Different Trials in Mechanical Thrombectomy for Acute Ischemic Stroke

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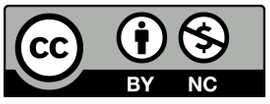

ABSTRACT

Acute Ischemic Stroke (AIS) is a leading cause of death and disability. It can be treated early with a favorable prognosis if intravenous recombinant tissue plasminogen activator (IV rt-PA) is given to eligible patients within 4.5 hours of its onset. For those patients who do not meet the criteria to undergo intravenous fibrinolysis, mechanical thrombectomy has been shown to be an effective alternative in patients presenting with occlusion of first segment of middle Cerebral artery (MCA) or of internal carotid artery (ICA), provided the intervention is performed within 24 hour according to previous trial. We herein review different randomized controlled trials on AIS undergoing mechanical thrombectomy.

Keywords: : Acute ischemic stroke; Anterior circulation; Intravenous recombinant tissue plasminogen activator; Mechanical thrombectomy.

INTRODUCTION

Acute ischemic stroke (AIS) which is defined as the acute loss of blood circulation to a brain territory, resulting in a corroborative loss of neurological function, akin to either a thrombotic or embolic phenomenon. It is one of the leading causes of death and disability. Ischemic core in brain tissue is destined to die rapidly, however, penumbra is a salvageable brain, which is redeemed to perform in a pre-stroke state area after restoration of its blood flow. The crucial time period, often labelled as a window period is the time frame within which an upfront intervention should be carried out to reverse neurological symptoms either partially or completely. Endovascular stroke therapy for acute ischemic stroke is much beneficial than IV thrombolysis alone. Patients with ischemic stroke with restricted perfusion imaging with a proximal cerebral arterial occlusion and salvageable brain tissue on CT perfusion imaging falls into intervening criteria for early thrombectomy. AIS can be treated early if intravenous recombinant tissue plasminogen activator (IV rt-PA) is given for eligible patients, within 4.5 hours of symptom onset.[1,2,13] Those who present later are candidates for mechanical thrombectomy up to 24 hour depending upon the clinical mismatch between symptoms and corroborative ischemic core.[4,15] Despite the increasing use of IV rt-PA, a large number of patients are deemed ineligible for this treatment because of narrow time frame, or in whom treatment is rendered questionable because of large cerebral occlusion. Mechanical thrombectomy has been shown to be effective for the treatment of acute ischemic stroke in patients presenting with occlusion of first segment of MCA or occlusion of ICA if treatment is commenced within 6 hours according to previous trial.[6-9] Various clinical trials of mechanical thrombectomy have been done so far with its own assets and liabilities. We herein review different randomized controlled trials on AIS undergoing mechanical thrombectomy on the chronological sequence of the result announcement.

METHODS

To point out trials on mechanical thrombectomy to AIS, we searched MEDLINE using PubMed for potentially entitled reports writtenand published in English. We used

the following search terms: “acute ischemic stroke” and “mechanical thrombectomy”. We reviewed 16 different trials and scrutinized their data

IMS-III

IMS-III was a multicenter, randomized controlled trial evaluating the effectiveness of endovascular treatment in addition to IV rt-PA.[1] Patients were assigned in a ratio of 2:1 to an additional endovascular treatment group and IV rt-PA alone group. The primary end point was the mRS 0-2 score after 90 days. The study was expected to enroll 900 patients, but was stopped early after no additional effectiveness was demonstrated in the results from 656 patients. The primary end point did not differ significantly between groups (additional endovascular treatment group, 40.8%; rt-PA alone group, 38.8%; 95% confidence interval [CI], 26.1 to 9.1). Even in a subgroup analysis comparing mild stroke (National Institutes of Health Stroke Scale score 8-19) and severe stroke (score ≥ 20), there was still no remarkable difference. Furthermore, no compelling differences were identified in mortality after 90 days (P 5 .52) or the rate of symptomatic intracranial hemorrhage after 30 hours (P 5 .83).

MR RESCUE

In the MR RESCUE study, patients treated within 8 hours of stroke onset who had large vessel occlusion (anterior circulation only) were evaluated by conducting magnetic resonance imaging perfusion imaging to demonstrate a penumbra region and randomly assigned to an endovascular treatment group or standard treatment group.[10] Outcomes were assessed according to the 90-day mRS. The results showed no difference in mean 90-day mRS score, which was 3.9 in both groups. Moreover, endovascular treatment appeared futile even in the group showing a penumbral pattern.

SYNTHESIS EXPANSION

The SYNTHESIS Expansion study randomized patients with acute ischemic stroke within 4.5 hours of onset to endovascular treatment or IV rt-PA.[11] The results showed no significant difference between the groups in the proportion of patients with a good outcome of mRS 0-1 (P 5.16). The rate of symptomatic intracranial hemorrhage was 6% in both groups. Median time from onset until initiation of treatment was 3.75 hours in the endovascular treatment group and 2.75 hours in the IV rt-PA group (P, .001). Endovascular treatment was thus performed 1 hour later.

RESCUE-JAPAN REGISTRY

The Rescue-Japan Registry, conducted in Japan is the first nationwide, prospective registry of acute cerebral large vessel occlusion.[11] This study was designed to assess the footprint of endovascular treatment on clinical outcome following approval of a mechanical clot retriever in the Japanese population. The study demonstrated that endovascular treatment was noteworthy with improved clinical outcomes in IV t-PA-failed and ineligible patients with proximal artery occlusion such as internal carotid artery. In this registry, endovascular treatment was started much earlier (210 minutes after onset in RESCUE-Japan versus more than 360 minutes in MR RESCUE), and the reperfusion rate was higher than those of IMS III and MR RESCUE (TICI 2b-3: 52.5% in RESCUE-Japan versus 26% in MR RESCUE).

MR CLEAN

This trial randomly assigned eligible patients to either intra-arterial treatment plus usual care or usual care alone. Eligible patientswere defined as those who had occlusion in proximal arterial arcade in the anterior cerebral circulation that was established on vessel imaging and that could be treated intra-arterially within 6 hours after symptom onset.[6]

There was an absolute difference of 13.5 percentage points (95% CI, 5.9 to 21.2) in the rate of functional independence in favor of the intervention (32.6% vs. 19.1%). However, no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage was concluded.

ESCAPE TRIAL

This trial randomly assigned participants to receive standard care (control group) or standard care plus endovascular treatment with the use of available thrombectomy devices (intervention group).[2] Eligible candidates were those who had a proximal intracranial occlusion in the anterior circulation and were included up to 12 hours after symptom onset. In contrary, patients with a large infarct core or poor collateral circulation demonstrated on computed tomography (CT) and CT angiography were excluded.

Results showed that in the intervention group, the median time from study CT of the head to first reperfusion was 84 minutes. The rate of functional independence was increased with the intervention (53.0%, vs. 29.3% in the control group; P<0.001). The primary outcome favored the intervention (common odds ratio, 2.6; 95% confidence interval, 1.7 to 3.8; P<0.001), and the intervention was

associated with reduced mortality (10.4%, vs. 19.0% in the control group; P=0.04). Symptomatic intracerebral hemorrhage occurred in 3.6% of participants in intervention group and 2.7% of participants in control group (P=0.75).

REVASCAT

This trial randomly assigned 206 patients who could be treated within 8 hours after the onset of symptoms of acute ischemic stroke. They were grouped into those who receive either medical therapy (including intravenous alteplase when eligible) and endovascular therapy with the Solitaire stent retriever (thrombectomy group) or medical therapy alone (control group).[12]

Results were favorable with thrombectomy which demonstrated reduced the severity of disability over the range of the modified Rankin scale (adjusted odds ratio for improvement of 1 point, 1.7; 95% confidence inte rval [CI], 1.05 to 2.8) and led to higher rates of functional independence (a score of 0 to 2) at 90 days (43.7% vs. 28.2%; adjusted odds ratio, 2.1; 95% CI, 1.1 to 4.0). At 90 days, the rates of symptomatic intracranial hemorrhage were 1.9% in both the thrombectomy group and the control group (P=1.00), and rates of death were 18.4% and 15.5%, respectively (P=0.60).

EXTEND IA

This study randomly assigned patients who suffered ischemic stroke and received 0.9 mg of alteplase per kilogram of body weight less than 4.5 hours after the onset of ischemic stroke either to undergo endovascular thrombectomy with the Solitaire FR (Flow Restoration) stent retriever or to continue receiving alteplase alone.[7] All the patients had occlusion of the internal carotid or middle cerebral artery with evidence of salvageable brain tissue and ischemic core of less than 70 ml as evidenced on computed tomographic (CT) perfusion imaging.

Reperfusion rate was higher in the endovascular group than in the alteplase-only group (median, 100% vs. 37%; P<0.001). It revealed an increased early neurologic symptom improvement at 3 days (80% vs. 37%, P=0.002) with improved functional outcome at 90 days.However, no significant differences in rates of death or symptomatic intracerebral hemorrhage was found.

SWIFT PRIME

This study randomly assigned eligible patients with stroke who were receiving or had received intravenous t-PA to continue with t-PA alone (control group) or to undergo endovascular thrombectomy with the use of a stent retriever within 6 hours after symptom onset (intervention group).[9]

The results showed that thrombectomy with the stent retriever plus intravenous t-PA reduced disability at 90 days over the entire range of scores on the modified Rankin scale (P<0.001). The rate of functional independence was higher in the intervention group than in the control group (60% vs. 35%, P<0.001). There were no significant between-group differences in 90-day mortality (9% vs. 12%, P=0.50) or symptomatic intracranial hemorrhage (0% vs. 3%, P=0.12).

ASTER TRIAL

The Contact Aspiration vs. Stent Retriever for Successful Revascularization (ASTER) study was a randomized, open-label, blinded end-point clinical trial conducted in 8 comprehensive stroke centers in France (October 2015-October 2016).[13] The inclusion criteria was patients presenting with AIS and a large vessel occlusion in the anterior circulation within 6 hours of symptom onset.

The study was formulated with the aim to compare efficacy and adverse events using the contact aspiration technique vs. the standard stent retriever technique as a first-line endovascular treatment for successful revascularization among patients with aforementioned inclusion criteria. Intervention group were randomly assigned to first-line contact aspiration (n = 192) or first-line stent retriever (n = 189) immediately prior to mechanical thrombectomy. Results showed that among 381 patients, 85.4% had a successful revascularization in the contact aspiration group and in the stent retriever group, it showed 83.1% revascularization. Nonetheless, there was no significant differences between groups in the functional clinical outcomes.Consequently, this study did not result in an increased successful revascularization rate at the end of the procedure.

THRACE TRIAL

This study was primarily aimed to analyze whether mechanical thrombectomy combined with IVT (IVMT) is cost-effective when compared with IVT alone.[14] Patients presenting with AIS with an occlusion of the intracranial internal carotid artery, the M1 segment of the middle cerebral artery, or the superior third of the basilar artery confirmed by computed tomography or magnetic resonance angiography; age 18 to 80 years; and receiving IVT alone or IVMT were enrolled. Clinical outcome in terms of functional independence at 90 days were compared.

Results showed treating acute ischemic stroke with IVMT (n=200) versus IVT (n=202) increased the rate of functional independence by 10.9% (53.0% versus 42.1%; P=0.028), at an increased cost of $2116 (€1909), with no significant difference in mortality (12% versus 13%; P=0.70) or symptomatic intracranial hemorrhage (2% versus 2%; P=0.71). Based on randomized trial data, this study demonstrates that IVMT used to treat acute ischemic stroke is cost-effective when compared with IVT alone.

FAMTAIS TRIAL

Fingolimod with Alteplase bridging with Mechanical Thrombectomy in Acute Ischemic Stroke (FAMTAIS) study is a randomized, open-label, multiple central trial.[15] This study enrolled 98 patients with anterior circulation large vessel occlusion acute ischemic stroke who are eligible for bridging therapywill be randomly assigned in a 1:1 ratio to receive oral fingolimod or standard care. The primary endpoint is the penumbra tissue salvage index and secondary outcomes focus on infarct growth and extent of clinical improvement from day 1 to day 7, frequency of parenchymal hemorrhage at day 1. If the hypothesis of FAMTAIS is confirmed, combination of fingolimod with bridging therapy is effective in attenuating reperfusion injury in patients with large vessel occlusion treated within 6 hours of stroke onset.

DAWN TRIAL

This trial enrolled patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume.[5] Random assignment of patients were made to thrombectomy plus standard care (the thrombectomy group) or to standard care alone (the control group).

The DAWN trial conveyed that outcomes for disability and functional independence at 90 days were better with thrombectomy plus standard medical care than with standard medical care alone. The mean score on the utility-weighted modified Rankin scale at 90 days was 5.5 in the thrombectomy group as compared with 3.4 in the control group and the rate of functional independence at 90 days was 49% in the thrombectomy group as compared with 13% in the control group.The rate of symptomatic intracranial hemorrhage did not differ significantly between the two groups (6% in the thrombectomy group and 3% in the control group, P=0.50), nor did 90-day mortality (19% and 18%, respectively; P=1.00).

DEFUSE TRIAL

This is a multicenter, randomized, open-label trial, with blinded outcome assessment, of thrombectomy in patients 6 to 16 hours after they were last known to be well and who had remaining ischemic brain tissue that was not yet infarcted.[4] The inclusion criteria were patients with proximal middle-cerebral-artery or internal-carotid-artery occlusion, an initial infarct size of less than 70 ml, and a ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of 1.8 or more. They were randomized and assigned to endovascular therapy (thrombectomy) plus standard medical therapy (endovascular-therapy group) or standard medical therapy alone (medical-therapy group).

In this trial, endovascular thrombectomy for ischemic stroke 6 to 16 hours after a patient was last known to be well plus standard medical therapy resulted in better 90-day functional outcomes scores than standard medical therapy alone among patients who had evidence of salvageable tissue on the basis of a formula that incorporated early infarct size and the volume of hypoperfused tissue on perfusion imaging. The 90-day mortality rate was 14% in the endovascular-therapy group and 26% in the medical-therapy group (P=0.05), and there was no significant between-group difference in the frequency of symptomatic intracranial hemorrhage (7% and 4%, respectively; P=0.75) or of serious adverse events (43% and 53%, respectively; P=0.18).

DEVT TRIAL

This is recent randomized, multicenter trial conducted at 33 stroke centers in China from May 20, 2018 to May 2, 2020.[16] This study enrolled 234 patients of age 18 year or older with proximal anterior circulation AIS. The window period was a span of 4.5 hours.

Intervention group was divided into endovascular treatment alone and intravenous alteplase plus endovascular treatment. The primary endpoint was functional independence of mRS 0-2 at 90 days. Results showed that 54 % in the endovascular group had achieved functional independence at 90 day follow-up. While in the combined treatment group it was 47%. Even so, there was no significant difference between groups in symptomatic intracerebral hemorrhage (ICH). This trial was stopped early because of efficacy when 234 of a planned 970 patients had undergone randomization.

SKIP TRIAL

This study, conducted in Japan, yet another recent multicenter, randomized, open-label clinical trial

conducted at 23 hospital networks from January ,2017 to July 31, 2019.[17] Intervention group were divided into two group i.e. mechanical thrombectomy alone and combined intravenous thrombolysis plus MT. The primary endpoint was a favorable outcome of mRS of 0-2 at 90 days. Results showed that 59% in the MT group has achieved a favorable outcome while 57% in the combined IV thrombolysis plus MT group with no significant difference. An ICH was observed less in the MT group which was significantly difference between 2 groups.

CONCLUSION

Mechanical thrombectomy in patients with stroke is usually performed within 6 hours after the onset of stroke to achieve a favorable neurological outcome. International stroke conference in 2013 declared ''Honolulu shock'' after knowing the results of three randomized controlled trials (IMS-III, MR RESCUE & SYNTHESIS Expansion) as inferiority.[18]

The recent trials have shown that the rate of functional independence in the thrombectomy group was similar to the rate reported in a pooled analysis of previous five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) of thrombectomy in which patients predominantly received treatment within 6 hours after stroke onset.8 The outcomes of thrombectomy in DEFUSE trial were paradoxically better than those in many trials that treated patients within 6 hours after the onset of stroke.[2] This finding may have been due to the selection bias, in that, patients in the DEFUSE 3 trial had favorable collateral circulation and slower infarct growth demonstrated on angiographic and perfusion scan. Among the recent trial of MT, DEVT trial met the prespecified statistical threshold for non-subordinate for the outcome of 90-day functional independence while the SKIP trial failed to demonstrate non-inferiority regarding favorable functional outcome.

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