ORIGINAL RESEARCH

Preclinical evaluation of the ANCD thrombectomy device: safety and efficacy in a swine clot model

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ABSTRACT

Background The Advanced Thrombectomy System (ANCD) provides a new funnel component designed to reduce clot fragmentation and facilitate retrieval in patients with stroke by locally restricting flow, allowing distal aspiration in combination with a stent retriever (SR).

Objective To evaluate the preclinical efficacy and safety of the ANCD in a swine clot model.

Methods Soft and firm clots were implanted in the lingual and cervical arteries of 11 swine to obtain Thrombolysis in Cerebral Infarction (TICI) 0 blood flow. Mechanical thrombectomy was performed with either a balloon guide catheter+Solitaire 2 stent retriever (BGC+SR, n=13) or ANCD+SR (n=13). TICI flow was evaluated and successful revascularization was defined as TICI 3 (normal perfusion). To characterize safety, a total of 3 passes were performed in each vessel independent of recanalization. Tissues were explanted for histopathological analysis after 3 and 30 days, respectively.

Results First pass reperfusion rates were ANCD+SR: 69% and BGC+SR: 46%. Reperfusion increased after the third pass in both groups (ANCD+SR: 100%, vs BGC+SR: 77%). Recanalization was achieved after an average of 1.4 and 1.9 passes in ANCD+SR and BGC+SR (p=0.095), respectively. Vessel injury was comparable in both groups; endothelial loss at 3 days was the most common injury seen (ANCD+SR: 1.78±1.22; BGC+SR: 2.03±1.20; p=0.73), while other histopathological markers were absent or minimal. Tissues downstream from targeted vessels also showed absence or minimal lesions across both groups.

Conclusions Results in a swine clot model support the high efficacy of the ANCD+SR without causing clinically significant vessel injury potentially related to the new funnel component.

INTRODUCTION

Endovascular treatment (EVT) is recognized as the most effective treatment for large vessel occlusion strokes.[1] The highest degree of recanalization[2] in the shortest time[3 4] with a minimum number of attempts[5] have been shown to correlate with improved clinical outcomes. Even though EVT is highly effective, failure to reach complete recanalization has been reported in about 20% of treated patients.[2 6] In order to improve patient outcomes, different devices and combinations are under development to increase the first pass complete reperfusion rate. The development of such devices includes preclinical testing in phantom models simulating the cerebrovascular human anatomy, and in animal models in which device-related vessel injury can be assessed. Each simulation model has its own characteristics and it is therefore recommended that the safety and efficacy of any new device or combination is proved in different conditions before final evaluation in a human study.

The Advanced Thrombectomy System (ANCD) is a new stroke thrombectomy device comprising a new funnel component. The new funnel component is a self-expanding radiopaque braid covered by a continuous polymeric coating, designed to reduce clot fragmentation and facilitate retrieval by inducing local flow restriction and allowing distal aspiration in combination with a stent retriever (SR). In a recent study using in vitro 3D phantom models replicating an M1 middle cerebral artery occlusion, ANCD+SR showed significantly better reperfusion rates in a lower number of passes than other commonly used device combinations.[7] In this study using a swine model, we aimed to evaluate the preclinical safety and efficacy of the ANCD, and specifically confirm that the use of the new self-expanding funnel is unrelated to more vascular injury in comparison with commonly used devices.

METHODS

Description of the ANCD device

The ANCD is a thrombectomy device comprising two coaxial catheters: the funnel catheter and the delivery catheter, made from variable stiffness sections.

The funnel catheter comprises highly flexible polymers on a braided metallic structure. It is intended to restrict the blood flow locally during the intervention. It is composed of a self-expanding funnel that, when unsheathed, can expand to the diameter of the blood vessel, and adapt to its shape, thereby restricting the blood flow. The funnel catheter can provide effective aspiration that serves as a complementary mechanism when combined with retrieval devices. The funnel is designed to have sufficient flexibility to adapt to the neurovascular tortuosity. The funnel comprises a radiopaque braid and a polymeric film.

The delivery catheter is the outermost catheter of the device, which navigates until reaching the target vessel. It has a hydrophilic coating to reduce friction during use, and a radiopaque marker on the distal end for angiographic visualization. The materials of

the catheter allow enhanced flexibility in the tip, and sufficient stiffness and pushability of the proximal portion.

The total usable length of the ANCD device is 1210 mm, the outer diameter of the delivery catheter is 2.11 mm, the outer diameter of the expanded funnel is 5.2 mm, and the internal diameter of the funnel catheter is 1.04 mm.

ANIMAL MODEL

The study was conducted at CBSET Inc (Lexington, Massachusetts, USA) in conformance with the US Food and Drug Administration's Good Laboratory Practices. All procedures were approved by the local institutional care and use committees. CBSET, Inc. is accredited by Assessment and Accreditation of Laboratory Animal Care (AAALAC) International and all procedures and conditions of testing followed the US Department of Agriculture and Animal Welfare Act[8]/Animal Welfare Regulations.[9] Standard veterinary practices were performed during quarantine, including physical examinations and clinical pathology, to determine health status before assignment of animals to the study. A nutritionally balanced diet appropriate for the species was offered daily to all animals with water ad libitum.

Eleven pigs were used in this study (female or castrated male Yorkshire pigs, weight 39–50 kg). The swine model was chosen as the experimental species for this study because the size and anatomy of the vascular system is clinically relevant for the purpose of testing catheter-based medical devices used for the treatment of vascular disease. Swine is an established animal model for vascular studies and generally accepted as a scientific standard.

Animals were anesthetized, intubated, and IV catheterized for the administration of supportive IV fluids and medications. The surgical procedures were performed under aseptic conditions. Physiological parameters were monitored through all the procedures. The femoral artery was accessed via a cutdown approach. A 9 F introducer sheath was advanced into the artery, and heparin (150 U/kg, IV) was administered to prolong the activated clotting time (ACT) to approximately 200–350 s. ACT levels were monitored every 45 min during all the procedures, and additional heparin was administered as needed to maintain the target ACT. Under fluoroscopic guidance, an 8 F Mach 1 guide catheter (CGC, Boston Scientific, Marlborough, Massachusetts, USA) was advanced through the sheath over a guide wire into the descending aorta and to the target arteries. Angiographic images of the vessels were obtained with contrast media to identify a suitable location for the treatment testing site. Angiograms were obtained throughout the procedure: baseline, after each pass, and before necropsy. The parameters assessed by angiography (qualitative and quantitative) were vessel anatomy, target testing site, device monitoring, vessel status injury, vasospasm, and blood flow (modified Thrombolysis in Cerebral Infarction (mTICI) scale).

Two different recanalization strategies were tested in accordance with instructions for use for the interventions in the target vessels: (1) balloon guide catheter (8 F FlowGate2 balloon guide catheter (BGC; 95 cm); Stryker Neurovascular, Fremont, California, USA)+stent retriever (Solitaire 2 4×40 mm; Medtronic Neurovascular), and (2) ANCD (Anaconda Biomed) through the 8 F conventional guide catheter (CGC+SR). Cervical and lingual arteries were targeted. These arteries cover a diameter range of between 2.2 and 5 mm for the ANCD System and Solitaire, and 2.7 to 5 mm for the FlowGate BGC, which represents the size of the target vessels in the cerebrovasculature (internal carotid artery and the middle cerebral artery).

ANCD+SR and BGC+SR devices were distributed among target vessels to ensure assessment was made in all vascular beds at each time point. Randomization of animals was not required for this study as each animal was evaluated with both ANCD+SR and BGC+SR devices.

In order to study the devices in a clinical simulation as a worst-case scenario, three passes in every study group were assessed in all cases (the maximum number of deployments and retractions allowable for the ANCD device and the Solitaire stent retriever according to the instructions for use). Any possible vascular injury caused by the devices (perforation, dissection, thrombosis) and vasospasm was also assessed during the angiographic procedure.

Preparation and delivery of clots

Firm (high fibrin content) and soft clots (high red blood cell content), previously generated with autologous blood (24–48 hours), were administered into the target treatment vessels: cervical and lingual arteries. Vessels and clot consistency were randomly selected to ensure even distribution of test and control devices. Firm clots were prepared using whole blood samples (50 mL) collected into standard tubes, centrifuged, and the serum layer plus 10% of the lower red blood cell layer, including the buffy layer, extracted. This extracted solution was then mixed and incubated for 2 hours. Swine blood (up to 30 mL) was incubated at room temperature for 2 hours to generate the soft clots. In both cases the solid component was stored at 4°C in contrast filled containers until the time of the procedure. Clots were cut to a size appropriate for the target vessel before administration. Clots were introduced to the target region through the 8 F guide catheter via a customized luer to minimize shear/fragmentation. Follow-up angiography was carried out to confirm vessel occlusion (TICI 0). Clots were allowed to stabilize in the vessel for 5–10 min before thrombectomy.

Thrombectomy procedures

Mechanical thrombectomy procedures were performed with the ANCD device or the BGC in combination with the SR for the assessment of the ability to retrieve clot. TICI flow (mTICI scale) and vasospasm were assessed following clot administration and after each thrombectomy attempt.

Intravascular devices were maneuvered under fluoroscopic guidance, and angiographic images of the vessels were obtained to identify the proper location of the device.

In all groups, a microcatheter (Rebar 18, Medtronic Neurovascular) was advanced over a 0.014'' microguidewire (Synchro; Stryker) to the proximal aspect of the occluding clot. In group 1, the BGC was positioned in the proximal section of the target vessel, 5–8 cm away from the clot in the portion of the target artery with the larger diameter, and it was inflated to arrest flow before thrombectomy was performed with the SR, according to the instructions for use and usual practice. Aspiration was then applied through the BGC while the SR was pulled out, with the microcatheter in place. In group 2, the ANCD delivery catheter was advanced to a position close to the proximal aspect of the clot (1–5 cm away from the clot) and the funnel deployed proximal to the clot creating local flow arrest. The microcatheter was then advanced through the clot and the SR deployed as in usual practice. At this point the microcatheter was completely withdrawn to increase aspiration force[10] through the ANCD funnel catheter. The SR was then slowly pulled until its proximal end was inside the ANCD funnel, aspiration was initiated, and the ANCD+SR were progressively conjunctively pulled out (figure 1).

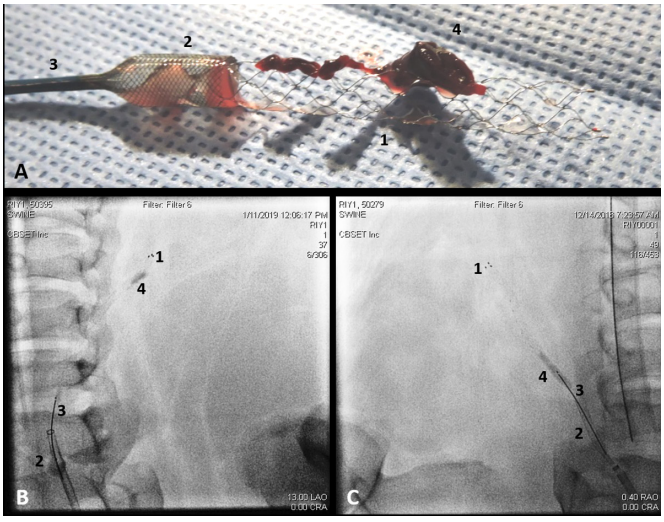

Figure 1 Representative images of interventions. (A) Advanced Thrombectomy System (ANCD) combined with Solitaire 2 holding a firm clot after a thrombectomy: (1) stent retriever (SR), (2) ANCD expanded funnel, (3) ANCD funnel catheter, and (4) firm clot. (B) Representative angiographic images of intervention with a balloon guide catheter (BGC) + stent retriever (SR) in the left cervical artery: (1) distal radiopaque marks of the deployed SR (Solitaire), (2) inflated balloon in the BGC, (3) radiopaque pusher of the SR (Solitaire), and (4) radiopaque clot. (C) Representative angiographic images of intervention with ANCD+SR in the right cervical artery: (1) distal radiopaque markers of the deployed SR (Solitaire), (2) ANCD expanded funnel, (3) radiopaque pusher of the SR (Solitaire), and (4) radiopaque clot.

In all groups, aspiration during the thrombectomy procedure was performed with a 60 cc syringe (Vaclock; Merit Medical) connected to a three-way stopcock through either the BGC (1), or the ANCD funnel catheter (2). For each clot, recanalization attempts with the same strategy were repeated in two more passes (last pass). An angiogram was obtained after each pass to assess reperfusion (TICI flow) and vasospasm. First and final pass recanalization rates (percentage of TICI 3) were used in the analysis.

Histopathology

Animals were euthanized after 3 or 30 days, respectively, and underwent a comprehensive necropsy. Treated vessels were dissected and relevant tissues/organs were collected, fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E) and Verhoeff's stain (specific staining of elastic fibers to visualize the disruption of the internal elastic lamina, tunica media, or external elastic lamina) for histological assessment. Each treated vessel was trimmed to yield at least six cross sections (two proximal, two mid, and two distal) within the putative area of treatment. The proximal and mid-sections were within the deployment site of the ANCD or BGC devices, the distal section was taken within the clot/stent retriever (Solitaire) region. For lingual treatments, the treated vessel sections were taken from the bread-loafed tongue sections and could include surrounding parenchyma. Additionally, untreated distal sections of the vessel were obtained located approximately 5 mm distal from the end of the putative treated area.

Light microscopy was used to determine histological scoring of parameters that reflected the degree and extent of the host response/repair process against the treatment in the target vessels. Histological markers included vascular injury, vascular mural compression lesion, inflammation, endothelialization, luminal fibrin/thrombus deposition, neointima formation, and adventitial fibrosis. Histological sections of vessels were also examined for other microscopic changes, including hemorrhage, necrosis, and type and relative amounts of inflammatory cell infiltrates. Sections of representative downstream tissues were evaluated for any adverse effects associated with treatment, including thrombosis, necrosis, inflammation, and presence of embolic material. Scores were calculated for every section and level, reported as an overall mean for each vessel, ranking from 0 (no injury) to 3 (highest possible degree of injury) in all markers, except for endothelialization, which ranked from 0 (absence of endothelial covering) to 4 (complete endothelial covering).

The study pathologist was blinded to the treatment matrix at the time of the pathology examination.

Statistical analysis

Frequency statistical analysis was obtained, and comparisons were made using the SPSS 17.0 statistical package (SPSS, Inc.). Statistical significance for intergroup differences was assessed by the Pearson χ^2 or Fisher exact test for categorical variables, whereas Student's t-test and analysis of variance were used for continuous variables. When indicated, Mann-Whitney U test and Spearman test were used. A probability value of <0.05 was considered significant for all tests.

RESULTS

Angiographic results

A total of 26 thrombectomies were performed in the 11 animals (BGC+SR: 13, ANCD+SR: 13).

Angiographic and histologic safety results at different follow-up time points are summarized in table 1. Figure 1 shows representative images of the angiographic procedures with devices.

After the first pass, reperfusion rates (TICI 3) were 69% in the ANCD+SR group and 46% in the BGC+SR group. With additional passes, reperfusion rates increased in both treatment groups: ANCD+SR: 100% versus BGC+SR: 77%. The mean number of passes to achieve complete reperfusion tended to be lower with ANCD+SR (1.4) than with BGC+SR (1.9) ($p=0.095$). No statistical significance was found in comparisons.

One distal embolization was observed by angiography and confirmed at 3 days in the BGC+SR group, while no distal thromboembolic events were seen in the ANCD+SR group.

Angiography revealed three dissections during the interventions: one in the ANCD+SR group and two in the BGC+SR group, none of them were related to the ANCD or Solitaire devices as they were seen immediately after catheterization of the target arteries either with the guiding catheter or the BGC. The second dissection in BGC+SR group was mild and not associated with further complications.

A total of seven occlusions were observed after 3 or 30 days, respectively. Two that were detected after 30 days (one for ANCD+SR and one for BGC+SR) were subsequent to severe dissections. Three others (one for ANCD+SR after 3 days, one for BGC+SR after 3 days and one for BGC+SR after 30 days), were considered inherent procedural complications. The last two occlusions observed at 3 days angiography (two for BGC+SR), were caused by the failure to retrieve the clot at the end of the procedure (up to three passes).

No vessel perforation was observed in either group.

Table 1 Angiographic assessments at days 0, 3, and 30 (*p<0.05 vs BGC+SR)

Angiographic assessment			Day 0 (intervention) ANCD+SR n=13	Day 0 (intervention) BGC+SR n=13	Day 3 ANCD+SR n=6	Day 3 BGC+SR n=6	Day 30 ANCD+SR n=6–7*	Day 30 BGC+SR n=6–7*
TICI flow (0, no perfusion; 1, minimal perfusion; 2a, <50.0%, 2b, ≥50.0%, 2c, near complete; 3, complete), % (number)	First pass	0	0.0% (0/13)	38.5% (5/13)	NA	NA	NA	NA
		2a	23.1% (3/13)	7.7% (1/13)				
		2b	7.7% (1/13)	7.7% (1/13)				
		3	69.2% (9/13)	46.2% (6/13)				
	Final pass	0	0.0% (0/13)	7.7% (1/13)	17% (1/6)	50.0% (3/6)	14% (1/7)	14% (1/7)
		2a	0.0% (0/13)	7.7% (1/13)	0.0% (0/6)	0.0% (0/6)	14% (1/7)	14% (1/7)
		2b	0.0% (0/13)	7.7% (1/13)	0.0% (0/6)	17% (1/6)	0.0% (0/7)	0.0% (0/7)
		3	100.0% (13/13)	76.9% (10/13)	83.0% (5/6)	33.0% (2/6)	72.0% (5/7)	72.0% (5/7)
	Number of passes to achieve complete recanalization (TICI 3)		1.4	1.9	NA	NA	NA	NA
Vessel spasm (0, absent, 1, absent/mild (<50.0% lumen reduction), 2, moderate (>50.0% lumen reduction), 3, severe flow limiting)), % (number)	Final pass†	0	46.2% (6/13)	30.1% (4/13)	83.3% (5/6)	83.3% (5/6)	100.0% (7/7)	100.0% (7/7)
		1	23.1% (3/13)	30.1% (4/13)	16.7% (1/6)	0.0% (0/6)	0.0% (0/7)	0.0% (0/7)
		2	15.4% (2/13)	15.4% (2/13)	0.0% (0/6)	16.7% (1/6)	0.0% (0/7)	0.0% (0/7)
		3	15.4% (2/13)	23.1% (3/13)	0.0% (0/6)	0.0% (0/6)	0.0% (0/7)	0.0% (0/7)
Complications, % (number)‡	Emboli		0.0% (0/13)	7.7% (1/13)	0.0% (0/6)	16.7% (1/6)	0.0% (0/7)	10.0% (0/7)
	Vessel dissection§		7.7% (1/13)¶	15.4 (2/13)**	17% (1/6)	17% (1/6)	14% (1/7)	14% (1/7)
	Vessel perforation		0.0% (0/13)	0.0% (0/13)	0.0% (0/6)	0.0% (0/6)	0.0% (0/7)	0.0% (0/7)
	Occlusions		0.0% (0/13)	23.1% (3/13)††	17% (1/6)‡‡	50.0% (3/6)§§	14% (1/7)¶¶	25.6% (2/7)***

*One vessel was discarded for histology assessment owing to severe dissection.
†Vessels with occlusion in which angiography assessment was difficult, were assigned to a score of 0 (absence of vasospasm).
‡Vessels with occlusion in which angiography assessment was difficult, were assigned to absence of complications.
§Only the dissections confirmed by both angiography and histology were considered.
¶This vessel dissection was related to the guide catheter.
**This vessel dissection was related to the BGC.
††One vessel showed a complete occlusion (TICI 0) due to failure to retrieve the clot (clot left within the vessel), and two vessels showed partial occlusions (TICI 2a and TICI 2b) due to failure to retrieve the complete clot (a clot fragment was left within the vessel).
‡‡This occlusion was detected by angiography at day 3 with no findings in the vessel by angiography at day 0.
§§Two occlusions detected at day 3 (TICI 0) were caused by the clot left within the vessel as BGC+SR failed to retrieve the clot after the third pass (TICI 0, TICI 2a, angiography day 0) and one was detected by angiography at day 3 with no findings in the vessel by angiography at day 0.
¶¶This occlusion was related to the severe dissection occurring during the intervention caused by the guide catheter (angiography at day 0).
***One occlusion detected by angiography at day 30 that was related to a severe dissection occurring during the intervention (angiography day 0), while the other occlusion was detected at day 30 with no findings by angiography at day 0.
ANCD, Advanced Thrombectomy System; BGC, balloon guide catheter; SR, stent retriever; TICI, Thrombolysis in Cerebral Infarction.

Vasospasm was a common observation to varying degrees in both groups (15.4% and 15.4% moderate vasospasm (score 2), 15.4% and 23.1% severe spam (score 3), in ANCD+SR and BGC+SR, respectively, after three passes; see table 1). This is a common observation in the swine model as pigs are prone to vasospasm.[11]

HISTOLOGICAL RESULTS

A total of 24 vessels and related downstream tissues were histologically assessed.

In general, all histological markers, including vascular injury, vascular mural compression, inflammation, thrombus, hemorrhage, and others, showed scores below or around 1 in both groups and time points (table 2). Endothelial coverage was low at 3 days (ANCD+SR: 1.78±1.22, BGC+SR: 2.03±1.20; p=0.73) but increased over time to be nearly fully circumferential by day 30 across both groups (ANCD+SR: 3.77±0.23, BGC+SR: 3.50±1.07; p=0.59).

Thus, vessel injury was absent to minimal, and comparable for both ANCD+SR and BGC+SR groups at days 3 and 30, respectively, as no statistically differences were found (see p values in table 2). Figure 2 shows representative histological images of both groups.

Other findings of inflammation, thrombosis, embolization, and necrosis in downstream tissues to the cervical arteries (brachiocephalicus muscle) and lingual arteries (tongue) were also absent to minimal in both groups and time points, with most scores being 0 or below 1 (table 2).

DISCUSSION

This study in a swine model, shows that the ANCD device in combination with the Solitaire 2 stent retriever has a safety profile comparable to that of the balloon guide catheter combined with the same stent retriever. Moreover, the observed efficacy profile parallels the finding achieved in previous preclinical studies using 3D printed phantoms,[7] despite differences in vessel tortuosity and experimental environment.

The findings in the histopathological analysis confirm that the ANCD device does not exert a deleterious impact on arterial walls with only minimal findings comparable to those seen in the BGC+SR group. In order to characterize the safety profile in situations mimicking real human cases, target arteries were selected to have a 2.7–5 mm diameter. These diameters are somewhat smaller than the arterial segments in which guide catheters and BGCs are usually placed, which may explain the few arterial dissections and occlusions that were observed secondary to guiding catheter/BGC manipulations before ANCD/SR deployment.

Theoretically, the innovative design of the funnel as a self-expandable, braided component that adapts to the vessel wall, combining aspiration and local flow arrest, could intuitively suggest an increased risk for significant vessel damage as compared with conventional intravascular devices used in routine thrombectomies. However, the funnel and the entire ANCD device were carefully designed to be atraumatic. The funnel has a smooth polymeric covering and a balanced radial force, sufficient to adapt to the vessel wall and allow aspiration,

Table 2 Histological assessments at days 3 and 30

Histological assessment		Day 3			Day 30		
		ANCD+SR n=6	BGC+SR n=6	P value*	ANCD+SR n=6	BGC+SR n=6	P value*
Treated arteries† ((Mean±SD)	Vascular Injury (0–3)	0.50±0.54	0.47±0.45	0.93	0.61±0.31	0.28±0.31	0.10
	Vascular mural compression lesion (0–3)	0.81±0.25	0.81±0.38	0.99	0.77±0.31	0.78±0.42	0.98
	Inflammation (0–3)	0.36±0.37	0.56±0.36	0.38	0.07±0.16	0.20±0.48	0.94
	Endothelialization (0–4)	1.78±1.22	2.03±1.20	0.73	3.77±0.23	3.50±1.07	0.59
	Luminal fibrin/thrombus (0–3)	0.36±0.81	1.11±1.17	0.23	0.00±0.00	0.28±0.68	0.70
	Neointima (0–3)	0.17±0.15	0.36±0.37	0.26	0.92±0.14	1.14±0.69	0.82
	Adventitial fibrosis (0–3)	0.00±0.00	0.22±0.27	0.18	0.03±0.08	0.00±0.00	0.70
	Hemorrhage (0–3)	0.03±0.07	0.53±0.75	0.09	0.09±0.14	0.28±0.68	0.82
	Necrosis (0–3)	0.64±0.39	0.67±0.30	0.90	0.00±0.00	0.00±0.00	1.00
Downstream tissue to lingual arteries (tongue)‡ (Mean±SD)	Thrombosis (0–3)	0.00±0.00	0.24±0.09	na	0.00±0.00	0.00±0.00	NA
	Necrosis (0–3)	0.00±0.00	0.00±0.00	na	0.09±0.12	0.00±0.00	0.77
	Inflammation (0–3)	0.29±0.40	0.86±0.38	0.25	0.47±0.05	0.07±0.10	NA
	Presence of embolic material (0–3)	0.29±0.21	0.05±0.08	0.25	0.37±0.28	0.00±0.00	NA
Downstream tissue to cervical arteries (brachiocephalicus muscle)§ (mean±SD)	Thrombosis (0–3)	0.00±0.00	0.00±0.00	na	0.00±0.00	0.00±0.00	NA
	Necrosis (0–3)	0.25±0.50	0.00±0.00	na	0.25±0.50	0.00±0.00	NA
	Inflammation (0–3)	0.75±0.50	0.67±0.58	1.00	0.00±0.00	0.00±0.00	NA
	Presence of embolic material (0–3)	0.25±0.50	0.33±0.58	1.00	0.00±0.00	0.25±0.50	NA

*Statistical comparations of downstream tissues were unable to be performed in some cases because values were 0 in all samples or the sample size was inferior to 3 (NA).
†The sample size for histology is n=6 in all groups, one vessel was discarded for histology assessment owing to severe dissection in groups ANCD+SR and BGC+SR with follow-up of 30 days.
‡ANCD+SR 3 days and 30 days, and BGC+SR 30 days n=2, BGC+SR 3 days n=3.
§ANCD+SR 3 days and 30 days, and BGC+SR 30 days n=4, BGC+SR 3 days n=3.
ANCD, Advanced Thrombectomy System; BCG, balloon guide catheter; SR, stent retriever.

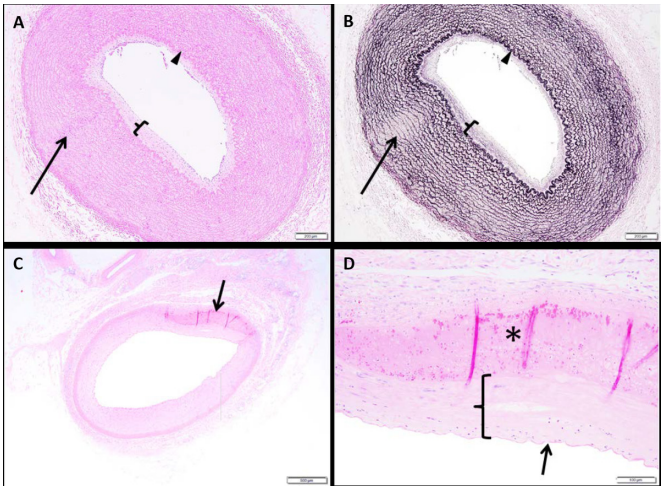

Figure 2 Representative histological images. (A) Right cervical artery, Advanced Thrombectomy System (ANCD) + stent retriever (SR), day 30. Example of vascular injury with faint disruption of tunica media (arrow), neointimal proliferation (bracket), and intact internal elastic lamina (arrowhead) (hematoxylin & eosin (H&E, 4x). (B) Right cervical artery, ANCD+SR, day 30, Verhoeff staining (VER) highlighting elastic fiber disruption in the tunica media (arrow) that was faintly visible on H&E staining; neointima (bracket) and internal elastic lamina (arrowhead) also visible (VER, 4x). (C) Right lingual artery. Balloon guide catheter (BGC) + SR, day 3. Low magnification illustrating a segment of mural necrosis (arrow) (H&E, 2x). (D) Right lingual artery, BGC+SR, day 3. Higher magnification illustrating a segment of mural necrosis (bracket) with necrotic debris (asterisk), and endothelial cell loss across the internal elastic lamina (arrow) (H&E, 10x).

but not excessively high aspiration to risk vessel damage. Additionally, the surface and tip of the catheters are smooth with lubricious coating to facilitate the navigation and avoid vessel trauma. The favorable safety profile in treated vessels is convincingly demonstrated by the histopathological and angiographical assessments clearly showing that the vessel injury caused by the ANCD device in combination with the SR is insignificant and similar to the injury seen after BGC combined with the SR. Histopathological markers of vessel wall injury were absent or minimal, no perforations occurred, and the few cases of dissection were unrelated to the ANCD device and associated with the procedure (BGC or guide catheter).

The ANCD thrombectomy device in combination with a stent retriever achieved high rates of complete recanalization in a low number of passes. The observed efficacy rates are in line with the reperfusion rates achieved in a recently published study in an in vitro model.[7] These rates are comparable with complete reperfusion rates in patients with stroke treated with stent retrievers supported with a BGC.[12] Moreover, the BGC+SR combination showed similar reperfusion results in both models and in real patients, which may indicate that the tested preclinical models could be considered as adequate platforms for final validation of new devices before their first use in human studies.

Recent publications have pointed out that a higher degree of reperfusion is associated with a better outcome and also that achieving the same degree of reperfusion in fewer passes, ideally in a single pass, is a predictor for improved long-term outcome.[2–5] These publications also point out that widely used thrombectomy devices can achieve first pass complete reperfusion rates of around 40–50%. In addition, the combination of balloon blood flow occlusion and aspiration to support mechanical thrombectomy has demonstrated improved reperfusion rates and clinical outcomes, and reduced procedure times.[12–15] New devices with improved

efficacy profiles able to increase the first and final pass success rate will probably lead to improved short- and long-term outcome in patients with stroke undergoing EVT.

The ANCD device is designed to induce local flow arrest in combination with a complete clot ingestion into the funnel, preventing fragmentation and distal embolization. These theoretical advantages are supported by the preclinical observations in both a phantom in vitro model[7] and the present animal study using soft and firm clots. These encouraging results should not be used as predictors of similar success rates in the first in human studies but are likely to represent the best preclinical evidence that can be achieved at this stage. Moreover, the results seen in this study show that ANCD+SR has a safety profile similar to that of the commonly used BGC+SR combination.

The reported study was performed under Good Laboratory Practice in an independent facility, and the results were directly obtained from the official regulatory report.

Limitations

Our study design included specific BGC and SR predicates, and the selection was made considering worldwide availability, impact in the literature, and market penetration. Possibly, other combinations of commercially available devices could show different efficacy profiles; however, owing to the increasing number of available devices it is not possible to test all combinations.

The animal vessels used in this study are less tortuous, without atherosclerosis but more prone to vasospasms than the human vasculature typically encountered in patients with stroke. In this study we tried to use representative clot analogues of human strokes, but the experimental radiopaque soft and firm clots prepared with swine blood do not represent the whole spectrum of possible mechanical properties of thrombi found in human large vessel occlusion strokes, and neither is the incubation time for experimental clots comparable to that of human clots occluding neurovasculature.

CONCLUSION

Preclinical results in the swine clot model support the high efficacy of the ANCD+SR without causing clinically significant vessel injury potentially related to the new funnel component. The efficacy profile in this in vivo study was similar to that in vitro phantom models (previously published), reinforcing the suggestion that the ANCD device when combined with stent retrievers is highly effective in mechanical thrombectomy, maintaining a similar safety profile to that of commonly used devices. This study completes the preclinical escalation testing process before assessing the safety and efficacy of the ANCD+SR in humans.

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Contributors Conception and design: LB, SS, MR, AR, HV, and IG. Procedures in animals: LB. Acquisition of the data: LB and RD. Histological analysis: RD. Analysis and interpretation of the data: LB, RD, MR, and SS. Drafting the article: SS, MR, and IG. Critically revising the article: TA, CC, and RN. Reviewed submitted version of manuscript: all authors. Study supervision: LB.

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Competing interests SS, HV, AR, and IG are employees of Anaconda Biomed. LB and RD are employees of CBSET, a not-for-profit research organization, which received research funding from Anaconda Biomed for the reported work. MR is a shareholder in Anaconda Biomed, consultant for Cerenovus, Medtronic, Stryker, Apta Targets, and Vesalio. TA is clinical consultant for Anaconda, Ablynx, Amnis Therapeutics, Cerenovus/Neuravi, Medtronic, and Rapid Medical. RN: Stryker Neurovascular (DAWN trial principal investigator- no compensation, TREVO Registry Steering Committee – no compensation, Trevo-2 trial principal investigator- modest; consultant - significant); Medtronic (SWIFT Trial Steering Committee - modest; SWIFT-Prime Trial Steering Committee – no compensation; STAR Trial Angiographic Core Lab - significant); Penumbra (3D Separator Trial Executive Committee – no compensation); Cerenovus/ Neuravi (ENDOLOW Trial Principal Investigator, EXCELLENT Registry Principal Investigator, ARISE-2 trial Steering Committee – no compensation, Physician Advisory Board, modest); Phenox (PROST Trial Principal Investigator, Physician Advisory Board, modest); Anaconda (Physician Advisory Board, modest); Genentech (Physician Advisory Board – modest); Biogen (CHARM Trial Steering Committee; Physician Advisory Board – modest). Pharmaceuticals (Physician Advisory Board – modest); Allm Inc. (Physician Advisory Board – no compensation); IschemaView (Speaker, modest); Brainomix (Physician Advisory Board, stock options); Sensome (Research Device Use – no compensation); Viz-AI (Physician Advisory Board, stock options); Philips (Research Software Use – no compensation, Speaker - modest); Corindus Vascular Robotics (Physician Advisory Board, stock options); Vesalio (Physician Advisory Board, stock options); Ceretrieve (Physician Advisory Board, stock options); Astrocyte (Physician Advisory Board, stock options). CC is consultant for Sequent Medical, MicroVention, Stryker and Codman.

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