Evaluation of using a double helical, closed-cell stent-retriever (Skyflow) for thrombectomy procedures in acute arterial occlusion: A preclinical study and a clinical trial

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ARTICLE INFO

Keywords:
Acute ischemic stroke
Skyflow stent-retriever
Thrombectomy
Efficacy
Safety

ABSTRACT

Background and purpose: Stent retriever thrombectomy is the standard therapeutic approach for ischemic stroke with acute large-vessel occlusion. This study evaluated the safety and efficacy of a new thrombectomy device (Skyflow) in the treatment of acute ischemic stroke.

Methods: After an arterial occlusion model was established, stent-retriever thrombectomy was performed. Digital subtraction angiography (DSA) and autopsy were carried out immediately after thrombectomy in six animals in the acute experimental group. Simulated stent-retriever thrombectomy was performed for three animals in the subacute experimental group, and follow-up angiography and vascular pathological examination were assessed 90 days after the operation. In the clinical trial, 192 patients with intracranial anterior circulation large vessel occlusion, within 8 h of symptom onset, were included to undergo thrombectomy with either Skyflow or Solitaire FR stent retriever. Efficacy and safety endpoints were recorded (including successful reperfusion, favorable clinical outcomes, time from puncture to reperfusion, instrument operation success rates and National Institutes of Health Stroke Scale (NIHSS) scores at 7 days for efficacy endpoints, and symptomatic intracranial hemorrhage (sICH), subarachnoid hemorrhage (SAH) and all-cause mortality rates for safety endpoints).

Results: All blood vessels achieved successful recanalization in the animal models. In the clinical trial, successful recanalization was attained in 88.4% of patients of the Skyflow group, which was comparable to that of the Solitaire FR group (82.5%) in the full analysis set of the clinical trial. There were no severe complications on DSA, an animal autopsy, or vessel pathological examination in animal experiments. Additionally, no statistically significant difference was observed between the Skyflow and Solitaire FR groups in the clinical trial regarding the safety endpoints.

Conclusion: This study showed that the new Skyflow stent retriever is safe and effective for the treatment of acute large vessel occlusion, as demonstrated in our animal study and human trial.

1. Background

Large vessel occlusion (LVO) accounts for approximately 30% of acute ischemic stroke (AIS) cases and can lead to devastating outcomes in patients without timely and effective recanalization. Intravenous tissue plasminogen activator (IV-rtPA) is an effective therapy. Nevertheless, a limited therapeutic time window and a low recanalization rate restrict its clinical application. Endovascular therapy (EVT) has achieved better recanalization and favorable outcomes in randomized controlled trials published in 2015. The therapeutic time window was extended to 16 and 24 h in the DAWN and DEFFUSE 3 trials, respectively. Currently, EVT has become the standard treatment for acute large-vessel occlusive
stroke.

A stent retriever is recommended as the first-line thrombectomy device according to the AHA/ASA guidelines. However, its clinical application is limited in our country due to its quasi-dependence on importation and high cost. In addition, some patients do not achieve successful recanalization due to refractory thrombi, unexpanded stents, or poor device performance. Furthermore, there are several potential procedural complications, such as vasospasm, endothelial cell damage, vessel perforation, vessel dissection, and device defect. In recent years, some special designs have been used in new thrombectomy devices to solve these problems, including increased effective length, segmented design (Embbotrap, Versi),

distal closure or small mesh (Revive SE),
dual-layer construct (EmboTrap II),
and adjustable and visual design (Tigertriever).

The Skyflow device (Skynor Medical, Shanghai Co., Ltd.) is a domestic stent retriever with a double-helical, closed-cell structure. Hence, it has the advantages of previous stent retrievers with an additional benefit owing to its unique structure. In this study, we aimed to evaluate the safety and efficacy of the new Skyflow thrombectomy device for treating AIS patients.

2. Materials and methods

2.1. Device description

The Skyflow stent has a self-expanding, nickel-titanium, double-helical closed structure, made by laser cutting with a closed-cell and a larger mesh in the middle, small meshes in the distal and proximal sides, and a shorter non-functional length. The distal, middle, and proximal ends of the stent are marked with a radiopaque platinum alloy. The pusher microguidewire is linked to the proximal stent, which can be released or retrieved by pushing or pulling the microguidewire, respectively. The distal part of the microguidewire is a variable-diameter structure coated with a platinum-alloy coil. Fig. 1 shows these structural details. Before the experiment, the device underwent CFDA (China Food and Drug Administration) registration.

2.2. Animal experiments

2.2.1. Animals and thrombus model preparation

Nine Bama pigs (30–35 kg) aged 6–7 months were fed quantitative food with unlimited water until preprocedural fasting. Then 325 mg/d aspirin and 150 mg/d clopidogrel were administered before the operation. These pigs were divided into two groups: the acute experimental group (group 1; n = 6) and the subacute experimental group (group 2; n = 3). The thrombus was made by mixing autologous blood, thrombin, and barium sulfate in proportion (autologous blood 10 mL: thrombin 200U: barium sulfate 1 g) in silicone tubes, similar to a study that used the JRecan thrombectomy device. To assess device performance, effectiveness, and safety, a vascular occlusion model was established by injecting a thrombus into different blood vessels. Thrombectomy was performed for six animals in group 1, and simulated stent-retriever thrombectomy was performed five times for each vessel in three animals in group 2.

2.2.2. Surgical operation

Femoral artery access was established under general anesthesia. After collecting arterial blood for thrombus preparation, heparin was administered to achieve an activated clotting time (ACT) >300 s. The target vessel, with a diameter of 1.5–5.5 mm, was evaluated by advancing the appropriate guide catheter and performing angiography. In six animals in group 1, thrombi with a length of 8–12 mm were delivered to 2–3 appropriate arteries, including the mandibular, renal, ascending pharyngeal, maxillary, and subclavian arteries. The thrombectomy device was delivered to the target vessel and the stent was released for 5 min. The thrombus was then removed with the stent from the vessel. After the above procedure, the pigs were euthanized. In three animals in group 2, simulating thrombectomy was performed five times in each selected blood vessel using an appropriate test device. Four arteries were selected from each animal, and the thrombectomy stent was delivered to the target location, released, retrieved from the sheath, and removed from the vessel during each attempt. After five attempts, we performed digital subtraction angiography (DSA) to reassess these vessels. Following the procedure, the pigs were maintained in an animal house for 30 d, and aspirin was administered at 100 mg/d. After a follow-up DSA at 30 d, the pigs were euthanized, and vascular specimens were processed and fixed for histopathological examination.

2.2.3. Outcome assessment

The angiographic evaluation included an assessment of vessel diameter before injecting thrombus, TICI score immediately and 30–60 min after thrombectomy and distal arterial embolization for group 1, vessel diameter before the operation, after 5 simulating thrombectomies and 30 days after the procedure for group 2. Additionally, vascular vasospasm and damage (including dissection, tearing, perforation, and structural integrity) were assessed for all groups. The potential severity of complications was described as none, mild, moderate, severe, or indeterminate. Device performance was evaluated by operators using five grades: excellent, good, fair, unsatisfactory, and bad. For pathologic assessment, an autopsy was performed after thrombectomy or at 30 days in groups 1 and 2, respectively. Target vessel segments were visually observed in group 1, and abnormalities in the main organs (heart, liver, spleen, lung, kidney, etc.) were observed in group 2. For group 2, vascular injury, inflammation, neointimal maturation, endothelialization, and thrombosis in the untreated vascular segment at the distal end and the proximal, middle, and distal vascular segments after thrombectomy were assessed through histopathological examination.

Fig. 1. Diagram of the Skyflow device. A large mesh in the middle and small meshes in the proximal and distal parts of the stent as well as a double helical structure are highlighted in Panel A. Integral stent retriever structure is shown in Panel B. Pushing wire (L1) with a variable-diameter structure coated with platinum alloy coil in the distal part (L2). The diameters of the stent were 3 mm for TD320; 4 mm for TD420, TD430, and TD440; and 6 mm for TD620 and TD630 (D). The stent retriever’s effective lengths were 20 mm for TD320, TD420, and TD620; 30 mm for TD430 and TD630; and 40 mm for TD440 (L). The radiopaque platinum alloy is shown in M.
2.3. Clinical trial

We conducted a prospective, multicenter, stratified, randomized, single-blinded, parallel-grouped, positive controlled, non-inferiority clinical trial. It compared the safety and efficacy of a new thrombectomy device, Skyflow, with the Solitaire FR blood flow reconstruction device for recanalizing an occluded blood vessel in patients with AIS, within 8 h of symptom onset. Patients who met the inclusion and exclusion criteria were randomized into treatment (using Skyflow) and control (using Solitaire FR) groups at a ratio of 1:1. The efficacy and safety endpoints were assessed according to the follow-up schedule. The details are described in our previously published trial protocol.17

2.4. Ethics and informed consent

Animal experiments and clinical trial protocols were approved by the local animal ethics committee and the ethics committee of each research center before implementation. The clinical trial conformed to the Declaration of Helsinki and the Medical Device Clinical Trial Quality Management Regulations. Written informed consent was obtained from the guardians of the patients.

3. Results

3.1. Results of animal experiments

In group 1, 15 blood vessels in 6 BAMA pigs were successfully occluded with prepared thrombi; the thrombi were implanted in two vessels in three pigs and three vessels in the other three pigs.

3.1.1. Efficacy and safety

In Group 1, the complete recanalization (TICI 3) rate was 100%. Fig. 2 shows a vessel occlusion model that achieved complete recanalization. Fourteen vessels were successfully recanalized with one pass of thrombectomy and one vessel was recanalized with two passes owing to a thrombus located in the renal artery bifurcation, occluding two branches. All devices used for the acute and subacute animal experimental groups had good sheathing, push, release, retraction, and stent performances with good guidewire visibility.

All vascular lumens were intact, after thrombectomy and simulated thrombectomy, without tear or dissection, thrombus fragmentation, or distal embolism, and were patent without stenosis, in both groups on DSA images or animal autopsy. Mild to moderate vasospasm occurred in six blood vessels in both groups and disappeared after injecting calcium-channel blockers with no flow disruption in these vessels and a TICI 3 score (complete reperfusion). In group 2, non-stenotic neointima formation was observed in some vessels, and endothelial cells on these vessel walls were relatively intact on histopathological examination. There was no inflammatory cell infiltration or thrombosis in the vessel lumen. No significant pathological differences were observed between the distal, middle, and proximal thrombectomy vessel segments and the distal vessel segment without simulated thrombectomy. Fig. 3 shows the histopathology of a blood vessel in group 2.

3.2. Clinical trial findings

3.2.1. Baseline data

From May 2018 to September 2019, a total of 192 patients from 14 centers were enrolled and analyzed, including 95 in the Skyflow group and 97 in the Solitaire group. A significantly higher proportion of men were found in the Skyflow group than in the Solitaire group (62 [65.3%] vs. 48 [49.5%]; P = 0.0267).

However, there were no significant differences in other baseline characteristics between the two groups. The baseline data are presented in Table 1.

![Fig. 2. Acute experiment of a swine model undergoing thrombectomy with the Skyflow stent retriever. (A) Digital subtraction angiograms (DSAs) showing the right subclavian ascending branch artery clot embolization. (B) Skyflow stent retriever deployment in the occluded segment of the artery through the microcatheter. (C) Angiogram showing complete recanalization of the occluded artery after the first pass of thrombectomy.]

![Fig. 3. Vessel pathology of the left common carotid artery in an animal of the subacute experimental group. No inflammatory cell infiltration, thrombosis, tear, or dissection in the untreated segment (A) and distal (B), middle (C), and proximal (D) parts of the thrombectomy segments. Endothelial cells on the lumen surface were intact for all vessel segments.]

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### Table 1
Patient key characteristics in clinical trial.

|                      | Skyflow group (n = 95) | Solitaire FR group (n = 97) | P   |
|----------------------|------------------------|-----------------------------|-----|
| Mean Age (y)         | 65.89 ± 11.45          | 65.89 ± 12.47               | 0.517 |
| Gender (Male)        | 62(65.3%)              | 48(49.5%)                   | 0.027 |
| Heart disease        | 51 (53.7%)             | 61 (62.9%)                  | 0.196 |
| Mean NIHSS score     | 15.45 ± 5.12           | 15.77 ± 5.17                | 0.667 |
| Mean ASPECT score    | 11.42 ± 2.07           | 11.56 ± 2.15                | 0.656 |
| pre-morbid mRS       | 0                      | 90(94.7%)                   | 0.166 |
|                      | 1                      | 5(5.3%)                     | 4(4.1%) |
|                      | 2                      | 0(0.0%)                     | 4(4.1%) |
| Occlusion site       |                        |                             |     |
| ICA                  | 24(25.3%)              | 22(22.7%)                   | 0.675 |
| MCA-M1               | 59(62.1%)              | 68(70.1%)                   | 0.241 |
| MCA-M2               | 15(15.8%)              | 9(9.3%)                     | 0.171 |
| Time from onset to puncture (min) | 285(200;370) | 270(204;340)               | 0.597 |
| Intravenous thrombolysis | 22(23.2%)          | 23(23.7%)                   | 0.928 |
| General anesthesia   | 57(60.0%)              | 53(54.6%)                   | 0.453 |
| Artery puncture to successful recanalization | 119.17 ± 46.61 | 120.34 ± 62.73 | 0.883 |
| Success rate of instrument operation | 100(100.0%) | 99(99.0%) | 1.000 |
| Number of stents     | 8(84.4%)               | 92 (94.8%)                  | 0.104 |
|                      | 1 stent                | 11 (11.6%)                  | 5 (5.2%) |
|                      | Adjuvant therapy       | 15(15.0%)                   | 16(16.0%) |
|                      | balloon dilatation     | 13(86.7%)                   | 12(75.0%) |
| Stenting             | 7(46.7%)               | 14(87.5%)                   | 0.023 |
| Outcomes             |                        |                             |     |
| mTICI:2b reperfusion | 84(88.4%)              | 80 (82.5%)                  | 0.241 |
| mRS (0–2)            | 46(48.4%)              | 40(41.2%)                   | 0.317 |
| NIHSS score at 7 ± 2 day | 10 (3–15)              | 10 (3–16)                   | 0.922 |
| Safety endpoints     |                        |                             |     |
| ICH at 24 h          | 23(24.2%)              | 26(26.8%)                   | 0.680 |
| sICH at 24 h         | 7(7.4%)                | 6(6.2%)                     | 0.744 |
| SAH at 24 h          | 7(7.4%)                | 8(8.2%)                     | 0.820 |
| SAIs                 | 35 (36.8%)             | 36 (37.1%)                  | 0.969 |
| Device-related SAIs  | 0(0.0%)                | 0(0.0%)                     | NA   |
| Device defects       | 0(0.0%)                | 11(1.0%)                    | 0.490 |
| Mortality at 90 day  | 17 (17.9%)             | 24 (24.7%)                  | 0.246 |

NIHSS, National Institutes of Health Stroke Scale.
APSCET, Alberta Stroke Program Early CT Score.
mRS, modified Rankin score.
ICA, internal carotid artery.
MCA, middle cerebral artery.
mTICI, modified infarction thrombolysis grading system.
ICH, intracranial hemorrhage.
sICH, symptomatic intracranial hemorrhage.
SAH, subarachnoid hemorrhage.
SAE, serious adverse event.

#### 3.2.2. Efficacy and safety

In the full analysis set (FAS), 84 (88.4%) patients achieved successful reperfusion in the Skyflow group and 80 (82.5%) in the Solitaire group, with no significant difference between the two groups (P = 0.24). After adjusting the combined center effect and National Institutes of Health Stroke Scale (NIHSS) score, the successful recanalization rate difference between the two groups was 7.8% (95% CI: 2.3% to 19.3%), with a non-inferiority test P-value of 0.0002 in the Cochran-Mantel-Haenszel chi-square test. In the per-protocol set, successful recanalization rates were 89.4% (84/94) and 82.5% (80/97) in groups 1 and 2, respectively (P = 0.1696), indicating a difference of 8.1% (95% CI: -2.0% to 19.6%) and a non-inferiority test P-value of 0.0002. Fig. 4 shows the DSA images of a patient with successful recanalization using the Skyflow device. There was no statistically significant difference in favorable clinical outcomes (mRS ≤ 2) at 90 days (Skyflow group [48.4%] vs. Solitaire group [41.2%]), time from puncture to reperfusion, instrument operation success rates, NIHSS scores at 7 days, and all safety endpoints including symptomatic intracranial hemorrhage (sICH), subarachnoid hemorrhage (SAH), and all-cause mortality rates, between the two groups. No device defects occurred in the Skyflow group, while a stent in the Solitaire group was not successfully placed because of obstacles in delivery.

#### 4. Discussion

This in-vivo study demonstrated the efficacy and safety of the Skyflow device for treating acute LVO ischemic stroke. All vessels achieved successful recanalization with the Skyflow device in acute thrombus occlusion pig models, and the recanalization rate was non-inferior to that of the Solitaire stent retriever in the clinical trial also. All test devices had excellent or good performances, and no device defects were observed in the Skyflow group during the clinical trial. In the pig model, there was no obvious vessel injury, stenosis, or thrombosis, as examined using DSA and histopathological analysis. The Skyflow exhibited acceptable complications and a safety profile comparable to that of the Solitaire.

In this study, both preclinical and clinical procedures were performed to assess the efficacy of the Skyflow device for recanalizing occluded vessels. It overcame the limitations of simple preclinical experiments and clinical trials, including architectural differences between animal arteries and human intracranial vasculature. Using vascular occlusion models, with no atherosclerotic arteries or fibrin clots (as in animal experiments), pathological and safety evaluations after several thrombectomy procedures are not possible in a clinical trial. Hence, the preclinical and clinical results could complement and fully demonstrate the performance, safety and efficacy of the new device (Skyflow) for thrombectomy procedures.

The design of stent retrievers is aimed at removing clots and avoiding complications; different devices have specific structures to achieve a...
balance between safety and efficacy. To improve the ability to entrap a thrombus, the Solitaire device using an open cell has an overlapping design to increase the stent-closet combination area. The Trevo device uses a closed and larger cell with thicker struts in a vertical orientation design, while the Tonbridge uses a hybrid design with a combination of closed and partially open cells. To prevent thrombus from escaping, Revive SE features a closed basket at its distal end. EmboTrap uses a segmented design to improve the thrombectomy efficacy in tortuous vessels. The Skyflow device combines some advantages of the above devices with a special design to ensure safety and efficacy during thrombectomy. A large mesh in the middle may provide a suitable radial force in a tortuous vessel and embed the thrombus as a whole to avoid small thrombotic fragments, while small pieces may be entrapped by a small mesh at the proximal and distal segments. The small mesh design also facilitates retracting the thrombus and avoiding thrombus displacement during stent withdrawal. The double helix and closed structure can balance the reduction in fracture resistance caused by large meshes and adjust the malposition and radial forces of closed-cell stents in tortuous vessels. Similar to Trevo ProVue, radiopaque markers in stents could help doctors determine the stent position, length, and deployment form, thus improving the procedure success rate.

Recanalization rate is the key indicator of a successful stent retriever thrombectomy. Solitaire FR achieved a complete recanalization rate (TICI 3) of 86.7% (13/15) in a swine model of acute vessel occlusion, and 71.1% of the patients achieved successful recanalization in a clinical trial. For the Trevo stent retriever, all occluded vessels achieved successful recanalization in swine and canine models of arterial thromboembolism. Recently, new devices, including Jeracan and Tonbridge, also showed ideal performance in animal vessel occlusion models, with 94.4% and 100% successful recanalization rates, respectively. In this study, all occluded vessels in the swine study model were successfully recanalized, corroborating the results of previous animal experiments. In our clinical trial, the successful recanalization rate of 88.4% in the Skyflow treatment group was comparable to that of the 88% and 83% reported in Chinese and German real-world clinical studies, respectively. There was also no statistically significant difference compared with Solitaire FR group in successful recanalization rate in our trial. Fewer vessels required rescue stent implantation in the Skyflow group for successful recanalization following stent-retriever thrombectomy only. The sample size only met the test power requirement of 80%. Enlarging the sample size would have increased the test power and led to a statistically significant difference in the successful recanalization rates. Rapid recanalization can prevent infarction progression, and the time from a puncture to successful reperfusion is an important efficiency index of EVT. In our animal study, all Skyflow devices were successfully employed, released, and removed, with the device performance being either excellent or good. In total, 93.33% of the vessels achieved recanalization after clot retrieval, with only one pass of thrombectomy. In previous clinical reports, the time from groin puncture to successful reperfusion ranged from 70 to 90 min in EVT. In our study, Skyflow device achieved a similar reperfusion time of 77.15 min. This is longer than previously reported studies using stent retriever thrombectomy only, but there was no statistical difference between the Skyflow and Solitaire groups in this study. There was no difference in the outcome at 90 days between the two groups, similar to a previous study. However, there was significant sex difference between the two groups, which has been reported to be associated with clinical outcomes. Further subgroup analysis in future studies may provide more information about the Skyflow stent retriever performance.

Vessel wall injury, including vessel perforation, artery dissection, endothelial cell damage, secondary intracranial hemorrhage, and vascular stenosis, is a common complication of thrombectomy. In this study, the Skyflow device showed excellent flexibility and an appropriate stent size for different vessels to avoid iatrogenic vascular damage. As a result, it achieved good safety with only mild vasospasm on DSA images and no obvious damage to vessel architecture. The rates of SAH were comparable between the two devices and similar to those obtained in a previous study using the Solitaire device; the occurrence of sICH was acceptable for both devices.

Embolization to a target territory or new arterial territory is related to poor functional outcomes. It can prolong the operation time and cause recanalization delay when intraoperative thrombus fragments escape into the distal blood vessels. Embolus in distal small vessels can cause permanent occlusion and infarction in a newly embolized area owing to being inaccessible to thrombectomy devices and insufficient collateral compensation. Distal embol occur in approximately 3%-10% of patients with LVO thrombectomies. Our study demonstrated no distal embolism in the clinical study, and only 3.1% of patients exhibited new infarcts due to distal embolism in the clinical trial, which was lower than previously reported values and may be associated with the hybrid design of the large and small meshes of the stent. There were no differences in other adverse events or serious adverse events between the Skyflow and Solitaire groups, and no device deficits occurred. All the above findings indicate that the Skyflow is an acceptable and safe device for thrombectomy procedures.

The present study had some limitations. First, the reference values for vessel pathology in animal experiments could be further improved because of the small sample size, and the vessel architecture differences between animals and humans might have underestimated the potential damage. Second, although this was a multicenter study, there was a large variation in the number of enrollments among centers, with seven centers enrolling fewer than 10 patients. There were also differences in the reperfusion rates among the centers. In addition, the operators were not blinded to the study, given the shape difference between the Skyflow and Solitaire devices.

In conclusion, the Skyflow device is safe and effective for the treatment of AIS with LVO as demonstrated in our preclinical study and clinical trial. This means that the domestic stent retriever (Skyflow) can substitute the imported device (Solitaire FR) to treat ischemic stroke with acute LVO. However, it is necessary to further investigate its efficacy in real-world clinical practice.

Authors’ contribution statements

Analyzed the data and wrote the paper: Huan Liu, Yanyan He. Conceived and designed the study: Yingkun He, Tianxia Li. Collected the data: Huan Liu, Yanyan He, Tengfei Zhou and Yao Zhao. Responsible for quality control: Liangfuzhu, Yonghong Ding, Yingkun He and Tianxia Li. All authors read and approved the final manuscript.

Funding

This work was supported by the Co-construction of Provincial and Ministry Youth Project (SBGJ2019003004) and Key Research and Development Program of Henan Province (Scientific and Technological Project of Henan Province) (202102310037).

Trial registration

The clinical trial was registered on 11 March 2018 with the Chinese clinical trial registry. The registration number is ChiCTR1800015166.

Ethical approval

The animal experiments and clinical trial protocols were approved by the local animal ethics committee and the ethics committee of each research center before implementation, and the clinical trial conformed to the Declaration of Helsinki, Medical Device Clinical Trial Quality Management Regulations and relevant Chinese laws and regulations. Written informed consent was obtained from the patients or their guardians.
Declaration of competing interest

The authors have no conflicts of interest to declare.

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