



Safety and efficacy of the SeparGate™ balloon-guiding catheter in neurointerventional surgery: A prospective, multicenter, single-arm clinical trial



Huan Liu^{a,1}, Rufeng Jia^{a,1}, Yanyan He^a, Tengfei Zhou^a, Liangfu Zhu^a, Yonghong Ding^b, Juha Antero Hernesniemi^c, Tianxiao Li^{a,**}, Yingkun He^{a,*}

^a Department of Cerebrovascular Disease, Zhengzhou University People's Hospital, Henan University People's Hospital, Henan Provincial People's Hospital, Henan Provincial Neurointerventional Engineering Research Center, Henan International Joint Laboratory of Cerebrovascular Disease and Henan Engineering Research Center of Cerebrovascular Intervention, Zhengzhou, 450003, China

^b Department of Radiology, Mayo Clinic, Rochester, MN, USA

^c "Juha Hernesniemi" International Center for Neurosurgery, Henan Provincial People's Hospital, Zhengzhou, China

ARTICLE INFO

Keywords:

SeparGate™ balloon guiding catheter
Safety and efficacy
Neurointerventional surgery

ABSTRACT

Objective: To evaluate the safety and efficacy of the SeparGate™ balloon-guiding catheter (BGC) for blocking flow and delivering devices in neurointerventional surgery.

Method: This prospective multicenter single-arm trial enrolled patients who received BGC adjuvant therapy to provide temporary blood flow arrest of the supra-aortic arch arteries and their branch vessels in interventional therapy. The primary endpoint was immediate procedural success rate in flow arrest, device delivery, and withdrawal. The efficacy endpoints were intraoperative product performance, including rigidity, smoothness, fracture resistance of the catheter wall, catheter push performance, compatibility and radiopaque display, integrity, adhesion thrombus after withdrawal and balloon rupture. The safety endpoints were adverse and serious adverse events associated with the test device and serious adverse events resulting in death or serious health deterioration.

Result: A total of 129 patients were included; of them, 128 were analyzed in the full analysis set (FAS) and per protocol set (PPS). Immediate procedural success was achieved in 97.7% of patients with FAS and PPS. The lower bound of the 95% confidence interval was 94.6%, higher than the preset efficacy margin of 94%. Device-related adverse events occurred in 2 (1.6%) cases. One was mild adverse event of vasospasm, which resolved spontaneously. The other was serious adverse event of dissection aggravation, which was treated with stenting angioplasty. No device defects were observed.

Conclusion: In neurointerventional surgery, the SeparGate™ BGC can be used to temporarily block the flow of the supra-aortic arch arteries and their branch vessels and guide the interventional device to the target vascular position.

1. Introduction

Cerebrovascular disease is the second leading cause of death.¹ In recent years, neurointerventional therapy has significantly improved the procedural success and favorable prognosis rates of these patients.^{2,3} However, some technical problems remain unresolved. Plaques that rupture during surgery escape to the distal vessel and cause ischemic

events in atherosclerotic patients.⁴ Intraoperative aneurysm rupture results in subarachnoid hemorrhage with high morbidity and mortality rates.⁵ Vascular tortuosity renders the interventional device inaccessible to the target vessel. This can preclude some patients from interventional therapy.⁶

The balloon-guiding catheter (BGC) can both deliver the intervention device as a support catheter and temporarily block blood flow by

* Corresponding author. Department of Cerebrovascular Disease, Zhengzhou University People's Hospital, No 7, Weiwu Road, Zhengzhou, Henan, 450003, China.

** Corresponding author. Department of Cerebrovascular Disease, Zhengzhou University People's Hospital, No 7, Weiwu Road, Zhengzhou, Henan, 450003, China.

E-mail addresses: dr.litianxiao@zhu.edu.cn (T. Li), heyinkun@zhu.edu.cn (Y. He).

¹ Co-first author: Huan Liu and Rufeng Jia have contributed equally to this study and should be considered as co-first authors.

inflating the balloon, which can prevent or reduce the above complications. However, the use of BGC is controversial considering puncture site hematoma, iatrogenic dissections, other complications, and additional medical expenses.^{7,8} The limited domestic BGC product options also impede its clinical use.

The domestic SeparGate™ BGC (Hunan Ruikangtong Technology Development Co., Ltd.) is registered with the China Food and Drug Administration (CFDA). This trial is the first to evaluate the safety and efficacy of SeparGate™ BGC in endovascular therapy for cerebrovascular disease.

2. Method

2.1. Study design and patients

This prospective multicenter single-arm study aimed to verify the safety and efficacy of the SeparGate™ BGC in neurointerventional surgery (registration number: ChiCTR1800014459). Between February 28, 2018, and September 28, 2019, 129 patients from seven hospitals in China were enrolled. Eligible patients were aged 18–80 years and required temporary blocking of the blood flow of the supra-aortic arch arteries and their branch vessels during interventional therapy. Patients were excluded if they were diagnosed with heart, lung, liver, kidney failure, or other serious diseases; generalized infection; severe coagulation disorders; or severe known contrast allergy. Before implementation, the ethics committee of each participating center approved the trial protocol. Written informed consent was obtained from patients or their legally authorized representatives before enrollment. Follow-up was performed preoperatively, intraoperatively, and at 7 days postoperative. The details are described elsewhere.⁹

2.2. Study device and procedure

The SeparGate™ BGC is a double-cavity catheter with steel wire mesh reinforcement including the catheter cavity to allow access to the interventional device and the balloon cavity to inject the contrast agent and water. The distal part of the catheter was equipped with radiopaque markers and a compliant balloon. When filled, the balloon can temporarily block the blood flow from the proximal to the distal vessel. The proximal portion of the BGC is a Y-joint connecting the catheter cavity and the balloon cavity. Fig. 1 shows the detailed structure of the device.

Patients who underwent BGC adjuvant therapy for arterial embolization, stent angioplasty, recanalization of arterial occlusion, or other procedure according to their medical history and the investigators' clinical diagnosis were included. The contrast agent and normal saline were mixed in a 1:1 ratio as a balloon inflation medium. To reduce the complications caused by air embolism, the balloon cavity was degassed until no air bubbles were aspirated. Next, the balloon was inflated and deflated to check for leaks or shape abnormalities. Intraoperatively, the catheter lumen was flushed with heparinized saline and the air was evacuated. According to surgical requirements, the BGC was inserted into the target vessel with the guiding wire under X-ray fluoroscopy, and then the guiding wire was removed. Angiography was performed to measure the vessel size and determine the balloon diameter for expansion and the required filling fluid volume. The filling fluid was then injected into the

balloon, and occlusion was simultaneously observed through digital subtraction angiography. After the necessary operation, the balloon was deflated to avoid prolonged ischemia of the distal blood vessels. The balloon was completely deflated prior to catheter withdrawal. Fig. 2 shows a typical case treated with the SeparGate™ BGC.

2.3. Outcome measures

The primary endpoint was the immediate operation success rate defined as successful delivery of the interventional devices to the target location, temporary blockage of the blood flow, and successful withdrawal. The secondary endpoints were intraoperative product performance evaluated by the operators on a scale of 1–5 of its rigidity, smoothness, and fracture resistance of the catheter wall, catheter push performance and compatibility, radiopaque display of the catheter under X-ray guidance, catheter integrity and adhesion thrombus after withdrawal, and incidence of balloon rupture.

The safety endpoints were adverse and serious adverse events. Adverse events were defined as unfavorable medical events occurring during a clinical trial, whether or not related to the test device, including hematoma or bleeding at the puncture site, vasospasm, vascular dissection, vascular perforation, air embolism, acute or subacute thrombosis, vascular occlusion, distal vessel embolism, infection, adverse reactions to antiplatelet/anticoagulant drugs or contrast agents, intracranial hemorrhage, stroke and death, and device defect rate including device fracture, poor compatibility, and error markers. Serious adverse events can result in death or serious health deterioration.

2.4. Statistical analysis

The sample size was determined by the assumption of an immediate procedural success rate of 99% with an evaluation standard of 94%, one-sided statistical significance level of 0.025, test power of 80%, and maximum dropout rate of 5%. Categorical data are summarized as numbers and percentages, while continuous variables are shown as mean \pm SD. The primary endpoint was analyzed based on the full analysis set (FAS) and per protocol set (PPS). The asymptotic normal or exact probability method was used to analyze the immediate procedural success rate and 95% confidence interval (CI). The lower-bound CI was compared with the preset target value with a one-sided significance level of 0.025 to judge whether the test product met clinical application needs. Baseline data, secondary endpoints, and safety endpoints were descriptively analyzed based on the FAS, with a two-sided significance level of 0.05. Adverse events are described as number and incidence, while the relationship between specific presentation, severity, and device implantation are described in detail.

3. Result

3.1. Patient and vascular disease characteristics

According to our statistical calculations, this study required at least 128 patients. A total of 129 patients were included; of them, 128 were included in the FAS and PPS, while one patient was excluded for no use of a matching arterial sheath. The mean patient age was 60.57 ± 12.37

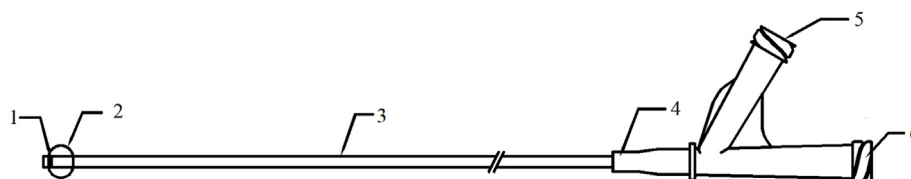


Fig. 1. Description of balloon guiding catheter structure. Radiopaque marker (1), balloon (2), catheter (3), catheter reinforcement structure (4), balloon filling seat (5), catheter seat (6).

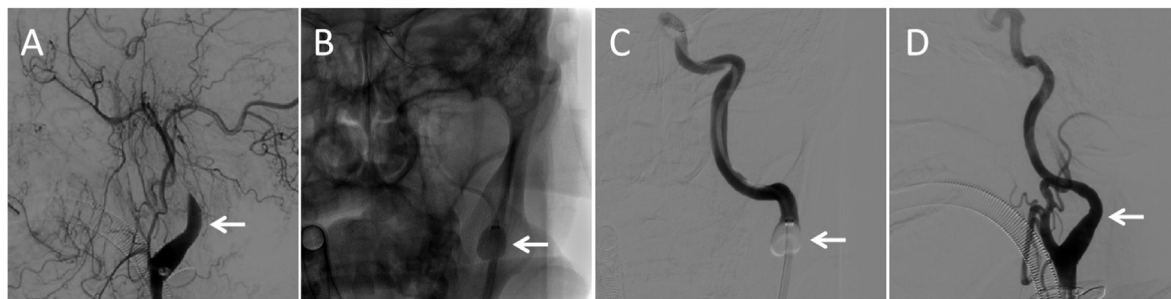


Fig. 2. Balloon guiding catheter use in an acute stroke patient with a left internal carotid artery occlusion (A). The balloon guiding catheter was dilated (B and C), and no dissection occurred at the site after recanalization (D).

years, and 87 (67.97%) patients were male. Preoperative diagnoses included intracranial aneurysm in 4.7% (6/128), intracranial artery stenosis or occlusion in 20.3% (26/128), carotid artery stenosis or occlusion in 38.3% (49/128), and other diseases such as acute cerebrovascular disease and cavernous sinus fistula in 78.9% (101/128) patients. The patients' baseline characteristics and medical history are summarized in Table 1.

3.2. Procedure

Intracranial aneurysm embolization was performed in 3.9% (5/128) of patients, intracranial stent angioplasty for arterial stenosis in 3.1% (4/128), recanalization and stent angioplasty for intracranial arterial occlusion in 8.6% (11/128), recanalization for acute cerebrovascular occlusion in 25.8% (33/128), stent angioplasty for carotid arterial stenosis in 22.7% (29/128), recanalization for carotid arterial occlusion in 18.8% (24/128), and other in 52.3% (67/128). Right femoral artery access was established in 96.9% of patients versus left femoral artery access in 3.1% patients. The target vessel location included the common carotid artery, internal carotid artery, vertebral artery, and other vessels. All BGC products successfully delivered interventional devices, including micro-guide wires, micro-catheters, guiding catheters, stent retrievers, and other devices. Temporary blockage of the blood flow failed in 2.3% of cases. All test devices were successfully withdrawn. The procedure details are summarized in Table 2.

Table 1
Patient baseline characteristics (n = 128).

Demographic	n (%)
Age (years)	60.57 ± 12.37
Female	41 (32.0%)
History of present and previous illness	
Hypertension	78 (60.9%)
Diabetes mellitus	35 (27.3%)
Hyperlipidemia	11 (8.6%)
Atrial fibrillation	18 (14.1%)
Coronary artery disease	18 (14.1%)
Smoking history	44 (34.4%)
Alcohol use	31 (24.2%)
Ischemic stroke	13 (10.2%)
Cerebral artery stenosis or occlusion	9 (7.0%)
Cerebral artery stenosis angioplasty or stent	2 (1.6%)
Carotid endarterectomy	0 (0.0%)
Surgical revascularization	2 (1.6%)
Severe allergy to contrast	2 (1.6%)
Preoperative diagnosis	
Intracranial aneurysm	6 (4.7%)
Intracranial artery stenosis or occlusion	26 (20.3%)
Carotid artery stenosis or occlusion	49 (38.3%)
Intracranial vascular malformation	0 (0.0%)
Others	101 (78.9%)
Anticoagulation during screening	13 (10.2%)
Antiplatelet during screening	67 (52.3%)

3.3. Efficacy outcomes

For the primary outcome, 97.7% (125/128) (95% CI, 94.6–100.0%, $P = 0.0146$) of patients achieved immediate procedural success rates in terms of FAS and PPS. The lower bound of the 95% CI was 94.6%, which is greater than the preset target value of 94%, indicating that the test device meets the clinical application requirements. For the secondary endpoints, most patients had a score of 4–5 in operation, radiopaque, and withdrawing performance with average scores of more than 4.5 and no cases of balloon rupture. Table 3 shows the details of the efficacy outcomes.

3.4. Safety outcomes

Adverse events occurred in 78.9% (101/128) cases, while serious adverse events occurred in 21.1%. Two (1.6%) were determined to be possibly related to the test device but not the technique. In one patient with acute ischemic stroke and left middle cerebral artery occlusion caused by an internal carotid dissection of moderate severity, the test device aggravated the dissection during balloon inflation and blood flow blockage. Stent angioplasty was performed for the dissection, and the lesion had disappeared by the 1-month follow-up. In the other device-related adverse event, vasospasm occurred in the C1 segment of the left internal carotid artery (ICA) during the delivery of a 7.5F balloon catheter, but it spontaneously disappeared. No device defects were observed.

Table 2
Procedural details (n = 128).

Surgical method ^a	n (%)
Intracranial aneurysm embolization	5 (3.9%)
Stent angioplasty for intracranial arterial stenosis	4 (3.1%)
Recanalization and angioplasty for intracranial arterial occlusion	11 (8.6%)
Recanalization for acute cerebrovascular occlusion.	33 (25.8%)
Stent angioplasty for carotid artery stenosis	29 (22.7%)
Recanalization and angioplasty for carotid artery occlusion	24 (18.8%)
Others	67 (52.3%)
Puncture site ^b	
Right femoral artery	124 (96.9%)
Left femoral artery	4 (3.1%)
Others	2 (1.6%)
Target vessel location of BGC ^c	
Common carotid artery	67 (52.3%)
Internal carotid artery	54 (42.2%)
Vertebral artery	3 (2.3%)
Others	7 (5.5%)
BGC operation	
Successfully temporary flow arrest	125 (97.7%)
Successfully withdrawing	128 (100.0%)
Successfully delivering device	128 (100.0%)

^a 45 patients received two interventional surgical treatment.

^b 2 patients received Puncture from both right femoral artery and radial artery.

^c both common carotid artery and internal carotid artery were blocked in 3 patients.

Table 3
Outcome details(n = 128).

Immediate operation success rate	125 (97.7%)
Score of rigidity	4.59 ± 0.67
Score of smoothness	4.70 ± 0.51
Score of fracture resistance	4.76 ± 0.45
Score of push performance	4.74 ± 0.59
Score of compatibility	4.62 ± 0.75
Score of radiopaque display	4.88 ± 0.40
Score of catheter integrity after withdrawing	4.97 ± 0.22
Score of adhesion thrombus	4.90 ± 0.54
AE	101(78.9%)
Device related AE	2 (1.6%)
SAE	27 (21.1%)
Device related SAE	1 (0.8%)
Device defects	0(0.0%)

during the trial. The mortality rate was 8.59% (11/128), and none of the deaths were related to the test device or procedural technique.

4. Discussion

This prospective multicenter single-arm study showed the efficacy of the SeparGate™ BGC at blocking anterograde blood flow and delivering an interventional device, with good product performance, radiopacity, and withdrawal processes during the procedural. The incidence of adverse events and severe adverse events associated with the test devices was low, suggesting that BGC is a safe and effective adjuvant therapy for cerebrovascular disease.

The immediate procedural success rate is the basic effectiveness index for evaluating surgical instruments, but few studies have reported it. The immediate procedural success rate was 97.7%, with a low boundary of 95% CI, higher than the preset efficacy margin. A Korean study published in 2019 using a similar BGC for interventional treatment of stroke showed an immediate procedural success rate of 97.2% (70/72),¹⁰ consistent with our results. This result primarily demonstrates the efficacy of BGC for blocking anterograde blood flow and delivering interventional devices and indicates that the tested BGC can meet the basic clinical application requirements. The main purpose of temporarily arresting the blood flow is to prevent ischemic events caused by clot fragmentation and distal embolization,^{11,12} improve coil stabilization during aneurysmal coiling and offload to utilize aneurysmal neck-remodeling balloons for additional adjunctive techniques or deploy rescue stents,^{13,14} and control bleeding caused by intraoperative vessel perforation or aneurysm rupture. This trial also enrolled patients with different cerebrovascular diseases. Although the additional benefits of BGC adjuvant therapy have not been analyzed, the device procedural success rate provides theoretical feasibility for the trial design of the BGC that verifies the adding benefit of improved patient prognosis for different cardiovascular diseases.

Device performance is an important factor affecting its popularity and application, and it determines the procedural success, risk of complications, and surgeons' consideration of specific devices. Compatibility and flexibility are common reasons for surgeon reluctant to use the BGC in previous investigations.^{7,8} In our trial, device performance was set as the secondary outcome, and more than 90% of researchers scored 4–5 points for each performance, indicating the good performance of the SeparGate™ BGC for interventional diagnosis and treatment. Delayed therapy and increased procedural time are essential reasons for unfavorable outcomes and complications, especially in cases of acute cerebrovascular disease.^{15,16} The time from a puncture to device placement in the target location and the entire operation time are more subjective and comprehensive indicators of device performance and, thus, should be considered for differences in disease types and vessel tortuosity in future studies.

Concerns about potential adverse events prevent the routine use of BGC in neurointerventional procedures. Common device-related adverse events included hematoma or bleeding at the puncture site, vasospasm,

and vascular dissection. A larger sheath is needed for BGC use which is reported as a risk factor for access site complications.^{17,18} However, a previous study showed that groin complication rates are very low, even with 8 Fr and 9 Fr sheaths¹⁹. In our study, no arteriopuncture-related complications occurred. In a recent report, the sheathless technique of BGC has been supported to reduce access site complications when a large sheath is required, such as for carotid artery stenting and coil embolization.²⁰ Therefore, it is unreasonable to abandon BGC adjuvant therapy when considering puncture complications.

Vasospasm and dissection are mainly caused by repeated procedures due to vascular tortuosity, surgeon inexperience, or inappropriate device size. In our trial, two patients (1.56%) had vasospasm (mild adverse events); one case was related to the test device, a finding that is consistent with that of a previous study of a 4.3% vasospasm rate in the Korean population for a similar device.¹⁰ A dissection in the ICA was aggravated during balloon inflation in one patient (0.8%). Previous studies also showed that BGC use did not increase carotid or groin complications, including carotid dissections, compared to the same procedure without BGC.^{21,22} The distal anchor of the BGC can provide support for the catheter system, which may even contribute to more distal device delivery and reduce surgical complications, especially in an extremely tortuous cervical carotid artery.²³ Gentle manipulation and suitable device selection can further reduce the risk of complications.

The present study has some limitations. First, it was a single-arm trial lacking a comparison group to compare the outcomes. Second, its non-randomized selection process may have resulted in selection bias. In addition, a subgroup analysis was not performed to verify the safety and efficacy of BGC for each cerebrovascular disease. Finally, efficacy does not indicate procedural success, favorable patient outcomes and additional benefits of BGC use.

5. Conclusion

The SeparGate™ BGC can effectively block blood flow and deliver an interventional device with a low complication rate in neurointerventional surgery. Further results in practical clinical applications can provide a reference for its selection and use.

Ethics approval statements

Before implementation, this trial had been approved by ethics committees of each participating center.

Contributorship statement

Huan Liu and Rufeng Jia analyzed the data and wrote the paper. Tengfei Zhou and Yanyan He selected the data. Yingkun He, Tianxiao Li, Liangfu Zhu, Yonghong Ding, and Juha Antero Hernesniemi were responsible for quality control. All authors read and approved the final manuscript.

Funding

This work was supported by the Co-construction of Provincial and Ministry Youth Project (SBGJ202003004) Scientific and Technological Project of Henan Province (202102310037).

Declaration of competing interest

The authors have no conflicts of interest to declare.

References

- GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* 2021;20:795–820.

2. Campos JK, Lien BV, Wang AS, et al. Advances in endovascular aneurysm management: coiling and adjunctive devices. *Stroke Vasc Neurol.* 2020;5:14–21.
3. Bageac DV, Gershon BS, De Leacy RA. The evolution of devices and techniques in endovascular stroke therapy. In: Dehkharghani S, ed. *Stroke [Internet]*. Brisbane (AU): Exon Publications; 2021 Jun 18 (Chapter 9).
4. Salsano G, Pracucci G, Mavilio N, et al. Complications of mechanical thrombectomy for acute ischemic stroke: incidence, risk factors, and clinical relevance in the Italian Registry of Endovascular Treatment in acute stroke. *Int J Stroke.* 2021;16:818–827.
5. Park YK, Yi HJ, Choi KS, et al. Intraprocedural rupture during endovascular treatment of intracranial aneurysm: clinical results and literature review. *World Neurosurg.* 2018;114:e605–e615.
6. Farooq J, Lee JY. Vascular tortuosity in endovascular mechanical thrombectomy. *Brain Circ.* 2021;7:3–7.
7. Goyal M, Kappelhof M, Ospel JM, et al. Balloon guide catheters: use, reject, or randomize? *Neuroradiology.* 2021;63:1179–1183.
8. Blanc R, Escalard S, Baharvadhath H, et al. Recent advances in devices for mechanical thrombectomy. *Expert Rev Med Dev.* 2020;17:697–706.
9. Liu H, Li T, Li Z, et al. Safety and efficacy of the SeparGate™ balloon-guiding catheter in neurointerventional surgery: study protocol of a prospective multicenter single-arm clinical trial. *J Interv Med.* 2020;3:93–97.
10. Yi HJ, Sung JH, Lee MH, et al. Experience of the new FlowGate² device as a balloon guide catheter for ischemic stroke intervention. *World Neurosurg.* 2019;126:e736–e742.
11. Chueh JY, Kang DH, Kim BM, et al. Role of balloon guide catheter in modern endovascular thrombectomy. *J Korean Neurosurg Soc.* 2020;63:14–25.
12. Schönfeld MH, Kabiri R, Knip HC, et al. Effect of balloon guide catheter utilization on the incidence of sub-angiographic peripheral emboli on high-resolution DWI after thrombectomy: a prospective observational study. *Front Neurol.* 2020;11:386.
13. Ohshima T, Dash C, Belayev A, et al. 8-F balloon guide catheter for embolization of anterior circulation aneurysms: an institutional experience in 152 patients. *Nagoya J Med Sci.* 2017;79:435–441.
14. Ohshima T, Miyachi S, Matsuo N, et al. Efficacy of the proximal balloon flow control method for endovascular coil embolisation as a novel adjunctive technique: a retrospective analysis. *Interv Neuroradiol.* 2018;24:375–378.
15. Enomoto Y, Uchida K, Yamagami H, et al. Impact of procedure time on clinical outcomes of patients who underwent endovascular therapy for acute ischemic stroke. *Cerebrovasc Dis.* 2021;50:443–449.
16. Alawieh A, Vargas J, Fargen KM, et al. Impact of procedure time on outcomes of thrombectomy for stroke. *J Am Coll Cardiol.* 2019;73:879–890.
17. Naddaf A, Williams S, Hasanadka R, et al. Predictors of groin access pseudoaneurysm complication: a 10-Year institutional experience. *Vasc Endovasc Surg.* 2020;54:42–46.
18. Stone PA, Campbell JE, AbuRahma AF. Femoral pseudoaneurysms after percutaneous access. *J Vasc Surg.* 2014;60:1359–1366.
19. Shah VA, Martin CO, Hawkins AM, et al. Groin complications in endovascular mechanical thrombectomy for acute ischemic stroke: a 10-year single center experience. *J Neurointerv Surg.* 2016;8:568–570.
20. Kimura R, Nakagawa I, Fukutome K, et al. Feasibility and efficacy of a 9-Fr balloon-guiding catheter sheathless insertion to reduce access site complications during mechanical thrombectomy for acute ischemic stroke. *World Neurosurg.* 2020;140:e266–e272.
21. Velasco A, Buerke B, Stracke CP, et al. Comparison of a balloon guide catheter and a non-balloon guide catheter for mechanical thrombectomy. *Radiology.* 2016;280:169–176.
22. Baek JH, Kim BM, Kang DH, et al. Balloon guide catheter is beneficial in endovascular treatment regardless of mechanical recanalization modality. *Stroke.* 2019;50:1490–1496.
23. Peeling L, Fiorella D. Balloon-assisted guide catheter positioning to overcome extreme cervical carotid tortuosity: technique and case experience. *J Neurointerv Surg.* 2014;6:129–133.