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## Safety and efficacy of the SeparGate™ balloon-guiding catheter in neurointerventional surgery: Study protocol of a prospective multicenter single-arm clinical trial

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## ABSTRACT

**Background:** The balloon-guiding catheter (BGC) reportedly reduces the number of retrievals and occurrence of distal emboli, achieving superior revascularization results and improved clinical outcomes in acute stroke. This study will aim to examine the efficacy and safety of the new SeparGate™ BGC.

**Design:** This prospective multicenter single-arm clinical trial will aim to include 128 patients who fulfill its inclusion and exclusion criteria. All patients will receive endovascular interventional therapy with BGC assistance. The primary endpoint will be the immediate surgical success rate, while the secondary endpoint will be product performance. The safety evaluation will include serious adverse events such as puncture site hematoma and bleeding, cerebral vasospasm, vessel dissection, vessel perforation, air embolism, thrombus (acute or subacute), vessel occlusion, distal embolization, infection, adverse reaction to antiplatelet and anticoagulant drugs, intracranial hemorrhage, stroke, death, and device defect.

**Discussion:** The prospective multicenter trial will provide safety and efficacy information for the SeparGate™ BGC. Its findings will provide a clinical reference for endovascular adjuvant therapy of cerebrovascular disease.

**Trial registration:** ChiCTR1800014459.

The incidence of cerebrovascular disease in adults is approximately 150–200 patients per 100,000 individuals. Ischemic cerebrovascular disease is the most common type, accounting for 75–85% of all cases. In recent years, endovascular interventional techniques have shown great potential in the prevention and emergency treatment of cerebrovascular disease. However, they can increase the risk of procedural-related complications (vessel dissection or perforation) and downstream emboli. Distal embolism is a common complication of recanalization of subacute/chronic intracranial large artery occlusion, which was sporadically reported in previous studies.<sup>1,2</sup> Embolization to unaffected or distal territories remains a major problem that can affect long-term clinical outcomes.<sup>3</sup> A previous carotid artery stenting study demonstrated that the severity of neurologic complications is associated with embolization degree.<sup>4</sup> The ADAPT and SOLUMBRA techniques reportedly minimize the risk of fragmentation and achieves a higher rate of recanalization in acute ischemic stroke (AIS) than stent retrievers.<sup>3,5–8</sup> However, the value and efficacy of the new techniques remain under investigation.

Considering these points, the balloon-guiding catheter (BGC) may be a useful tool for reducing the incidence of these complication and achieving successful recanalization during intraarterial thrombectomy, for it can both deliver interventional instruments (e.g. wire and catheter) and temporarily block blood flow. The SeparGate™ BGC is an independent R&D product of Hunan Ruikangtong Technology Development Co., Ltd. The pipe shaft was designed by hardness gradient, and it has a highly compliant balloon, larger balloon filling cavity, and larger lumen size. Several studies reported that BGC use resulted in less frequent distal emboli and good clinical outcomes.<sup>9,10</sup> However, these trials were retrospective and included a few centers or post hoc analyses of registries or clinical trials and focused more on clinical efficacy. There are also concerns about complications such as dissection and endothelial injury related to distal navigation of the BGC.<sup>11,12</sup> This trial is the first prospective clinical study to evaluate the safety and efficacy of the SeparGate™ BGC.

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**1. Method**

**1.1. Objectives**

This trial will aim to assess the safety and effectiveness of the SeparGate™ BCG for successfully guiding the interventional device to the target vessel and temporarily blocking the blood flow during interventional therapy of the supra-aortic arteries and branch vessels.

**1.2. Study design**

This prospective multicenter single-arm clinical trial aimed to examine the safety and efficacy of the SeparGate™ BCG manufactured by Hunan Ruikangtong Technology Development Co., Ltd. The study will be conducted in 6 centers and will enroll a total of 128 patients who fulfill its inclusion and exclusion criteria. Related data will be collected to evaluate the safety and effectiveness of the SeparGate™ BCG at successfully guiding the interventional device to the target vessel and temporarily blocking the blood flow.

The complete study flow chart is represented in Fig. 1.

**1.3. Participants**

This study will enroll patients who require interventional diagnosis and treatment of the supra-aortic arteries and branch vessels and BGC

assistance according to the researcher’s judgment.

**1.3.1. Inclusion criteria**

Patients eligible for inclusion will meet the following criteria:

- 1) 18–80 years of age;
- 2) require temporary blocking of the blood flow of the supra-aortic arch arteries and their branch vessel in the interventional therapy; and
- 3) patient or their guardian agrees to participate in the study and provides written informed consent.

**1.3.2. Exclusion criteria**

Patients will be excluded if they meet any of the following criteria:

- 1) heart, lung, liver, or kidney failure or other serious diseases;
- 2) generalized infection;
- 3) severe coagulation disorders;
- 4) history of severe allergy to contrast medium;
- 5) refuse to undergo interventional therapy;
- 6) currently pregnant or lactating;
- 7) life expectancy less than 30 days; or
- 8) actively participating in another drug or device trial.

**1.3.3. Withdrawal criteria**

Patients can quit the study at any time during the research process

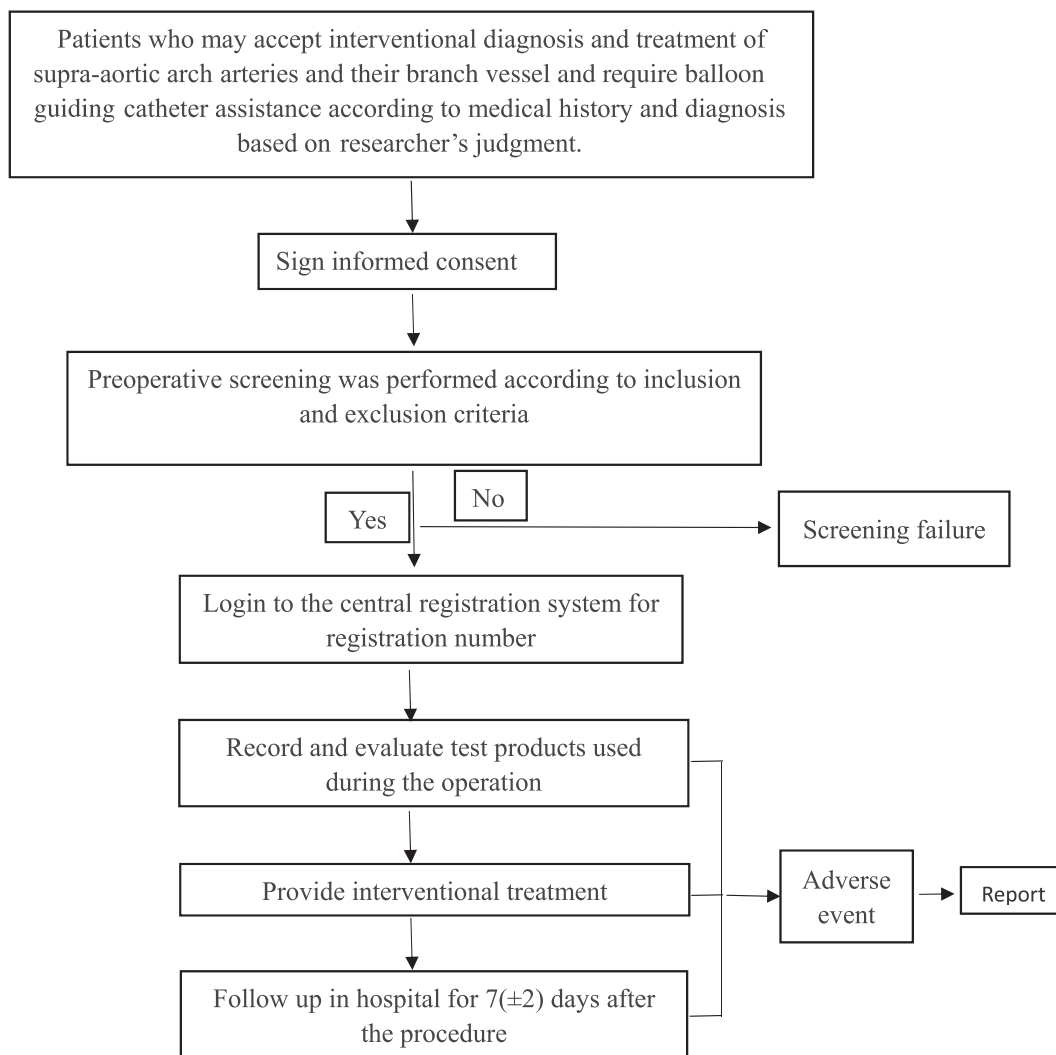


Fig. 1. Study flow chart.

without reason. Patients can also choose not to accept any intervention. If the patient has provided informed consent but chooses not to accept any intervention, they must inform the investigator. Regardless, they have the right to continue to receive standard treatment.

The researcher can withdraw patients at any time during the study based on medical judgment.

The patients can discontinue treatment in advance or withdraw from the study due to any circumstances but not limited to the following:

- 1) for medical or safety reasons based on the investigator's judgment;
- 2) after enrollment, upon not meeting the inclusion criteria or meeting the exclusion criteria;
- 3) voluntary subject withdrawal;
- 4) serious protocol violation (determined by the main researchers);
- 5) loss of follow-up (subject cannot be reached to return to the clinic for a visit evaluation or examination by telephone, mail, etc. for successive two times);
- 6) researchers and sponsors terminate the study; or
- 7) patient death.

The researcher will attempt to obtain the reason for withdrawal from the trial of all subjects, such as adverse events, correcting futile treatment, decisions based on researcher, or other reasons and record it in the electronic data capture system. The subjects who are withdrawn in advance should finish the visit according to the follow-up process schedule.

Subjects who withdraw from the study will not be replaced, which means the randomized number is exclusively relevant to each subject and cannot be reused.

#### 1.4. Outcome measures

##### 1.4.1. Primary efficacy outcomes

The primary efficacy endpoint is the immediate operation success rate. Surgical success must meet the following two conditions simultaneously: 1) BGC successfully delivers the interventional devices to a specific location; and 2) BGC temporarily blocks the blood flow and is withdrawn successfully. We inject the contrast agent through the BGC lumen or another catheter. If the contrast agent does not spread from the distal end of the balloon to the proximal end, the BGC blocks the blood flow successfully; otherwise, it fails. Immediate operation success rate = number of patients with immediate operation success/number of patients using the SeparGate™ BCG × 100%.

##### 1.4.2. Secondary efficacy outcomes

The secondary efficacy endpoint is product performance, evaluated as follows:

- 1) operation performance including rigidity, smoothness, and fracture resistance of the catheter wall and catheter push performance and compatibility;
- 2) display effect of catheter marker under X-ray;
- 3) catheter integrity and existence of adhesion thrombus when the catheter is withdrawn from the body; and
- 4) whether the balloon ruptured.

#### 1.5. Safety evaluation

##### 1.5.1. Serious adverse event

Adverse events during the trial will be recorded including but not limited to the following: puncturing site hematoma and bleeding, cerebral vasospasm, vessel dissection, vessel perforation, air embolism, thrombus (acute or subacute), vessel occlusion, distal embolization, infection, adverse reaction to antiplatelet and anticoagulant drug, intracranial hemorrhage, stroke, and death.

(Serious) adverse event rate = number of subjects with (serious) adverse event/total number of subjects using SeparGate™ BCG × 100%

##### 1.5.2. Device defect

Any device defect in the trial including instrument fracture, balloon rupture, bad compatibility, marking error etc.

Device defect rate = number of defective devices/total number of devices × 100%

#### 1.6. Sample size

We plan to include a total of 128 patients according to the research hypothesis and an estimate of the expected effect according to statistical principles. The sample size calculation was based on the primary endpoints represented by the immediate operation success rate.

According to a literature report, clinical experience, and sponsor's confirmation, the immediate operation success rate is hypothesized to be 99%, while the evaluation standard, that is the target value, is set at 94% based on a one-sided test with a significance level of 2.5%, study power of 80%, and maximum possible dropout rate of 5% during the study. As a result, the enrollment of 128 patients is required.

#### 1.7. Statistical analysis

- 1) Descriptive analysis: Categorical data are described as frequency and constituent ratio. Measurement data are described using means, standard deviations, median, 25th quantile and 75th quantile, and maximum and minimum.
- 2) Baseline demographic analysis: Descriptive analysis will be the main method. For comparisons that may involve subgroups, the likelihood ratio chi-square test will be used for intergroup comparisons of categorical data. Fisher's exact test will be used when the theoretical frequency of cell values over 25% is less than 5. When the measurement data are normally distributed, a t-test will be used for intergroup comparisons; otherwise, the Wilcoxon rank sum test will be used.
- 3) Curative effect analysis: All patients using the research product will be included in the analysis. For a primary efficacy parameter, an asymptotic normal procedure or Fisher's exact test will be used to estimate the immediate operation success rate and 95% confidence interval. We will then compare the lower limit of the confidence interval with a preset target value to determine whether the experimental product meets the needs of the clinical application. For other curative effect indexes, the analysis is the same as baseline data. The intra-group secondary curative effect will be compared using a paired t-test if the measurement data are normally distributed; if not, the Wilcoxon signed rank test will be used. Intra-group qualitative index values will be compared using McNemar's chi-square test.
- 4) For the safety evaluation, adverse events will be described by cases and incidence. At the same time, the specific performance and extent of adverse events and their relationship with the instrument's implantation will be described in detail.
- 5) For the primary endpoint, a one-sided statistical analysis will be performed with a significance level of 2.5%; for the other endpoints, a two-sided statistical analysis will be performed with a significance level of 5% (unless specified). SAS® version 9.4 will be used to analyze the data.

#### 1.8. Ethics approval

The trial has been approved by all relevant local ethics boards. The investigator will obtain written approval before being allowed to conduct and participate in the study. Any changes to the research protocol will receive approval from the ethics committee prior to being implemented. The investigator will be responsible for timely submission of serious adverse events to the ethics committee in writing during the clinical trial.

Details of the clinical trial, including test content, test purpose, expected efficacy, possible adverse events, and corresponding coping measures, will be relayed to the subjects or guardians, who will then be asked for informed consent.

### 1.9. Trial monitoring and supervision

The CRC (clinical research coordinator) assists investigators in managing specific affairs of non-medical judgment. Meanwhile, the monitoring officer appointed by sponsors conducts regular supervision and visits to the trial hospital to ensure all content of the protocol is strictly adhered to and the content from EDC (Electronic Data Capture) system is consistent with the original data.

## 2. Discussion

Ischemic cerebrovascular disease has a high incidence, and the key to endovascular treatment should be achieving successful recanalization with few complications.<sup>13</sup> In CAS and the recanalization of acute large vessel occlusion (LVO), distal embolism is a common complication, especially in patients with atherosclerotic lesion, which makes endovascular recanalization technically challenging.<sup>14–16</sup> Once the plaque is disrupted, it flows into the distal vessel and forms a cerebral embolism, which can cause partial paralysis or even be life-threatening. Several recent studies have indicated the use of a BCG to significantly reduce the risk of distal embolization during mechanical thrombectomy for acute ischemic stroke with LAO.<sup>13,17–20</sup> In addition, using a BGC with a stent retriever resulted in superior revascularization, a decreased need for adjuvant therapy, a shorter procedure time, a less frequent need for a stent retriever, and improved clinical outcomes.<sup>10,13,20–22</sup> Moreover, BGC with a wide lumen is useful for thrombus aspiration in ICA (simple aspiration using the balloon catheter technique),<sup>23,24</sup> which can also contribute to shortening of the puncture-to-reperfusion time by the aspirating thrombus without additional procedures, enabling less invasive thrombectomy due to the use of simple manual aspiration, and can shift immediately to subsequent procedures such as delivering a stent retriever or ADAPT. One report detailed the advantages of BGC for aneurysm embolization, including improved navigation of a tortuous arterial anatomy, coil stabilization during aneurysmal coiling, and freedom to utilize aneurysmal neck remodeling balloons as additional adjunctive techniques or deploy rescue stents.<sup>25</sup> However, these were not prospective multicenter randomized clinical trials, which limits the value of their evaluations. They overemphasize the efficiency but neglect potential complications such as dissections related to navigation of the BGC into the distal vessel and patient intolerance of cerebral vessel occlusion.<sup>12,26</sup> Operational difficulty due to tortuosity and/or vessel diameter is also a problem. In these patients, BCG preparation and placement can be more difficult and time consuming, causing a delay in recanalization associated with an unfavorable prognosis. When using a BGC, one must use an 8 Fr or 9 Fr groin sheath, which is larger than the typical 6 Fr access needed for traditional interventional therapy. A larger sheath size is associated with an increasing rate of access site complications<sup>27</sup>; however, previous studies show very low groin complication rates with 8 Fr and 9 Fr sheaths.<sup>28</sup> Further research should be conducted to validate these findings, as most of these trials included only patients with AIS due to LVO of the anterior circulation.

This prospective multicenter clinical study will aim to assess safety and efficacy simultaneously and include patients of AIS with LVO or subacute/chronic LAO and aneurysms. The design of BGC consisting of hardness gradient, a highly compliant balloon, and larger lumen size increases its security and operability. The results of this trial may provide a clinical reference for BGC use in the future. However, the trial protocol has some limitations. First, its efficacy outcomes are immediate operation success rate and product performance, not including modified Rankin

scale scores beyond 3 months. Second, this will be a non-randomized clinical study; whether to use the BGC will be determined by a neuro-interventionist. And finally, the bias of the patient selection process may influence the study's outcome.

### Patient Consent

Written informed consent was obtained from patients for publication of these case reports and any accompanying images.

### Declaration on interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this week.

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