Endovascular thrombectomy can be beneficial to acute ischemic stroke patients with large infarcts

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OBJECTIVE This study aimed to assess whether patients with acute ischemic stroke (AIS) and large infarct lesions benefit from reperfusion management. To determine the efficacy of different recanalization managements on AIS patients with Alberta Stroke Program Early CT Score (ASPECTS) < 6, the authors retrospectively analyzed hospitalized patients with AIS.

METHODS Eighty-nine patients with AIS and ASPECTS < 6 were screened from 13,285 hospitalized patients treated by thrombolysis, thrombectomy, or conventional care in two stroke medical centers. Logistic regression or Fisher’s exact test was performed for comparison of the outcome and risk events between patients treated by thrombectomy (or thrombolysis) and conventional care. The modified Rankin Scale (mRS) score was used to assess the major clinical outcome of patients 3 months after disease onset. Disease outcome was also examined by analyzing symptom improvement at discharge. In particular, mortality and symptomatic intracranial hemorrhage (sICH) were evaluated as risk factors.

RESULTS This study included 21 patients who received thrombolysis, 36 patients receiving thrombectomy, and 32 patients receiving conventional treatment. Among these 3 treatments, only the thrombectomy group clearly showed the most encouraging clinical outcome (mRS score 0–2; p < 0.05, Fisher’s exact test) and marked improvement (OR 25.84, 95% CI 2.44–273.59) compared with conventional treatment. It is noteworthy that the mortality rate of the thrombectomy and thrombolysis group was similar to that of the conventional group, and thrombectomy and thrombolysis increased the risk of sICH in comparison with conventional care (p < 0.05, Fisher’s exact test).

CONCLUSIONS Patients with AIS and ASPECTS < 6 definitely benefited from thrombectomy with higher sICH risk, whereas thrombolysis management showed similar efficacy to the control group.

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KEYWORDS acute ischemic stroke; thrombectomy; ASPECTS; large infarcts; vascular disorders; thrombolysis

Acutely ischemic stroke (AIS) is a serious disease with high morbidity and mortality rates. It is generally believed that timely reperfusion in ischemic stroke patients is an effective therapy to decrease long-term morbidity. Intravenous (IV) thrombolysis and endovascular thrombectomy are two major priority strategies to achieve vascular recanalization. Therapy with intravenous recombinant tissue-type plasminogen activator (r-tPA) is the mainstay early treatment for patients with AIS eligible for thrombolysis, which is commonly used in the clinical setting. However, the narrow time window and restrictive selection criteria limited its scope of use. Most recently, the endovascular intervention (mechanical thrombectomy) has shown significant advantages over thrombolysis in patients with large vascular occlusions. As a result, either thrombectomy or thrombolysis is considered for reperfusion with a low risk as soon as the disease occurs. Therefore, according to the updated guideline, the American Stroke Association (ASA) recommends IV thrombolysis in patients within 4.5 hours of symptom onset, with a target of 60 minutes to first dose.17 Furthermore, the choice between thrombectomy and thrombolysis should be individualized based on patient factors, such as age, comorbidities, and the extent of ischemia in the affected territory.18

ABBREVIATIONS AHA/ASA = American Heart Association/American Stroke Association; AIS = acute ischemic stroke; ASPECTS = Alberta Stroke Program Early CT Score; CI = confidence interval; IV = intravenous; MCA = middle cerebral artery; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; OR = odds ratio; r-tPA = recombinant tissue-type plasminogen activator; sICH = symptomatic intracranial hemorrhage.


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Heart Association/American Stroke Association (AHA/ASA) Stroke Council recommended that thrombectomy should be followed by thrombolysis treatment as an early management strategy for patients with AIS and large-vessel occlusion.19 CT and MR images are very useful tools for evaluating the infarct lesion of the brain. It is the general consensus that the Alberta Stroke Program Early CT Score (ASPECTS) is a reliable and useful grading system for standardized quantification of CT images.1 The low grading of ASPECTS suggests a large, diffuse, ischemic territory of the middle cerebral artery (MCA), and the baseline ASPECTS is a predictor of clinical outcome.6,27 Because the low ASPECTS evaluation is critical to determine poor outcome in patients managed by reperfusion therapies, the updated AHA/ASA guidelines use the selection criteria for thrombectomy therapy as ASPECTS ≥ 6.19 However, the benefit from endovascular therapy in patients with AIS and ASPECTS < 6 remains uncertain. Thus, the data from the patients with poor ASPECTS (< 6) are needed for estimating the efficacy of endovascular thrombectomy.

In the present study, we reviewed and analyzed clinical data of patients with AIS treated by thrombectomy or thrombolysis that were recorded and collected in the two medical centers. To compare the efficacy of different therapies in patients with ASPECTS < 6, we selected the patients who were treated by endovascular intervention or by thrombolysis. We compared the major disease outcome, the modified Rankin Scale (mRS) score at 3 months after treatment, and the symptomatic improvement at discharge in the patients receiving endovascular intervention or IV thrombolysis versus conventional treatment. We also compared the data of symptomatic intracranial hemorrhage (sICH) at 24 hours after treatment as well as the mortality rate of patients managed by thrombolysis versus thrombectomy with the rate in conventional treatment.

Methods

Patients and Selection

This retrospective study was approved by the Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University, and the Ethics Committee of the First People's Hospital of Changzhou, Soochow University. There were 13,285 stroke patients who were hospitalized at Xinhua Hospital or The First People's Hospital of Changzhou from December 2010 to May 2015 who were included in this study. Among these selected patients, 396 received IV thrombolysis management, 98 received endovascular mechanical thrombectomy, and 12,791 were treated by conventional procedures with neither thrombolysis nor thrombectomy. Due to insufficient clinical data and our specific requirement of patient selection (ASPECTS < 6, National Institutes of Health Stroke Scale [NIHSS] score ≥ 10, anterior artery occlusion, and age < 80 years), the final results reported in the present study include a total of 89 consecutive patients. Among these patients, 36 were in the endovascular thrombectomy group, 21 in the IV thrombolysis group, and 32 in the conventional care group. The detailed screening processes are shown in Fig. 1.

The patients’ clinical data were carefully recorded, including age, sex, NIHSS score at admission and discharge, cause of stroke, symptom of hemorrhage, time from onset to presentation or management, blood pressure, blood glucose level, serum lipid and cholesterol levels, and medical history (such as atrial fibrillation, hypertension, and diabetes). As the ASPECTS criteria were not added into the treatment guideline of our two centers, the ASPECTS was not measured immediately after CT angiography and did not affect the choice of management strategy. The ASPECTS were evaluated by two neurosurgeons at the initial stage of this retrospective study (C.J.G., Y.L., M.C., and Y.P. contributed to this work). The ASPECTS of 15 patients given by these two neurosurgeons were inconsistent, and a third opinion was requested. Intracranial hemorrhagic transformations in 24 hours were determined by two clinical phenotypes, silent or symptomatic, and then classified into different categories. Hemorrhage was scored by using the Pessin criteria and formalized in the European Cooperative Acute Stroke Study trials (hemorrhagic infarction, types 1 and 2; parenchymal hematoma, types 1 and 2).9,10,18 Symptomatic intracranial hemorrhage was defined as any parenchymal hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage associated with the NIHSS score by 4 or more within 24 hours.20 The mRS score was measured by the attending neurosurgeons at 90 days, or recorded when the end point event (death) occurred. The characterizations for mRS were obtained by telephone follow-up or from the records of reexamination at 3 months. Functional dependence was defined as a score of 3–6 on the mRS at 90 days. Functional independence was defined as a score of 0–2 on the mRS at 90 days. The conventional care group enrolled patients who were subject to high risks during thrombolysis or thrombectomy, or when families of the patients refused to allow thrombolysis or thrombectomy, and when the onset to admission time was within 6 hours.

Patient Treatment Processes

The patients in the thrombectomy group were treated as described previously.11 Briefly, on admission, a stroke neurologist examined all patients clinically; cranial CT or multimodal MR angiography was performed prior to every intervention to confirm the diagnosis of large-vessel occlusion and to rule out ICH. Interventional treatment was initiated within the first 6 hours from the onset of stroke. Technical details of the endovascular procedure were described in a previous study.12 The main processes included transfemoral access with a 6-Fr sheath (Terumo Radifocus Introducer) into the right femoral artery, and conventional cerebral angiography showing the location of the occlusion and collateral circulation. Then, a Rebar 18 microcatheter (eV3) was navigated through the thrombus with a microwire, and the Solitaire stent (eV3) was deployed in the clot and allowed to remain in place for 2–3 minutes. The entire system, consisting of the stent and the microcatheter, was completely retrieved. After retrieval, the clot typically could be seen entangled within the meshwork of the stent, and control angiography was performed following each retrieval until success. The femoral sheath was removed and the wound closed with an Angio-Seal (St. Jude Medical, Inc.) vascular closure device.
For thrombolysis treatment, we followed the AHA guideline. Briefly, a clinical stroke neurologist checked the patients with AIS to verify there were no contraindications for thrombolysis, such as systolic/diastolic > 200/120 mm Hg, active hemorrhage or intracranial tumors, cerebral vascular malformations, surgery within 2 weeks, receiving oral anticoagulation medication, or bleeding diathesis with severe heart, liver, or kidney substantive organ diseases, and confirmed the onset time within 4.5 hours. Patients were given alteplase at a dose of 0.9 mg/kg weight, and the maximum dosage was 90 mg. While 10% of the total dosage was injected intravenously, the remaining dose of alteplase was infused within 1 hour. Within 24 hours after thrombectomy or thrombolysis, administration of anticoagulants or antiplatelet agents was prohibited. After 24 hours, if there was no intracranial hemorrhage, antiplatelet or anticoagulant therapy was used.

In the conventional care group, patients were given lipid-lowering drugs orally, such as atorvastatin calcium. All conventional care patients without intracranial hemorrhage received anticoagulation treatment after admission examination. The CT scan was reviewed during hospitalization; if intracranial hemorrhage occurred, anticoagulation therapy was terminated and the treatment regimen adjusted. No extra thrombolysis or thrombectomy management was performed on conventional care patients.

**Statistical Analysis**

We present the baseline variables as means and SDs, or medians and ranges, and variables as percentages. For comparisons between different therapies (thrombolysis vs conventional care, and thrombectomy vs conventional care) and outcomes, we used a 2-sided Fisher’s exact test; significance was set as p < 0.05. The associations between different management options and symptomatic improvement or some other risk events were analyzed by multivariable logistic regression analysis. We also adjusted the odds ratio (OR) and secondary effects factors for potential imbalance in major prognostic variables. The parameters involved in adjustment were age, occluded vessel, NIHSS admission score, plasma glucose level, atrial fibrillation, and diabetes. We report ORs with 95% confidence intervals (CIs). All statistical analyses were performed using SAS software (version 9.4, SAS Institute).
Results

Because the efficacy of reperfusion management in patients with AIS and large infarcts is uncertain, we explored the clinical significance of cases with ASPECTS < 6 in two stroke management centers and analyzed the outcomes of different treatments.

Characteristics of the Patients and Stratification

From December 2010 to May 2015, 13,285 stroke patients were admitted to Xinhua Hospital and The First People’s Hospital of Changzhou. For this retrospective study, we screened these patients as presented in Fig. 1 (the main screening criteria were detailed in the Methods). After screening, there were 89 patients in 3 different management methods. In these 89 patients, 21 patients received IV r-tPA thrombolysis treatment (thrombolysis group), 36 patients underwent endovascular thrombectomy treatment (thrombectomy group), and the remaining 32 patients were managed by conventional care without IV r-tPA treatment or thrombectomy (control group). The mean ages of these 3 groups ranged from 60 to 70 years (average age for thrombolysis was 66.19 years, for thrombectomy 60.83, and for control 63.13; Table 1). Whereas 48% of male patients were included in the thrombolysis group, 53% were male in the thrombectomy group, and 56% in the conventional care group. The main vascular occlusions were in the MCA. There were 100%, 72%, and 88% of patients with an occluded MCA in the thrombolysis group, thrombectomy group, and conventional care group, respectively. Nearly half of the patients’ symptoms were caused by large artery atherosclerosis in the thrombectomy (36%) or thrombolysis (53%) groups, while 81% of stroke cases resulted from large artery atherosclerosis in the conventional care group. Stroke causes were cardioembolic in 43% of thrombolysis-managed patients, 53% of thrombectomy-treated patients, and 13% of conventional care patients. The detailed baseline characteristics of these three groups are listed in Table 1.

The major outcome variable, mRS score at 3 months, was compared between the thrombectomy group (or thrombolysis group) and the conventional care group.
Considering that ASPECTS are generally negatively correlated with NIHSS scores, we also checked symptom improvement after different management techniques. To estimate how much symptoms improved after treatment, we compared the clinical improvement (discharge NIHSS score – admission NIHSS score ≥ 4) and marked improvement (discharge NIHSS score – admission NIHSS score ≥ 10) rate of patients treated by endovascular intervention or IV thrombolysis with conventional care. The difference in sICH and mortality risk between thrombectomy (or thrombolysis) and conventional care was also estimated.

Outcomes

Six (17%) of 36 patients achieved functional independence (mRS score ≤ 2 at 3 months) in the thrombectomy group, whereas there were no functionally independent patients in either the IV thrombolysis group or the conventional care group at 3 months after treatment (Fig. 2, Table 2). The favorable outcome rate (mRS score ≤ 2 at 3 months) of the thrombectomy group was higher than that of the conventional care group, with statistical significance (p = 0.026, Fisher’s exact test; Table 2). It is noteworthy that the distribution of mRS scores at 3 months in the IV thrombolysis group was very similar to that in the conventional care group (Fig. 2).

The clinical improvement rate of the thrombectomy group was 71% (15 of 21 patients), which was higher than that in the conventional care group (adjusted OR 14.62, 95% CI 2.77-77.20; unadjusted OR 10.83, 95% CI 2.96-39.66; Supplemental Table I). Twenty-eight (78%) of 36 patients clinically improved after endovascular intervention (Supplemental Figure I), and also showed an elevated clinical improvement rate compared with the conventional care group (adjusted OR 21.75, 95% CI 4.7-113.38; unadjusted OR 15.17, 95% CI 4.63-49.63; Supplemental Table I).

Clinical signs in 44% (16 of 36) of thrombectomy-managed patients and in 14% (3 of 21) of IV thrombolysis-treated patients markedly improved at discharge (Table 3). Correspondingly, only 1 (3%) of 32 patients in the conventional care group achieved marked symptomatic improvement at discharge. The marked improvement rate in the thrombectomy group was higher when compared with the conventional care group (adjusted OR 25.84, 95% CI 2.44-273.59; unadjusted OR 24.8, 95% CI 3.05-201.92), whereas IV thrombolysis treatment did not show obvious advantages over the conventional care group (adjusted OR 4.31, 95% CI 0.34-55.13; unadjusted OR 5.17, 95% CI 0.5-53.45; Table 3).

Mortality and sICH

The mortality rates of the three groups were approximately 40% (control 41% [13/32], thrombolysis 48% [10/21], and thrombectomy 33% [12/26]; Supplemental Table II). Symptoms of intracranial hemorrhage during therapy are risk factors for disability outcome. There were 7 (19%) and 4 (19%) patients who suffered sICH during or 24 hours after treatment in the thrombectomy and thrombolysis groups, respectively, whereas no sICH (0%) occurred 24 hours after conventional care (Table 4). The sICH was more frequent in the thrombectomy and thrombolysis groups when compared with the conventional care group (thrombectomy vs conventional care, p = 0.012, thrombolysis vs conventional care, p = 0.012, Fisher’s exact test; Table 4).

Discussion

AIS is a serious, harmful, acute disease. Presently, IV thrombolysis, endovascular thrombectomy, and conventional treatment are the major therapies for this dis-

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**TABLE 2. Comparison of the major outcome variable (mRS score) among different therapies and conventional management**

<table>
<thead>
<tr>
<th>Group</th>
<th>mRS score ≤2 (%)</th>
<th>mRS score &gt;2 (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombolysis</td>
<td>0 (0)</td>
<td>21 (100)</td>
<td>—</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>6 (17)</td>
<td>30 (83)</td>
<td>0.026*</td>
</tr>
<tr>
<td>Control</td>
<td>0 (0)</td>
<td>32 (100)</td>
<td>—</td>
</tr>
</tbody>
</table>

* Analysis performed using a 2-sided Fisher’s exact test.
recovery. Endovascular thrombectomy, as a new management method, could more quickly achieve recanalization than other therapies. It is generally believed that AIS patients with ASPECTS ≥ 6 strikingly benefited from endovascular thrombectomy, especially by using a third-generation stent.\(^2\,\,4\,\,6\,\,8\,\,13\,\,21\) However, there is a significant controversy concerning whether patients with ASPECTS < 6 should be subjected to endovascular thrombectomy.\(^19\) In this study, we retrospectively compared the outcome and risk of three moderately severe and severe AIS patient groups (NIHSS score ≥ 10 and ASPECTS < 6) that were managed by endovascular thrombectomy, IV thrombolysis, and conventional care. Only the thrombectomy group showed better favorable outcome rates and an elevated marked improvement rate when compared with the conventional care group. The postoperative sICH risk in 24 hours was higher in the thrombectomy and IV thrombolysis groups in comparison to the conventional care group, and the mortality rates of these 3 groups were similar.

Because patients with large ischemic infarcts lesion have been excluded in most thrombectomy clinical trials, the benefits of endovascular therapy in these patients with ASPECTS < 6 remains uncertain.\(^19\) A recent MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) trial enrolled the AIS patients with large infarcts (ASPECTS 0–5) and analyzed the effects of ASPECTS on efficacy of intraarterial treatment. However, these investigators still did not give us a clear answer for whether endovascular intervention improved the mRS score of patients with large infarcts at 3 months, because the sample size was too small.\(^26\) In our study, the sample size (68 patients with ASPECTS 0–5) was more than twice that of the MR CLEAN trial (30 patients with ASPECTS 0–4) in the thrombectomy and conventional care groups. Unlike MR CLEAN, our analysis showed intraarterial treatment improved the mRS scores of patients with large infarcts at 3 months with statistical significance. Not only was this found in the long-term outcome (3 months), but it also showed a higher symptomatic improvement rate in the thrombectomy group than in the conventional care group in our study. This strongly indicated that endovascular thrombectomy might be beneficial for improving the outcomes of patients with AIS and large infarcts. Interestingly, when patients were managed by conventional care, there was no functional independent recovery in patients with large infarcts in either our study or the MR CLEAN trial.\(^26\) This suggested that conventional treatment might not be helpful for patients with large infarcts recovering to a functional independent state in 3 months.

For patients managed using IV thrombolysis, there was no benefit of a functional independent recovery from therapy when compared with conventional care. The same lack of favorable outcome for patients treated using injection of alteplase or conventional care was the convincing evidence of a poor benefit for IV thrombolysis. With respect to the outcome at 3 months, the proportions of mRS scores of 3, 4, or 5, and deceased patients, were nearly consistent between the thrombolysis and conventional care group. Additionally, there was no statistically significant marked symptomatic improvement at discharge in patients administrated r-tPA when compared with patients who received conventional care. The previous studies also showed that low ASPECTS (< 6) was an independent predictor for a poor outcome after IV thrombolysis.\(^16\,\,24\) This finding supports the idea that patients with ASPECTS 0–5 would hardly benefit from alteplase injection. Therefore, endovascular thrombectomy appears to be the only feasible therapy for managing patients with AIS and unfavorable ASPECTS (< 6) to achieve good outcome.

Reperfusion of ischemic brain tissues might increase to intracranial hemorrhage, and a low ASPECTS was frequently associated with sICH during management.\(^14\,\,22\) The sICH rate was increased to nearly 20% in reperfusion management groups, in patients with low ASPECTS. The sICH often occurred in patients who were managed by conventional care beyond 24 hours after treatment. Therefore, the total sICH rate in conventional care patients was also at a high level before discharge. Because sICH is a strong predictor for poor outcome, this high sICH rate in patients with low ASPECTS might partially explain why the efficacy of thrombolysis or thrombectomy became worse in these patients.

**Limitations of the Study**

As this is a retrospective analysis, we could not keep all baseline factors balanced. These unbalanced factors, such as incidence of diabetes and stroke etiology, might bias the results. However, not only did we acquire the clinical

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**TABLE 3. Comparison of marked improvement among different therapies and usual management**

<table>
<thead>
<tr>
<th>Group</th>
<th>Non-Marked Improvement (%)</th>
<th>Marked Improvement (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombolysis</td>
<td>18 (86)</td>
<td>3 (14)</td>
<td>5.17 (0.50–53.45)</td>
<td>4.31 (0.34–55.13)</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>20 (56)</td>
<td>16 (44)</td>
<td>24.80 (3.05–201.92)</td>
<td>25.84 (2.44–273.59)</td>
</tr>
<tr>
<td>Control</td>
<td>31 (97)</td>
<td>1 (3)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Determined using logistic regression; the adjusted variables were age, occluded vessel, NIHSS admission score, plasma glucose level, atrial fibrillation, and diabetes.

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**TABLE 4. Comparison of sICH among different therapies and conventional management**

<table>
<thead>
<tr>
<th>Group</th>
<th>No sICH (%)</th>
<th>sICH (%)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombolysis</td>
<td>17 (81)</td>
<td>4 (19)</td>
<td>0.020</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>29 (81)</td>
<td>7 (19)</td>
<td>0.012</td>
</tr>
<tr>
<td>Control</td>
<td>32 (100)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
</tbody>
</table>

* Value obtained using a 2-sided Fisher’s exact test.
data properly according to the criteria as noted above, but we have also carefully analyzed and verified the patient’s condition selected for generating all the provided data. Another limitation of the study is the small sample size; we could not analyze which features the patients benefited from during endovascular interventional therapy.

Conclusions

In patients with large ischemic infarcts (ASPECTS < 6), mechanical thrombectomy showed advantages, although it increased the sICH risk within 24 hours when compared with conventional care. The efficacy of IV thrombolysis was similar to that of conventional care management, but with a higher sICH risk.

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Pan, Jiang, Peng, Jing. Acquisition of data: Peng, Jing. Analysis and interpretation of data: Jiang, Jing. Drafting the article: Jiang, Peng, Fei. Critically revising the article: Jiang. Reviewed submitted version of manuscript: Peng. Approved the final version of the manuscript on behalf of all authors: Pan. Statistical analysis: Fei, Wang, Chen. Administrative/technical/material support: Wang, Gao, Li. Study supervision: Pan, Gao, Chen, Li.

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