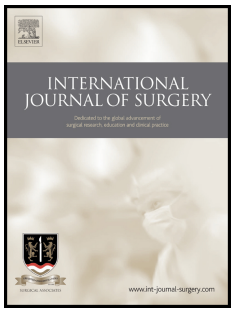
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Abstract

Background: Acute ischemic stroke (AIS) is a worldwide serious health problem. Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA) is the standard treatment; however, only a small number of patients benefit from it due to the strict application restrictions. Recently, more and more evidence prove mechanical thrombectomy is an effective and safe therapy of AIS.

Patients and Methods: From December 2010 to March 2015, 83 patients who underwent mechanical thrombectomy were collected as a sample pool. All patients met the following criteria: National Institutes of Health Stroke Scale (NIHSS) score ≥10, treatment performed within 6 hours from the onset of symptoms, no large hypodensity on CT or multimodal MRI, and angiography revealed occlusion of a major cerebral artery. Recanalization rates were assessed immediately post-procedure by follow-up angiography according to the thrombolysis in cerebral infarction score criteria. Assessment of the modified Rankin Scale was performed 90 days after treatment.

Results: The mean age of patients was 63.3 years, and NIHSS scores 19.12±4.60 at presentation. The vessel occlusions occurred in the middle cerebral artery (68.7%), distal internal carotid artery(7.2%), internal carotid artery with tandem middle cerebral artery occlusion(14.5%), basilar artery(2.4%), and vertebral artery (7.2%). Successful recanalization (TICI 3/2b) was achieved in 56 of 83 patients (67.5%). At 90-day follow-up, good clinical outcome (mRS≤2) was achieved in 33 of 83 patients (39.8%), while 20 patients died (24.1%).

Conclusions: This study revealed mechanical thrombectomy with Solitaire Stent device was an effective and safe therapy, which achieved a high rate of angiographic recanalization and independent outcome accompanied by a low mortality rate.

Keywords: Acute ischemic stroke, large vessel occlusion, mechanical thrombectomy, endovascular therapy, Solitaire stent.

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Introduction

Acute ischemic stroke is a worldwide health problem and associated with high morbidity and mortality rates. In recent years, intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA) has become the standard treatment for acute ischemic stroke[1]. However, only a small percentage of acute ischemic stroke patients received rt-PA because of the narrow time window and other restrictions such as a history of intracranial hemorrhage, coagulation abnormalities, et, al.[2,3]. Moreover, intravenous alteplase appears to be less effective while opening proximal occlusions of the major intracranial arteries, which account for more than one third of cases of acute anterior-circulation stroke[4].

To improve the outcome of acute ischemic stroke, intra-arterial treatment was developed as a potentially effective therapy. Endovascular mechanical thrombectomy has shown advantages over intravenous thrombolysis treatments for proximal lesions, including more rapid achievement of recanalization, enhanced efficacy in treating large-vessel occlusions, potentially lower risks of hemorrhagic complication, a longer therapeutic window and higher recanalization rate[5]. Recent studies indicated that rapid thrombectomy treatment after stroke onset resulted in higher reperfusion rate, better functional recovery and similar safety compared with IV rt-PA treatment[6-8]. Mechanical approaches have shown great potential of replacing locally applied thrombolytic agents as first-line therapy[9] .

Here we report our experience of mechanical thrombectomy using Solitaire stent device in Chinese patients. We also compare our results to other main trails in recent years.

Patients and Methods

This work is in line with the STROBE criteria [10].

This study had been approved by Ethics Committee of The First People's Hospital of Changzhou, Soochow University. From December 2010 to March 2015, 83 patients underwent mechanical thrombectomy using Solitaire stent. All the patients met the following criteria: National Institutes of Health Stroke Scale (NIHSS) score ≥10,

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treatment performed within 6 hours from the onset of symptoms, no large hypodensity on CT or multimodal MRI, and angiography revealed occlusion of a major cerebral artery.

On admission, a stroke neurologist examined all patients. The baseline NIHSS score, a clinical measure of neurologic deficit with a range from 0 (no deficit) to 42 (maximum possible deficit), was used to identify patients. Patients with a NIHSS score of 10 or more have a greater than 80% likelihood of a major arterial occlusion[11]. Cranial CTA or multimodal MRA were obtained prior to every intervention to confirm the diagnosis of large vessel occlusion and to rule out intracranial hemorrhage (ICH). Interventional treatment was initiated within 6 hours from onset of stroke symptoms. The “time of symptom onset” was defined as the acute onset of symptoms as observed by the family members. The “door time” was defined as the time when the patient arrived at the emergency room and the “needle time” was the time groin puncture was performed.

Endovascular Procedure

All interventions were performed by consultant neuro-interventionalists Ya Peng and his colleagues on a biplane system (Artis Zee Biplane; Siemens, Erlangen, Germany) under local or general anesthesia. The choice of general anesthesia or conscious sedation for each particular procedure was at the operator’s discretion. Using transfemoral access, a 6F sheath (TERUMO RadifocusTM Introducer, Tokyo, Japan) was placed into the right femoral artery. An intravenous bolus of 3,000 IU of heparin was administered. Conventional cerebral angiography showed the location of the occlusion and collateral circulation. A 6-Fr guiding catheter was placed in internal carotid artery (ICA) or vertebral artery (VA). A Rebar 18 microcatheter (eV3, Irvine, California, USA) was navigated through the thrombus with microwire. The 4mm×20mm Solitaire stent (eV3, Irvine, California, USA) was deployed in the clot and allowed to wait for 2 or 3 minutes. The entire system, comprised of the stent and the microcatheter, were completely retrieved while the assistant produced suction by placing a large syringe at the ‘Y’valve of the guiding catheter, allowing the thrombus to be successfully removed. After retrieval, the clot typically could be seen entangled

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within the meshwork of the stent. Control angiography was performed following each retrieval until success. DynaCT (Artis ZeeBiplane; Simens, Erlangen, Germany) was immediately performed to evaluate the presence of any intracranial hemorrhage. The femoral sheath was removed and the wound closed with an Angio-Seal (St. Jude Medical, Inc, St. Paul, MN) vascular closure device. The thrombolyses in cerebral infarction (TICI) scores were estimated from angiographic runs before and after the procedure. Assessment of angiographic images was performed in consensus by 2 experienced neuroradiologists. Concurrent endovascular interventions, such as intra-arterial thrombolysis and detachment of stent or balloon angioplasty after Solitaire stent thrombectomy, were attempted in some of cases. Tirofiban, which is a fast-acting GB IIb/IIIa inhibitor that prevents platelet aggregation and improves cerebral perfusion was administered in 4 cases of stent-assisted angioplasty administered intravenously at an initial dose of 0.4 mg and continued at 0.1μg/kg/min for 24 hours. In one case, vasospasm was found in the M1 segment of the middle cerebral artery (MCA). After injecting 90mg papaverine, the vessel spasm was successfully relieved.

The extent of recanalization was assessed immediately post-procedure by follow-up angiography. Following the procedure all patients were managed in the neuro critical care unit by an experienced team of neuro-intensivists. Thrombolysis in Cerebral Infarction scores were used to evaluate the extent of pre-procedure clot burden, the post-intervention residual clot burden, and the success rate of the procedure. Most cases of this group got a CT and MRI scan on day 1 and an MRA on day 3 to evaluate infarction, hemorrhage and patent of lesion artery. The patient outcomes were assessed by certified examiners at discharge (NIHSS) and the three-month follow-up (mRS).

Statistics

The mean value, standard error and percent value were calculated by the *Microsoft Excel* 2007, and Chi-square test performed by SPSS (Version 17.0).

Results

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There were altogether 83 patients in our series. The mean patient age was over 60 years (range 21-85), and male patients accounted for 60.2% of the pool. Detailed characteristics of stroke patients are presented in Table 1. One 21-year-old male patient was implanted with a CRT-D defibrillator because of end-stage dilated cardiomyopathy with atrial fibrillation, on daily oral warfarin. This patient suffered from acute ischemic stroke with occlusion of MCA.

Distributions of vascular occlusion are presented in Table 2. In 38 patients, stroke etiology was assumed to be cardiogenic embolic. In 20 patients, an additional underlying vessel stenosis within the occluded vessel segment was identified angiographically. Additionally, 5 patients with vessel dissection were diagnosed. One patient's angiography is presented in Figure 1.

Data from the procedure is presented in Table 3. After the thrombectomy procedure, Dyna CT was routinely performed in order to evaluate intracerebral hemorrhage (ICH). Symptomatic hemorrhagic complications were observed in ten patients (12%), one of whom (1.2%) had a subarachnoid hemorrhage and died during hospitalization. Overall, there were 20 fatal outcomes. Fourteen patients died due to extensive brain infarction, five patients died due to a subarachnoid hemorrhage after successful recanalization of the MCA, and one patient died due to multi-organ failure. As listed in Figure 2, a good clinical outcome (mRS at 90 days $\leq$2) was achieved in 33 (39.8%) of the 83 patients, 17 of which showed no signs of any significant neurological deficit, mRS=0). Twenty two (26.5%) patients had a fair outcome (mRS=3 or 4), and 28 (33.7%) patients had a poor outcome or died (mRS=5 or 6). There were no occurrences of technical failure or procedure-related complications such as subintimal necrosis, arterial rupture or dissection, groin complications requiring surgery, or blood transfusion.

Discussion

In this study we report a single center experience in Chinese patients with acute ischemic stroke who underwent mechanical thrombectomy using Solitaire stent thrombectomy device. Our results showed that the thrombectomy with Solitaire stent

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device reached high angiographic recanalization rate and efficiency, while the safety remains same.

Compared with other clinical studies of mechanical thrombectomy

There have been some other clinical studies of mechanical thrombectomy for acute ischemic stroke, including the Penumbra pivotal study[12], the Multi MERCI Trial[13] , the SWIFT trial(SolitaireTM arm) study[14], the MR CLEAN trial[8], the EXTEND-IA trial[7] and the ESCAPE trial[6]. The main indexes of these trials are presented in Table 4. Compared with the results of those trials our study showed a relatively lower reperfusion rate than the Penumbra pivotal study, SWIFT trial and EXTEND-IA trail. The rate of symptomatic intracranial hemorrhage (sICH) and mortality rate in our study were higher than the ESCAPE trial and the EXTEND-IA trial. Also, our percentage of good outcome (mRS≤2 at 3-month) was lower than the ESCAPE trial and the EXTEND-IA trial. This might be caused by the different patient selection criterions. The median NIHSS score of our patients was 19, while this number was 17 in the ESCAPE trial and the EXTEND-IA trial. Additionally, compared to the NIHSS score on admission in the ESCAPE and EXTEND-IA trials, which ranged from 13 to 20, the range of initial NIHSS score in our patients was from 10 to 34,of which 28 patients in our study were scored above 20. An NIHSS score is the most powerful predictor for long-term outcome (three months)[15]. Because of this, our study contained a higher risk and suffered a worse outcome, which is a reasonable explanation for the resulting differences. The outcome at three months and sICH in our study were similar with the Penumbra pivotal study, the Multi MERCI trial, the SWIFT trial and the MR CLEAN trial, except the lower rate of mRS≤2 at 3 months in the Penumbra pivotal study and a lower sICH risk in the SWIFT trial.

Advantages of Solitaire stent

Our experience has shown many advantages of Solitaire stent. First, It is especially useful for removing occlusions at major cerebral arteries because it can directly trap the thrombus into its cells and remove it, then restore blood flow immediately[16]. Considering most of our cases suffered from occlusion of MCA and ICA, this device is extremely valuable. It can also be electrolytically detached when a permanent stent

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placement is necessary[17]. In our series, the stent was completely detached in the C4 segment of the right ICA because of a dissection in one patient. In two other patients, the stents were also detached in the proximal MCA (M1) to treat underlying severe stenosis and to maintain vessel patency and blood flow. As the incidence of stenosis is high in stroke patients, this feature of Solitaire stent shows high convenience for the treatment. Other advantages of this device include that it may be deployed multiple times. In our study, 2.2 stent retrievals were performed to achieve final recanalization on average. Furthermore, our experience also shows that Solitaire stent can be used in curved and narrow distal vessels which were thought to be very dangerous and ineffective for thrombectomy.

About our treatment protocol

In other studies where intracranial arterial occlusion was found on MR angiography, treatment with intravenous rt-PA was started if symptom onset was within three hours. Patients who were symptomatically refractory to IV thrombolysis or ineligible for using IV rt-PA were transferred to the angiography room for endovascular intervention directly. However, in our study, when angiography revealed occlusion at major cerebral artery, mechanical thrombectomy was carried out immediately without applying IV rt-PA. Our rationales are based on the following arguments. First, Del et al[18] found that the combination of a high NIHSS score and hyperdense MCA sign implies a large clot burden, usually with a poor response to IV rt-PA. Additionally, the rate of early recanalization was less than 30% in patients with large vessel occlusions (MCA, BA and carotid terminus) treated by IV rt-PA[18,19]. In our study, the mean initial NHISS score was 19.12±4.60 and more than a half of patients (68.7%) had hyperdense MCA confirmed by either CTA or MRA results. Also, almost half of the cases (48.2%) have significant cardiac history which is a criterion of non-optimal for treatment with IV t-PA. More importantly, research has shown that shortening reperfusion time was very useful for improving clinical outcome in acute ischemic stroke[20], and 30-minute delay was associated with a 10% decrease in the probability of functional independence[21,22]. Therefore, our efforts were focused on reducing time of achieving recanalization, and directly endovascular thrombectomy

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was our first choice.

Our experiences from special circumstances

There are some technical considerations that we learned from our experiences. In The ESCAPE trial, suction through a balloon guide catheter in the relevant internal carotid artery was recommended during thrombus retrieval [6]. However, there is no balloon-occlusion guiding catheter yet in China. Therefore, while the entire system of stent and microcatheter were being retrieved, an assist suction was generated by a large syringe was applied at the "Y" valve of the guiding catheter to create flow reversal, which could aspirate clots from the guiding catheter. When the system was ready for retrieval, we pulled back the stent for indenting the proximal marker of stent into the microcatheter about 5 mm. This process inhibits the proximal stent from forming a cone shape and minimizes vessel wall damage. Additionally, in two of our cases, M3 segment thrombi were retrieved successfully. These two cases supported that Solitaire stent can be used even in small peripheral vessel branches (e.g., M3 segments). Furthermore, our experiences indicate that administering dual anti-platelet agents after the procedure is very important, regardless whether Solitaire stent is used as a clot retriever or left as an implant.

Disadvantage of Solitaire stent

Given the complexity of our stroke patients, high recanalization rate cannot be reached by mechanical thrombectomy with Solitaire stent alone. Twenty-five of 83 patients (30.1%) were found to have stenosis or dissection of a large artery and five of our patients (6.0%) were found distal arterial embolism. While using the Solitaire stent alone, the recanalization rate is 50.6%. In comparison, by using Solitaire stent combined with IA urokinase, balloon angioplasty and/or stent angioplasty, the rate of recanalization potentially reaches 67.5%. This reveals the importance of multi-mode mechanical thrombectomy.

Limitations

Some of the limitations in the current study are a retrospective nature with relatively small number of patients. There was no concurrent control group for comparison. Our results are also limited to immediate post-procedure angiography and do not correlate

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the angiographic outcome with long-term clinical improvements.

Conclusions

Our study shows that mechanical thrombectomy by using a Solitaire stent is effective in recanalizing occluded large cerebral arteries. The application of a Solitaire stent device in Chinese population also achieved a high recanalization rate with low procedure-related complications where approximately 40% of patients showed favorable functional outcome.

Ethical approval

This study had been approved by Ethics Committee of the The First People's Hospital of Changzhou, Soochow University.

Fundings

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Author contribution

Shaowei Jiang and Hairong Wang participated in the design of the study and did the statistical analysis and drafted the manuscript. Qiang Lin, Ya Peng and his colleague performed all the operation, Aihua Fei and Shuming Pan carried out data collection and contributed to the design of the study and helped to draft the manuscript.

Conflict of interest

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent- licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Figure 1. Angiography of occlusion site before, during and after mechanical thrombectomy procedure.

1a, Emergency CTA showed middle cerebral artery M1 occlusion at the left side; 1b, AP angiography showed left middle cerebral artery M1 occlusion; 1c. AP angiography showed after 1st retrieve thrombus moved to the bifurcation of L-ICA; 1d, AP angiography showed after 2nd retrieve embolus moved to C5 of L-ICA; 1e, AP angiography showed after 3rd retrieve revascularization of L-MCA. 1f, CTA follow-up 1 month later showed patent of L-MCA without stenosis.

Figure 2. The modified rankin score of acute ischemic stroke patients at 3 months after mechanical thrombectomy.

At 3 months after thrombectomy procedure, 17 in 83 patients (20.5%) recover to total functional independence, 4 patients (4.8%) and 12 patients (14.5%) was identified as mRS 1 and 2 respectively. Bad clinical outcomes (mRS=3, 4, 5) were identified in 30 patients(36.1%), while 20 patients (24.1) died (mRS=6) in the 3 months.

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Table 1 Patient characteristics

Age,years mean±(SD) (range)	63.34±13.70 (21-85)
Sex (male : female) — no.(%)	1.52 : 1 (60.2 : 39.8)
Atrial fibrillation — no.(%)	40(48.2)
History of hypertension — no.(%)	49 (59.0)
Blood Pressure, mmHg mean±(SD) (range)	
Systolic	144.71±27.46 (70-192)
Diastolic	83.65±13.83 (50-120)
History of diabetes — no.(%)	13(1)
Serum glucose,mmol/l mean±(SD) (range)	8.33±3.98(3.9-27.1)
TG>2.02mmol/l — no.(%)	22(26.5)
Triacylglycerol, mmol/l mean±(SD) (range)	1.86±1.10 (0.68-6.06)
TC>5.7mmol/l — no.(%)	13(15.7)
Cholesterol, mmol/l mean±(SD) (range)	4.40±0.90 (2.19-6.89)
High homocysteine — no.(%)	2(2.4)

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Table 2. Distribution of vascular occlusion, stenosis and dissection

Site of occlusion	
ICA — no.(%)	18(21.7)
Tandem carotid(ICA- MCA) — no.(%)	12(14.5)
MCA(M1/ M2/ M3) — no.(%)	57(68.7)
BA — no.(%)	2(2.4)
VA — no.(%)	6(7.2)
Site of Stenosis	
MCA — no.(%)	11(13.3)
ICA — no.(%)	6(7.2)
BA — no.(%)	1(1.2)
VA — no.(%)	2(2.4)
Site of Dissection	
ICA — no.(%)	4(4.8)
VA — no.(%)	1(1.2)

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Table 3. Data from the procedure

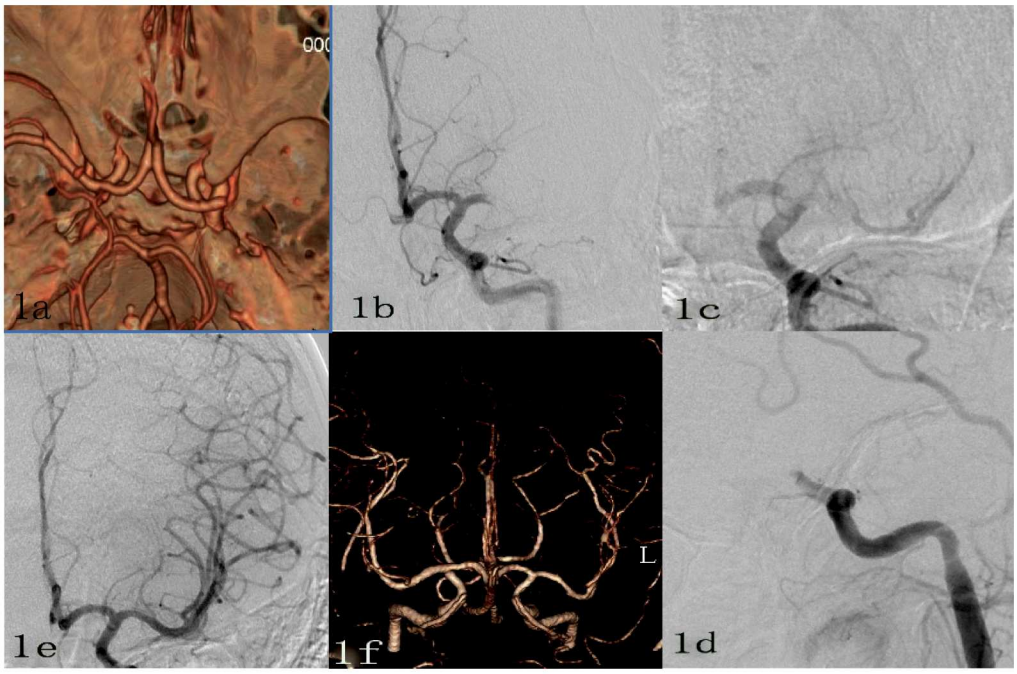
Onset to needle,min mean±(SD)(range)	170.49±68.60(50-346)
Door to needle,min mean±(SD)(range)	68.42±35.40(30-245)
Needle to recanalization,min mean±(SD)(range)	115.08±65.80(30-420)
Number of device passes mean±(SD)(range)	2.20±1.24(1-7)
IA urokinase — no.(%)	30(36.14)
Dose of urokinase 10,000 IU mean±(SD)(range)	27.33±12.58 (10-55)
Balloon — no.(%)	26(31.3)
Stent-assisted angioplasty — no.(%)	25(30.1)
Decompressive craniectomy — no.(%)	12(14.5)
Success of recanalization — no.(%)	73(88.0)
Complete recanalization (TICI 3) — no.(%)	33(39.8)
Partial recanalization (TICI 2a/2b) — no.(%)	40(48.2)
Recanalization failure (TICI 0/1) — no.(%)	10(12.0)
NIHSS score, mean±(SD)(range)	
Initial	19.12±4.60 (10-34)
At discharge	10.73±11.25(0-42)
Improvement of clinical symptom (NIHSS ≥4) — no.(%)	61(73.5)
Complete recovery (NIHSS = 0) — no.(%)	12(14.5)
Marked improvement (NIHSS ≥10) — no.(%)	44 (53.0)
mRS ≤ 2 at 90 days — no.(%)	33(39.8)
Symptomatic intracranial Hemorrhage — no.(%)	10(12.0)
Death in 90 days — no.(%)	20(24.1)

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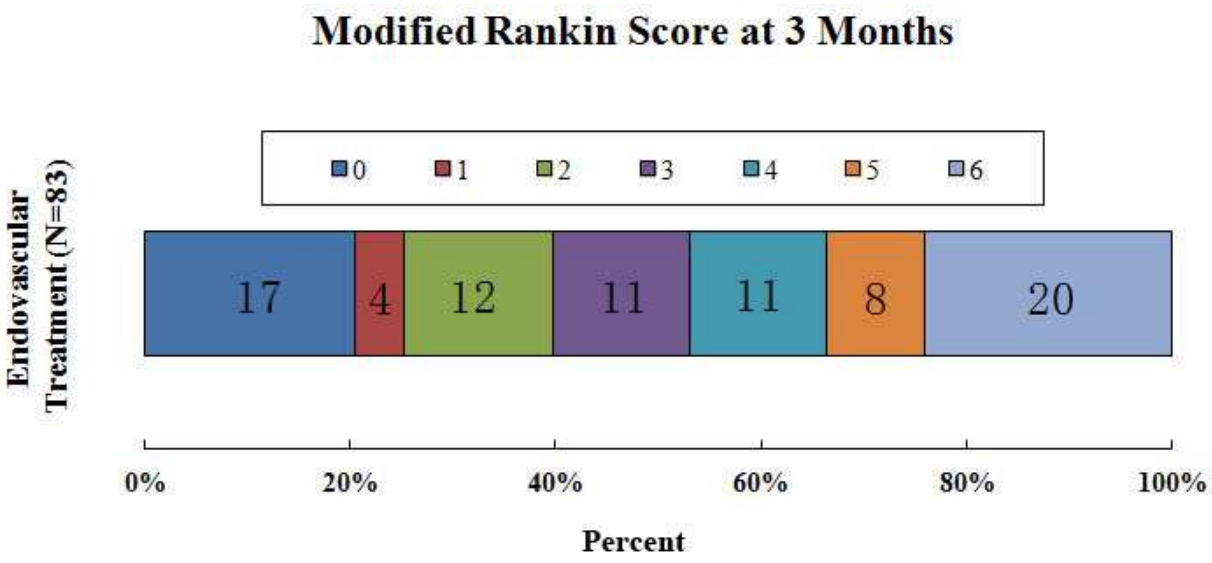
Table 4. The outcomes of the present study compared to the results from six other trials assessing intra-arterial treatment for acute ischemic stroke

	Multi-MERCI	Penumbra pivotal stroke trial	SWIFT trial (SolitaireTM)	MR CLEAN	ESCAPE	EXTEND-IA	Present study
Sample n	164	125	58	233	165	35	83
Recanalization — no.(%)	112 (68.2)	102 (81.6) *	48 (88.9) *	141/187(75.4)	113/156 (72.4)	35(100)***	56(67.5)
Symptomatic intracranial Hemorrhage — no.(%)	16 (9.8)	14 (11.2)	1 (1.7)*	18 (7.7)	6 (3.6)*	0(0)*	10（12）
3-month mortality — no.(%)	56 (34.1)	41 (32.8)	10 (17.2)	44 (18.9)	17/164 (10.4)**	3(9)***	20（24.1）
3-month mRS≤2 — no.(%)	59 (36)	31 (24.8)***	32 (58.2)	76(32.6)	87/164 (53.0)*	25(71)**	32（38.6）

* indicated $P<0.05$, ** indicated $P<0.01$ and *** indicated $P<0.001$.



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Highlights:

1. Data of mechincal thrombectomy with the 3rd generation stent are from Chinese.
2. Mechnical Thrombectomy without the balloon guide catheter.
3. The 3rd generation stents combined with some other tools were used in this study.

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