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Effects of mechanical thrombectomy for acute stroke patients with etiology of large artery atherosclerosis

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ABSTRACT

Aims: Atherosclerosis is more prevalent in Asian population. This distinct etiology of stroke might disadvantage Asian patients when applying.

mechanical thrombectomy (MT). The purpose of this research was to evaluate the efficacy and safety of MT in a cohort of Chinese patients with acute ischemic stroke.

due to large artery atherosclerosis (LAA).

Methods and results: A total of 649 patients treated with MT were included. Patients were classified according to etiology of stroke as LAA and cardioembolism ones. Successful revascularization was defined as modified Thrombolysis in Cerebral Infarction (mTICI) grade ≥ 2b. Favorable outcome was defined as modified Rankin Scale (mRS) score ≤ 2 at 90 days. Logistic regression was used to identify predictors for functional outcomes. The patients with stroke of LAA etiology had significantly higher rate of favorable functional outcome (50.2% vs 36.5%, $p < .001$) and good collateral (grade of ASITN/SIRI: 2–3) (58.8% versus 43.2%, $p < .001$), and lower median baseline National Institutes of Health Stroke Scale score (NIHSS) (15.6 versus 18.2, $p < .001$), compared to patients with stroke of cardioembolism etiology. There was no significant difference in the rate of successful postprocedural mTICI between groups (84.5% versus 83.2%, $p = .671$). Rates of symptomatic intracranial hemorrhage (20.0% versus 11.7%, $p = .004$) and mortality (31.8% versus 18.8%, $p < .001$) within 3 months were notably higher in the cardioembolism group than that in the LAA group.

Conclusion: Mechanical thrombectomy may be more efficacious in treating acute ischemic stroke of LAA etiology than that of cardioembolism etiology.

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1. Introduction

Mechanical thrombectomy (MT) is emerging as the first-line treatment for acute.

ischemic stroke (AIS) due to large artery occlusion (LAO) in anterior circulation [1–6]. Despite the high ratio of successful recanalization, the clinical outcomes of MT vary among studies. This varied effectiveness may be a reflection of the discrepant treatment indications and different stroke etiology [7,8]. Atherosclerotic occlusion, for example, may be more difficult to be recanalized with stent-like retrievers, because the passage of guidwire or stent system may be challenged by atherosclerotic lesions. Even after successful recanalization, atherosclerotic occlusions may be more likely to reocclude due to in situ thrombosis [9]. Ischemic stroke due to large artery atherosclerosis (LAA), therefore, may be less responsive to MT [10]. Nevertheless, with the rapid development of interventional technology, the challenges on the revascularization therapy for LAA stroke may be settled partially by MT [11–13].

Atherosclerosis is more prevalent in Asian populations [9], which may remarkably increase the proportion of stroke with LAA etiology. Whether this distinct etiology of stroke would disadvantage Asian patients when applying MT?

To answer this question, it is important to clarify the response of LAA stroke to MT in Asian patients. Although a few studies have investigated the effects of MT for AIS with different etiology [12,14–17], the discrepant results attract more focous on this issue. Research regarding this issue is still absent in Chinese population, thus, analysis of the efficacy and safety of MT in a cohort of Chinese patients with AIS due to.

LAA may be of benefit.

2. Materials and methods

2.1. Patient

The patients were those registered in MT for Acute Anterior Circulation Ischemic Stroke Registry (ACTUAL) from January 2014 to June 2016. ACTUAL is a registry program for AIS patients with MT, involved 21 stroke centers in China. Each center performed at least 30 cases of MT annually. This study was approved by the Ethic Committees of Nanjing Jinling Hospital and the participating centers. In general, patients received MT if they fulfilled the following criteria: (1) The patients were diagnosed with AIS due to LAO in anterior circulation, (2) age ≥ 18 years, (3)premorbid modified Rankin Scale (mRS) < 2, (4) pretreatment National Institutes of Health Stroke Scale score (NIHSS) > 5, and (5) could be treated within 6 h of stroke onset. For selected patients who did not meet these criteria, MT was still performed based on a favorable benefit-risk ratio on estimate.

2.2. Baseline characteristics

The baseline characteristics such as demographic data, history of medicine, laboratory measures, systolic blood pressure, imaging data, time from onset to treatment, and procedure-related indices were recorded. Stroke etiology was evaluated and defined according to the criteria of Trial of ORG 10172 in Acute Stroke Treatment (TOAST) [18]. Stroke severity at admission was assessed by NIHSS score [19]. The baseline Alberta Stroke Programme Early Compute Tomography Score (ASPECTS) (ranged from 0 to 10) was used to quantify early ischemicchanges on CT scan, 8 to 10 indicating small infarction cores [20]. Collateral status was evaluated with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) grading on DSA, defining from no collateral (grade 0) to complete and rapid collateral perfusion to the ischemic bed (grade 4) [21]. All imaging data were retrospectively reviewed independently by two experienced physicians (YH and HW). In case of disagreement, advice from the third physician (WZ) was acquired for a final decision.

2.3. Endovascular therapy

All patients were treated according to the guidelines for managing AIS. Patients received intravenous alteplase treatment within 4.5 h of stroke onset, if they met the criteria for intravenous thrombolytic therapy. Patients were directly treated with MT, if the time for intravenous treatment was beyond 4.5 h of stroke onset or there was any contraindication to intravenous thrombolysis. Solitaire retriever (Covidien, Irvine, CA) was used in most cases, with other stent-like retrievers permitted. The mTICI score of 2b or 3 was defined as successful recanalization. If the score of mTICI was less than 2b, meaning failed recanalization of the targeting artery, rescue therapies, including aspiration devices, balloon angioplasty, stent placement, intra-arterial thrombolysis, or intracatheter tirofiban infusion, might be performed.

2.4. Outcome measures

The functional outcome was evaluated by mRS at 3 months after stroke onset, favorable functional outcome was defined as mRS 0–2 [22]. The extent of cerebral tissue reperfusion was assessed with the mTICI scale, successful reperfusion was the state of 2b or 3 grade [21]. Intracranial hemorrhage (ICH), as safety outcome including sICH and asymptomatic intracranial hemorrhage (aICH) were diagnosed and classified according to Heidelberg Bleeding Classification [23]. Other outcome variables such as time from groin puncture to reperfusion, the number of passes of stent retriever and incidence of pneumonia were also collected.

2.5. Statistical analysis

Continuous variables were analyzed by the Student *t*-test or Mann–Whitney *U* test according to their normality of distribution. Categorical variables were analyzed by the χ^2 or Fisher exact tests. We used the ordinal logistic regression analysis to evaluate independent predictors of functional outcome. Entered factors included those with at least marginal significance ($p < .1$) on univariate analysis. Statistical analysis were performed using SPSS 22.0 (IBM, Armonk, NY), and two-tailed p values of < 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 649 patients treated with MT were enrolled in this study, according to the inclusion and exclusion criteria. The baseline characteristics of the selected patients are shown in Table 1. There were 309 (47.6%) LAA patients and 340 (52.4%) cardioembolism patients. The median baseline NIHSS score was significantly lower in the LAA group compared with the cardioembolism group [15.6 (IQR 11,19) versus 18.2 (IQR 13,22), $p < .001$]. Patients with LAA stroke were younger (mean age, 64 versus 67 years, $p = .001$), with larger proportion of male (74.4% versus 47.1%, $p < .001$), with lower ratio of valvular heart diseases (0.6% versus 18.9%, $p < .001$), with a higher prevalence of hypertension (69.9% versus 60.0%, $p = .008$) and cigarette smoking (35.3% versus 19.4%, $p < .001$) than those with cardioembolism stroke. There were no significant differences concerning baseline ASPECTS [8.7 (IQR 8,10) versus 8.4 (IQR 8,10), $p = .069$] and other stroke risk factors [diabetes mellitus, hyperlipidemia, glucose, the ratio of neutrophil to lymphocute (NL), history of transient ischemic attack and intracranial hemorrhage] between LAA and cardioembolism group.

The characteristics of endovascular procedures are provided in Table 2. MT was performed in all patients. The percentage of

Table 1
Baseline characteristics of study patients.

Variable	All (n = 649)	LAA (n = 309)	Cardioembolism (n = 340)	p[a]
Demographics				
Age, mean (SD), y	65.4 (11.7)	63.8 (12.1)	66.8 (11.2)	0.001
Male, no. (%)	390 (60.1)	230 (74.4)	160 (47.1)	< 0.001
Medical history				
Hypertension, no. (%)	420 (64.7)	216 (69.9)	204 (60.0)	0.008
Diabetes mellitus, no. (%)	125 (19.3)	60 (19.4)	65 (19.1)	0.923
Hyperlipidemia, no. (%)	59 (9.1)	32 (10.4)	27(7.9)	0.285
Atrial fibrillation,[∫] no. (%)	283 (43.7)	15 (4.9)	268(79.1)	< 0.001
Coronary heart diseases,[∫] no. (%)	157 (24.2)	42 (13.6)	115 (33.9)	< 0.001
Valvular heart diseases,[§] no. (%)	66 (10.2)	2 (0.6)	64 (18.9)	< 0.001
History of ischemic stroke, no. (%)	94 (14.5)	34 (11.0)	60 (17.6)	0.016
History of transient Ischemic attack, no. (%)	9 (1.4)	5(1.6)	4 (1.2)	0.885
History of intracranial hemorrhage, no. (%)	10 (1.5)	6 (1.9)	4 (1.2)	0.637
Current smoke, no. (%)	175 (27.0)	109 (35.3)	66 (19.4)	< 0.001
Laboratory measures				
NL,[†] mean (SD)	9.79 (10.4)	9.89 (11.5)	9.70 (9.3)	0.595
LDL,[‡] mean (SD), mmol/L	2.5 (0.9)	2.6 (0.9)	2.4 (0.8)	0.010
Glucose,[⫻] mean (SD), mmol/L	7.8 (3.5)	7.8 (3.7)	7.8 (3.2)	0.197
Clinical characteristics				
Systolic blood pressure				
Median (IQR), mmHg	147 (130,160)	150 (133,163)	144 (127,160)	0.011
Baseline NIHSS score < 0.001				
≤10, no. (%)	103 (15.9)	67 (21.7)	36 (10.6)	
11–20, no. (%)	372 (57.3)	183 (59.2)	189 (55.6)	
≥21, no. (%)	174 (26.8)	59 (19.1)	115 (33.8)	
Baseline ASPECTS[∬] 0.137				
0–7, no. (%)	138 (22.0)	58 (19.5)	80 (24.4)	
8–10, no. (%)	488 (78.0)	240 (80.5)	248 (75.6)	

Abbreviations: ASPECTS, Alberta Stroke Program Early CT Score; IQR, interquartile range; LAA, large artery atherosclerosis; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; NL, the ratio of neutrophil to lymphocute; SD, standard deviation.

[a] Comparison between the LAA and Cardioembolism groups.
[∫] Missing data in 1 patient.
[§] Missing data in 2 patients.
[∬] Missing data in 23 patients.
[⫻] Missing data in 43 patients.
[†] Missing data in 50 patients.
[‡] Missing data in 108 patients.

permanent stent implantation (27.2% versus 10.6%, p < .001) and application of antiplatelet therapy during MT (29.4% versus 18.8%, p < .001) were both higher in the LAA group. The collateral (grade of ASITN/SIRI: 2–3) in the LAA group was better than that in the cardioembolism group (58.8% versus 43.2%, p < .001). The rate of application of rescue therapy (55.3% versus 40.3%, p < .001) and number of stent retriever < 3 (74.7%versus 61.1%, p < .001) were higher in the LAA group, whereas the percentage of time from groin puncture to reperfusion ≤90 min (36.5% versus 44.8%, p = .032) was lower in patients with LAA. There were no significant differences in the percentage of time from onset to treatment ≤60 min (76.7% versus 81.8%, p = .111) and rate of intravenous thrombolysis performance (35.3% versus 32.6%, p = .480) between the two groups.

3.2. Clinical outcomes

Favorable outcomes (mRS 0–2 at 3 months) were significantly more frequent in the LAA group than in the cardioembolism group (50.2% versus 36.5%, p < .001) (Table 3). The distribution of mRS scores of 0–6 at 3 months is elucidated in Fig. 1. Substantial reperfusion were achieved in 84.5% patients with LAA etiology and 83.2% patients with cardioembolism (p = .671, Table 2).

3.3. Safety outcomes

SICH was more frequently in the cardioembolism group than in the LAA group (20.0% versus 11.7%, p = .004). More patients with cardioembolism died than that with LAA (31.8% versus 18.8%, p < .001) during the 3-month follow-up period. The incidence of aICH and pneumonia did not differ between the two groups (Table 3).

3.4. Predictors of functional outcome at 90 days

The multivariable analysis showed that age (odds ratio, 1.06; 95% CI, 1.03–1.06; p < .001), NIHSS score at admission (11–20 versus ≤10: odds ratio, 2.97; 95% CI, 1.64–5.39; p < .001. ≥21 versus ≤10: odds ratio, 5.32; 95% CI, 2.68–10.58; p < .001), and passes of thrombectomy (≥3) (odds ratio, 2.17; 95% CI, 1.20–3.92; p = .010) were independent predictors of poor functional outcome, and collateral state(2–3) (odds ratio, 0.49; 95% CI, 0.33–0.73; p < .001) was protective predictors (Table 4).

4. Discussion

The main findings of this report were as following: rates of successful postprocedural mTICI in the patients with stroke of LAA etiology was as high as that in patients with cardioembolism etiology (84.5% versus 83.2%). Rates of favorable functional outcome was higher in patients with stroke of LAA etiology than that in patients with stroke of cardioembolism etiology (50.2% vs 36.5%). Rates of sICH (20.0% versus 11.7%) after MT and mortality (31.8% versus 18.8%) within 3 months were notably higher in patients with cardioembolism etiology than that in patients with LAA etiology.

In this study, a similar frequency of successful revascularization

Table 2
Characteristics of endovascular procedures.

Variables	All (n = 649)	LAA (n = 309)	Cardioembolism (n = 340)	p[a]
Anesthesia, no. (%)				0.835
General anesthesia	128 (19.7)	62 (20.1)	66 (19.4)	
Local anesthesia	521 (80.3)	247 (79.9)	274 (80.6)	
Collateral (ASITN/SIRI),[∫] no. (%)				< 0.001
0–1	318 (49.4)	126 (41.2)	192 (56.8)	
2–3	326 (50.6)	180 (58.8)	146 (43.2)	
Occlusion site, no. (%)				< 0.001
ICA	95 (14.6)	69 (22.3)	26 (7.6)	
ICA–T	158 (24.3)	46 (14.9)	112 (32.9)	
MCA M1	354 (54.5)	173 (56.0)	181 (53.2)	
MCA M2	36 (5.5)	16 (5.2)	20 (5.9)	
ACA	6 (0.9)	5 (1.6)	1 (0.3)	
Intravenous thrombolysis, no. (%)				0.480
Yes	220 (33.9)	109 (35.3)	111 (32.6)	
No	429 (66.1)	200 (64.7)	229 (67.4)	
Rescue therapy, no. (%)				< 0.001
Yes	308 (47.5)	171 (55.3)	137 (40.3)	
No	341 (52.5)	138 (44.7)	203 (59.7)	
Time from onset to treatment, no. (%)				0.111
≤ 60 min	515 (79.4)	237 (76.7)	278 (81.8)	
> 60 min	134 (20.6)	72 (23.3)	62 (18.2)	
Time from groin puncture to reperfusion,[∫] no. (%)				0.032
≤ 90 min	263 (40.8)	112 (36.5)	151 (44.8)	
> 90 min	381 (59.2)	195 (63.5)	186 (55.2)	
Postprocedural mTICI, no. (%)				0.671
0–2a	105 (16.2)	48 (15.5)	57 (16.8)	
2b–3	544 (83.8)	261 (84.5)	283 (83.2)	
Number of stent retriever,[∫∫] no. (%)				< 0.001
< 3	399 (67.3)	201 (74.7)	198 (61.1)	
≥ 3	194 (32.7)	68 (25.3)	126 (38.9)	
Permanent stent site, no. (%)				< 0.001
ICA	40 (6.2)	33 (10.7)	7 (2.1)	
MCA	75 (11.6)	46 (14.9)	29 (8.5)	
ACA	3 (0.5)	3 (1)	0 (0)	
ICA + MCA	1 (0.2)	1 (0.3)	0 (0)	
MCA + ACA	1 (0.2)	1 (0.3)	0 (0)	
Antiplatelet regimen, no. (%)				0.002
YES	155(23.9)	91(29.4)	64(18.8)	
No	494(76.1)	218(70.6)	276(81.2)	

Abbreviations: ACA, Anterior cerebral artery; ASITN/SIRI, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; ICA, internal carotid artery; ICA–T, internal carotid artery terminus; LAA, large artery atherosclerosis; MCA M1, Middle cerebral artery first segment; MCA M2, Middle cerebral artery second segment; mTICI, modified thrombolysis in cerebral infarction.

[a] Comparison between the LAA and Cardioembolism groups.

[∫] Missing data in 5 patient.

[∫∫] Missing data in 56 patients.

(mTICI grade 2b or 3) were achieved in patients with underlying LAA (84.5%) and cardiembolism (83.2%), consistent with the results in other studies [17,24]. Previously, the revascularization rate in LAA group was lower than that in other etiology group, especially the cardioembolism group, attributing to the challenge for navigating a guidwire or stent system through atherosclerotic lesions and the re-occlusion tendency due to in situ thrombosis even after successful recanalization. So, additional rescue treatments such as aspiration devices, angioplasty, intracranial stenting, and tirofiban infusion were applied in the MT for LAA patients [25]. In the current study, the usage of rescue therapy in the LAA group (55.3%) was significantly higher than that in the cardioembolism group (40.3%), contributing to the high revascularization rate in the patients with LAA.

A recent study [6] reported age is a strong independent predictor of outcome in patients with LAO stroke. In our study, the patients in the LAA group were remarkably younger than those in the cardioembolism group, which predicting favorable outcome in the patients with LAA. Patients with LAA had better collateral flow(ASITN/SIRI grade 2 or 3) than those with underlying cardioembolism in the present study, assumably because there is a longer time for the complete arterial occlusion in patients with LAA, acquiring the chance to develop adequate collateral flow via anterior and posterior communicating arteries, leptomeningeal or dural collaterals before the onset of acute stroke. Several previous studies have supported the association of enow collateral flow with better recanalization, reperfusion, and clinical outcomes [14,26]. We also found good collateral flow was an independent predictor of favorable functional outcome at 3 months in the multivariate analysis. The baseline NIHSS score, another independent predictor of functional outcomes in the multivariate analysis, in the LAA group was remarkably lower than that of cardioembolism group. The result is in line with that of recent studies [16,24], suggesting that the lower NIHSS score might be attributed to the lower clot burden in the patients with LAA compared with the cardioembolism group. We did not evaluate the situation of the clot burden in the current research.

SICH may increase the risk of mortality and induce less favorable functional outcomes at 90 days [27,28]. In a previous study, the proportion of sICH was observably higher in AIS paitents with etiology of LAA than cardioembolism [15]. However, the incidence of sICH after MT and mortality at 3 months in this study were significantly lower in patients with LAA stroke. The important observation of lower incidence of sICH in LAA group is also found in other researches [27,29]. Hao et al. [29] clarified cardioembolic stroke, poor collateral circulation and multiple passes with stent retriever device may increase the risk of sICH. SugiuraIn et al. [27] demonstrated NIHSS score ≥ 19 was an independent predictor of sICH. In the current research, the proportion of baseline NIHSS score < 19, the ratio of better collateral circulation (ASITN/SIRI grade 2 or 3) and the rate of passes of retriever < 3, an independent predictor of favorable neurological outcoms, in LAA group were notably higher than that in cardioembolism group. Therefore, the blood-brain barrier disruption and vascular injury, both of which were reported associating with increased ICH [30], might be less serious in the patients with LAA, contributing to the lower occurrence of sICH.

Several limitations in the present study should be addressed. As a registry study, system biases may be generated from the retrospectively collected data. Different protocols of endovascular treatment and different follow-up schemes may be applid in the adopted centers. Duing to the absent of preprocedural CTA examination for all patients, thrombus burden was not evaluated before MT. Limited number of patients underwent angiography at 24 h after MT, so vessel recanalization could not be evaluated properly, which may have suffered re-occlusion. Some values were missed from the original reporting data.

5. Conclusion

MT may be more efficacious in treating acute ischemic stroke of LAA etiology than that of cardioembolism etiology.

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Table 3
Clinical and safety outcomes.

Variable	All (n = 649)	LAA (n = 309)	Cardioembolism (n = 340)	p[a]
Efficacy outcomes				
Modified ranking scale score at 90 days				< 0.001
0–2, no. (%)	279 (43.0)	155 (50.2)	124 (36.5)	
3–6, no. (%)	370 (57.0)	154 (49.8)	216 (63.5)	
Safety outcomes				
Mortality at 90 days, no. (%)	166 (25.6)	58 (18.8)	108 (31.8)	< 0.001
sICH, no. (%)	104 (16.0)	36 (11.7)	68 (20.0)	0.004
aICH, no. (%)	202 (31.1)	85 (27.5)	117 (34.4)	0.058
Pneumonia, no. (%)	169 (26.0)	74 (23.9)	95 (27.9)	0.247

Abbreviations: aICH, Asymptomatic; LAA, large artery atherosclerosis; sICH, Symptomatic intracranial hemorrhage intracranial hemorrhage.
[a] Comparison between the LAA and Cardioembolism groups.

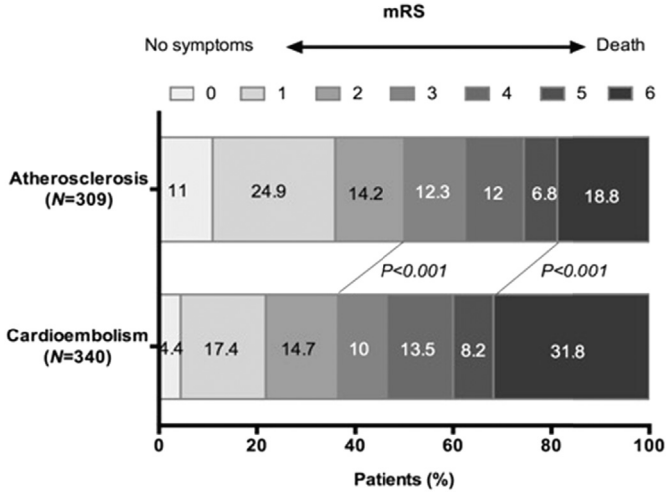

Fig. 1. The distribution of mRS scores of 0–6 at 3 months.

Table 4
Multivariable analyses of functional outcome.

Variables	Odds ratio	95% Confidence interval	p
Age	1.06	1.03–1.06	< 0.001
Collateral state (2–3)	0.49	0.33–0.73	< 0.001
NIHSS score			
≤10	1	Reference	< 0.001
11–20	2.97	1.64–5.39	< 0.001
≥21	5.32	2.68–10.58	< 0.001
Passes of thrombectomy (≥3)	2.17	1.20–3.92	0.010

Abbreviations: NIHSS, National Institutes of Health Stroke Scale.

Declarations of interest

None.

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BS, JP, and ZS prepared the draft of the report. SY, HW, DY, YH, ML, WK, WL, FG, YB, SZ, ZL, SL, MZ, and WZ participated in data collection, data analysis, and interpretation. BS and JP did the statistical analyses. WZ and GX critically revised the report. WZ and XL did the study design. All authors participated in patient enrollment and reviewed the report and approved the final version.

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