 65 | 39 | 1.95 | 3.90 | 5.85 | 7.80 | 9.75 | 1.63 |
| 70 | 42 | 2.10 | 4.20 | 6.30 | 8.40 | 10.50 | 1.75 |
| 75 | 45 | 2.25 | 4.50 | 6.75 | 9.00 | 11.25 | 1.88 |
| 80 | 48 | 2.40 | 4.80 | 7.20 | 9.60 | 12.00 | 2.00 |
| 85 | 51 | 2.55 | 5.10 | 7.65 | 10.20 | 12.75 | 2.13 |
| 90 | 54 | 2.70 | 5.40 | 8.10 | 10.80 | 13.50 | 2.25 |
| 95 | 57 | 2.85 | 5.70 | 8.55 | 11.40 | 14.25 | 2.38 |
| 100 | 60 | 3.00 | 6.00 | 9.00 | 12.00 | 15.00 | 2.50 |

Note: *Loading dose = continuous pumping for 1 min at this pump speed

#Rapid pump dose = dose given to mechanically ventilated patients prior to sputum aspiration

Dexmedetomidine hydrochloride injection (2mL: 48mL) speed calculation table

| Weight (kg) | Maintenance pump speed (mL/h)* | | | | | |
|---|---|---|---|---|---|---|
| | 0.1μg/kg/h | 0.2μg/kg/h | 0.3μg/kg/h | 0.4μg/kg/h | 0.5μg/kg/h | 0.6μg/kg/h |
| 30 | 0.75 | 1.50 | 2.25 | 3.00 | 3.75 | 4.50 |
| 35 | 0.88 | 1.75 | 2.63 | 3.50 | 4.38 | 5.25 |
| 40 | 1.00 | 2.00 | 3.00 | 4.00 | 5.00 | 6.00 |
| 45 | 1.13 | 2.25 | 3.38 | 4.50 | 5.63 | 6.75 |
| 50 | 1.25 | 2.50 | 3.75 | 5.00 | 6.25 | 7.50 |
| 55 | 1.38 | 2.75 | 4.13 | 5.50 | 6.88 | 8.25 |
| 60 | 1.50 | 3.00 | 4.50 | 6.00 | 7.50 | 9.00 |
| 65 | 1.63 | 3.25 | 4.88 | 6.50 | 8.13 | 9.75 |
| 70 | 1.75 | 3.50 | 5.25 | 7.00 | 8.75 | 10.50 |
| 75 | 1.88 | 3.75 | 5.63 | 7.50 | 9.38 | 11.25 |
| 80 | 2.00 | 4.00 | 6.00 | 8.00 | 10.00 | 12.00 |
| 85 | 2.13 | 4.25 | 6.38 | 8.50 | 10.63 | 12.75 |
| 90 | 2.25 | 4.50 | 6.75 | 9.00 | 11.25 | 13.50 |
| 95 | 2.38 | 4.75 | 7.13 | 9.50 | 11.88 | 14.25 |
| 100 | 2.50 | 5.00 | 7.50 | 10.00 | 12.50 | 15.00 |

Propofol solution for injection (600mg:60mL) speed calculation table

| Weight (kg) | Loading dose (mL) | Maintenance pump speed (mL/h)* | | | | |
|---|---|---|---|---|---|---|
| | | 0.3mg/kg/h | 1mg/kg/h | 2mg/kg/h | 3mg/kg/h | 4mg/kg/h |
| 30 | 0.90 | 0.90 | 3.0 | 6.0 | 9.0 | 12.0 |
| 35 | 1.05 | 1.05 | 3.5 | 7.0 | 10.5 | 14.0 |
| 40 | 1.20 | 1.20 | 4.0 | 8.0 | 12.0 | 16.0 |
| 45 | 1.35 | 1.35 | 4.5 | 9.0 | 13.5 | 18.0 |
| 50 | 1.50 | 1.50 | 5.0 | 10.0 | 15.0 | 20.0 |
| 55 | 1.65 | 1.65 | 5.5 | 11.0 | 16.5 | 22.0 |
| 60 | 1.80 | 1.80 | 6.0 | 12.0 | 18.0 | 24.0 |
| 65 | 1.95 | 1.95 | 6.5 | 13.0 | 19.5 | 26.0 |
| 70 | 2.10 | 2.10 | 7.0 | 14.0 | 21.0 | 28.0 |
| 75 | 2.25 | 2.25 | 7.5 | 15.0 | 22.5 | 30.0 |
| 80 | 2.40 | 2.40 | 8.0 | 16.0 | 24.0 | 32.0 |
| 85 | 2.55 | 2.55 | 8.5 | 17.0 | 25.5 | 34.0 |
| 90 | 2.70 | 2.70 | 9.0 | 18.0 | 27.0 | 36.0 |
| 95 | 2.85 | 2.85 | 9.5 | 19.0 | 28.5 | 38.0 |
| 100 | 3.00 | 3.00 | 10.0 | 20.0 | 30.0 | 40.0 |