

# The Effects of Remimazolam versus Propofol on Endovascular Thrombectomy for Acute Ischemic Stroke: Study Protocol for a Randomized Controlled Trial

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**Background:** While general anesthesia has been widely used in endovascular thrombectomy for acute ischemic stroke (AIS), the optimal anesthesia medication for hemodynamic management remains unclear.

**Purpose:** To compare the effects of remimazolam and propofol on endovascular thrombectomy for AIS.

**Methods:** This study is a single-center, double-blind and randomized controlled trial. Eligible patients will be randomly allocated into the remimazolam group and propofol group. Remimazolam and propofol will be administered to induce and maintain anesthesia respectively. The primary outcome is the incidence of intraoperative hypotension. The secondary outcomes include frequency of hypotension, the largest difference value of mean arterial pressure (MAP), dosage of vasopressors, extubation time, operation time, modified thrombolysis in cerebral infarction (mTICI) level, National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin scale (mRS) score.

**Conclusion:** This study evaluates the influences of remimazolam versus propofol on endovascular therapy for AIS patients. Results of this study are expected to provide more evidence of the choice of anesthetics in this kind of operation.

**Trial Registration:** This study has been registered at the Chinese Clinical Trial Registry (ChiCTR2300076880).

**Keywords:** remimazolam, acute ischemic stroke, endovascular thrombectomy, intraoperative hypotension, outcomes

## Background

Stroke has become the second leading cause of death worldwide.<sup>1</sup> Ischemic stroke is estimated to cause approximately 3.6 million deaths and 70 million prevalence globally, and over 1.1 million deaths and 20 million prevalence in China.<sup>2</sup> Acute ischemic stroke (AIS) endovascular thrombectomy, restoring effective blood flow in the brain as soon as possible, is an effective treatment for patients with AIS.<sup>3,4</sup> However, the optimal anesthesia strategy for acute ischemic stroke is still inconclusive.

The advantages of general anesthesia include absolute immobilization, pain management and airway protection. A meta-analysis published in JAMA showed that propofol-based general anesthesia was associated with a significant reduction in disability at the 3rd postoperative month compared with sedation.<sup>5</sup> But a recent multicenter study indicated that general anesthesia and procedural sedation had similar influences on outcomes of AIS patients who underwent endovascular therapy.<sup>6</sup> Moreover, an earlier meta-analysis demonstrated that the improvement effects on outcomes of general anesthesia was not as good as procedural sedation, but it should not be the hindrance to the use of general

anesthesia.<sup>4</sup> One possible reason for controversial role of general anesthesia on outcomes may be intraoperative hypotension.<sup>4,5</sup> A primary mission for anesthesiologists during endovascular thrombectomy is to avoid significant decline of blood pressure.<sup>7</sup> Unfortunately, this is common in general anesthesia, especially under propofol-based protocols.

Remimazolam has been approved in China since 2020. It is a new kind of ultra short-acting benzodiazepine anesthetic and can be antagonized by specific reversal agent flumazenil, which shows some characteristics of the ideal intravenous anesthetic.<sup>8</sup> Previous studies have proved that remimazolam led to less hypotension than propofol did.<sup>9,10</sup> Moreover, general anesthesia with remimazolam has little impact on cardiac output and has been reported to successfully applied to high-risk patients with severe aortic stenosis.<sup>11–13</sup> Thus, remimazolam is promising to be an ideal anesthetic in endovascular thrombectomy for AIS. The present study aims to investigate the effects of remimazolam on AIS endovascular therapy.

## Methods

### Aims of this Study

The primary aim of our study is to determine the effects of remimazolam on hemodynamics during endovascular thrombectomy. The secondary aims are to investigate the role of remimazolam on the outcomes of AIS patients. We expect to propose a better choice of anesthetics in this field.

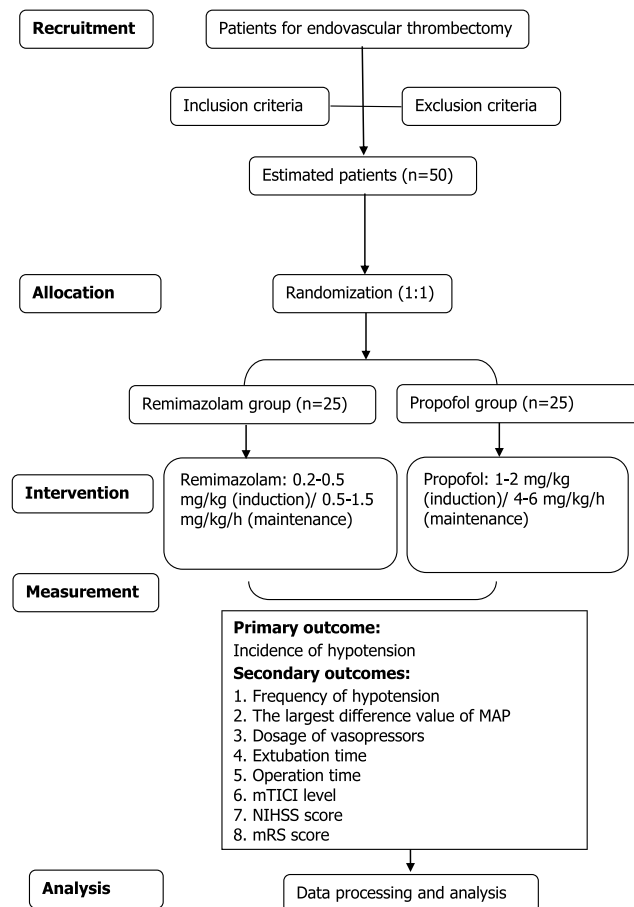
### Study Design and Settings

The present study is designed as a double-blind, single-center, randomized and controlled clinical trial. Patients will be allocated into remimazolam group or propofol group and receive remimazolam- or propofol-based anesthesia. The study procedure is planned to be performed in Deyang People's Hospital, a comprehensive tertiary hospital in China. The study protocol (version 3.0) is in line with the SPIRIT statement.<sup>14</sup> Figures 1 and 2 shows the schedule and flowchart respectively.

Time Point	Study Period					
	Enrollment	Allocation	Intraoperative period	End of operation	Postoperative day 1	Discharge
<b>Enrollment</b>						
Eligibility screening	X					
Informed consent	X					
Allocation		X				
<b>Interventions</b>						
1.Remimazolam			X			
2.propofol			X			
<b>Assessments</b>						
Demographic data	X					
Past medical history	X					
DPT			X			
PT	X					
Vital signs	X		X	X		
Extubation time				X		
Operation time				X		
Dosage of vasopressor				X		
mTICI level				X		
Blocked artery				X		
NIHSS score	X				X	X
mRS score	X					X

**Figure 1** Study schedule.

**Abbreviations:** DPT, door-to-puncture time; PT, pharmacological thrombolysis; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.



**Figure 2** Study flowchart.

**Abbreviations:** mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

## Ethics and Trial Registration

The study protocol (version 2.0) was reviewed and approved by the Ethics Committee of Deyang People's Hospital, and got an approval number of 2023-03-021-K02 on 11 September 2023. The modified protocol (version 3.0) was approved on 20 March 2024. We registered this trial at the Chinese Clinical Trial Registry on 23 October 2023, and obtained a registration number of ChiCTR2300076880.

The written informed consent will be obtained from patients or their legal representatives after introduction of this study. This step will be performed by the attending anesthesiologists during preoperative evaluation. The subjects can withdraw at any time. All investigators declare that they will conduct the study in accordance with the Declaration of Helsinki. The personal privacy and data confidentiality of the subjects will be protected during the study.

## Subjects

AIS patients undergoing endovascular thrombectomy will be screened for eligibility.

The inclusion criteria are as follows: (1) 18- to 80-years-old, the American Society of Anesthesiologists (ASA) level IV; (2) Diagnosis of large vessel occlusion of the anterior circulation; (3) The modified Rankin Scale (mRS) score  $\leq 3$  points before stroke; (4) National Institutes of Health Stroke Scale (NIHSS) score 0–30 points.

The exclusion criteria include patients with endotracheal intubation before enrollment and refusal of participation by the patients or their legal representatives.

Patients will be eliminated from analysis if other kinds of anesthetics are used, such as sevoflurane, sufentanil and ciprofol.

## Randomization and Blind Methods

SPSS 26.0 (IBM SPSS Statistics, USA) will be used to generate random numbers by an independent investigator. The numbers will be encoded to represent grouping information. Inclusion ratio of the groups is 1:1. Then, the investigator will seal the grouping information in opaque envelopes. The attending anesthesiologists will open the envelopes in order upon subject enrollment. The investigators who are responsible for recording study parameters and follow-up will keep outside the digital subtraction angiography (DSA) operating room. In this way, the subjects and observers will be blinded.

## Study Procedure

After admission, the patients will be reviewed immediately by the attending anesthesiologists. For patients who are eligible, the study will be explained to the patients and their legal guardians. After getting written informed consent, basic information such as preoperative vital signs, NIHSS score and mRS score will be recorded. Consequently, pre-anesthesia preparation will be performed immediately in the operating room.

Electrocardiogram, non-invasive blood pressure (every 3 minutes) and pulse oxygen saturation ( $\text{SpO}_2$ ) will be routinely monitored. Oxygen inhalation by mask will be maintained at 6 L/min flow rate. Sodium lactate Ringer solution will be infused via the peripheral intravenous access, followed by injection of 4 mg ondansetron. Anesthesia induction will be initiated by injecting remimazolam (0.2–0.3 mg/kg) or propofol (1–1.5 mg/kg) according to the grouping information. When the patients lost consciousness, remifentanyl (0.5–1  $\mu\text{g/kg}$ ) and mivacurium (0.2 mg/kg) will be injected. The tracheal tube will be inserted after muscular flaccidity. Then, patients in the remimazolam group will be continuously infused with remimazolam (0.5–1.5 mg/kg/h) and remifentanyl (0.05–0.1  $\mu\text{g/kg/min}$ ), while propofol (4–6 mg/kg) and remifentanyl (0.05–0.1  $\mu\text{g/kg/min}$ ) are for those in propofol group. Medications of remimazolam, propofol and remifentanyl were titrated to a proper dose according to heart rate (HR), blood pressure (BP) and body movements. Top-ups of mivacurium will be administered if necessary. When the mean arterial pressure (MAP) is less than 65 mmHg or 80% of the baseline during operation, metaraminol 20  $\mu\text{g}$  will be injected intravenously to improve blood pressure. HR <45 beats/min accompanied by hypotension will be treated with atropine 0.5 mg.

At the end of operation, all infusing drugs will be stopped. Then flumazenil (0.5 mg), neostigmine (0.04 mg/kg) will be used to reverse the effects of remimazolam and mivacurium respectively, if necessary. Atropine (0.02 mg/kg) will be injected to prevent bradycardia induced by neostigmine. For patients who meet the criteria of extubation, endotracheal tube can be pulled out. After an observation of 30 minutes, patients with stable vital signs will be sent back to the ward and other patients will be sent to the intensive care unit.

The attending anesthesiologists will take charge of perioperative management and dealing with emergency situations. Major adverse events such as cardiac arrest and inspiration of gastric contents will be reported to related department.

## Outcomes

The primary outcome is the incidence of intraoperative hypotension. Hypotension is defined as the MAP <65 mmHg or 80% of the baseline.

The secondary outcomes are as follows:

1. Frequency of hypotension: the number of MAP <65 mmHg or 80% of the baseline.
2. The largest difference value of MAP.
3. Dosage of vasopressor.
4. Extubation time: the time from drug withdrawal to extubation.
5. Operation time: the time from opening artery to pulling out the tube.
6. Modified thrombolysis in cerebral infarction (mTICI) level: level 0–2a means insufficient recanalization of the blocked brain artery and 2b–3 means sufficient recanalization.
7. NIHSS score: pre-operation, discharge of operation room, 1<sup>st</sup> postoperative day and discharge of hospital. Higher scores indicate worse neurofunction.
8. mRS score: premorbid period and discharge. Lower scores indicate better neurofunction.

## Data Collection and Management

Demographic data (sex, age, BMI, etc.), past medical history (stroke, cardiovascular diseases, lung diseases, liver and kidney diseases, endocrine diseases, etc.), grouping information, door-to-puncture time (DPT), pharmacological thrombolysis (PT), blocked artery and medication records will be collected by the attending anesthesiologists. The observer will record vital signs, extubation time and operation time during operation, and record mTICI, NIHSS and mRS from the medical records postoperatively.

The data will be integrated by the data managers of our study group. Two investigators (Wencai Jiang and Yuansheng Cao) will input data into the SPSS software. Professor Jia Han and Dan Zhou have access to these data. All members of our study group have been trained and obtained the Good Clinical Practice (GCP) certificate.

## Sample Size Determination

Since few articles reported the use of remimazolam in endovascular thrombectomy for AIS, we obtained the incidence of hypotension through a pilot study. The incidence of hypotension in propofol group and remimazolam group was 80% and 53%, respectively.

We hypothesize the type I error, type II error and dropout rate are 5%, 20% and 10%, respectively. Based on the PASS software, 74 patients are needed.

## Recruitment Plan

As AIS patients usually receive treatment in the emergency ward, an advertisement will be posted in the consulting room of neurology emergency. In addition, the attending anesthesiologists will be informed when there are AIS patients scheduled for endovascular thrombectomy, and the anesthesiologists will introduce this study to them. We started recruitment on 1 July 2024 and planned to end on 31 December 2025.

## Statistical Analysis

SPSS 26.0 software is the tool of statistical analysis for our study. Count data will be analyzed using the chi-square test or Fisher's exact test. For continuous data, normality of the data will be firstly determined by the Kolmogorov–Smirnov test. Normally distributed data will be analyzed using *t*-test, whereas abnormal data will be compared via the Kruskal–Wallis test. Statistical significance is defined as  $P < 0.05$ . Subgroup analyses will be performed to investigate the differences between patients with hypertension and without hypertension, and patients with high NIHSS score and low NIHSS score.

## Discussion

When conducting endovascular thrombectomy for AIS, patients are not expected to have body movements. General anesthesia is an option for its advantages in absolute immobilization, pain management and airway protection. However, stroke patients are more likely to suffer intraoperative hypotension under general anesthesia.<sup>14</sup> Therefore, we primarily focus on intraoperative hypotension rather than hypertension. Remimazolam has been widely used in sedation and general anesthesia, and is associated with more stable hemodynamics than propofol, which makes it a superb candidate for these patients.<sup>10,15,16</sup> Nevertheless, the effects of remimazolam on AIS patients have been merely reported.

Definition of intraoperative hypotension is a long-lasting controversy. Bijker et al<sup>17</sup> did a systematic literature review and found 140 definitions for intraoperative hypotension. They also concluded that there was no unified and fixed definition of intraoperative hypotension, even though both systolic blood pressure  $< 80$  mmHg and  $> 20\%$  decrease of baseline were most commonly used. More recently, Weinberg et al<sup>18</sup> reviewed over 300 studies, among which 78.3% used a certain value to define hypotension and 21.7% used some decrease of baseline. One dominant reason for this suspended issue is that different vessel beds have different autoregulation ranges and organ flow can be influenced by arterial lesions.<sup>19,20</sup> According to a nationwide study that included over 563 thousand stroke patients, over 60% of them had elevated blood pressure.<sup>21</sup> To be specific, 69% of the patients' systolic blood pressure was  $>$  or  $= 140$  mmHg. This change of blood pressure makes it difficult to use a single standard to define hypotension. Thus, absolute and relative

threshold are applied in our study. However, we do not intend to report the duration of hypotension. Because hypotension should be timely treated according to the study protocol.

To demonstrate the effects on hemodynamics as fully as possible, we also include the frequency of hypotension, the largest difference of MAP and dosage of vasopressor. In addition, subgroup analysis will be performed to investigate the influence of remimazolam or propofol on patients with or without hypertension before stroke.

Another concern of this study is the relationship between intraoperative hypotension and prognosis. This issue has been discussed for a long time and has not reached a consensus. Löwhagen et al<sup>22</sup> compared the effects of general anesthesia and conscious sedation on AIS patients. In their study, NIHSS scores were comparable in the two groups despite the significantly higher incidence of >20% reduction of MAP in general anesthesia group. Rasmussen et al<sup>23</sup> performed a randomized trial investigating the influence of blood pressure on the neural recovery of AIS patients. They examined a set of blood pressure changes, including >20% decrease of MAP and MAP <70 mmHg. The results did not indicate significant difference of mRS in different blood pressure groups. On the contrast, a cohort study with 378 subjects showed that even a 10% MAP drop of the baseline during endovascular thrombectomy was associated with worse mRS at the 3rd postoperative month.<sup>24</sup> Similar results were observed in other two studies.<sup>25,26</sup>

Despite the disagreements, it is better to maintain a more stable hemodynamic status. From a different perspective, anesthesiologists would have more energy to take a panoramic view of the intraoperative management rather than focusing on blood pressure.

The present study has some limitations. Duration of hypotension is not considered in this protocol. As previously mentioned, the attending anesthesiologists are required to deal with hypotension immediately. So, it seems little necessity to record hypotension seconds. Moreover, the primary aim of this study is to compare the effects of remimazolam and propofol on hemodynamic stability. The parameters we collect are sufficient. In addition, we do not monitor intraoperative bispectral index or Narcotrend index. Because the association between acute stroke and anesthesia depth monitoring is unclear. Instead, the attending anesthesiologists determine the intraoperative anesthesia depth by HR, BP and body movements.

## Conclusion

In conclusion, this is a randomized controlled study investigating the effects of remimazolam in endovascular thrombectomy for AIS patients. The results will provide evidence on the choice of remimazolam or propofol.

## Trial Status

Patient recruitment started on 1 July 2024 and the first subject was enrolled on 18 July 2024. According to the annual population of AIS patients underwent endovascular thrombectomy in our hospital, the last one is supposed to finish on 31 December 2025.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

There is no personal financial support. All authors declare no conflict of interest.

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