Advances in Stroke Management 2018: A Literature Review

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Abstract

The past 2 years have witnessed several landmark clinical trials showing better functional outcomes regarding acute stroke care. Endovascular intervention (including both the mechanical thrombectomy and intra-arterial thrombolysis) has unequivocal short term and long term clinical benefits as compared to conventional stroke management. In light of these major trials, AHA/ASA has now accredited endovascular thrombectomy as a gold standard intervention within 6 hours of stroke symptoms onset. Two recent trials DAWN and DEFUSE-3, showed positive outcome of delayed or extended window mechanical thrombectomy up to 16-24 hours after the stroke onset in selected patients. Promising results are seen regarding efficacy of PFO closure in stroke recurrence prevention. Similarly, in patients with atrial fibrillation with coexisting valvular heart disease, novel non-vitamin K antagonist oral anticoagulants’ (NOACs) use for stroke prevention is justified.

ABBREVIATIONS

AHA: American Heart Association; ASA: American Stroke Association; PFO: Patent Foramen Ovale; CT: Computed Tomography; HR: Hazard Ratio; CI: Confidence Interval; AF: Atrial Fibrillation

INTRODUCTION

Stroke is one of the major causes of both mortality and disability all around the world, with various improvements constantly being made in its management to meet the ever-changing need of stroke as a disease [1]. Major clinical breakthroughs were seen in the field of stroke medicine in the past two years with publication of various landmark trials that have the potential to change stroke care guidelines. Recent advancements in the stroke management mainly include that of endovascular intervention, blood pressure control in acute stroke, cardiac interventions to limit the incidence of stroke, and stroke rehabilitation.

Stroke medicine has recently achieved great developments with new reperfusion therapies and expanded therapeutic window for intervention procedures. Previously intravenous alteplase therapy used to be the only reperfusion therapy with proven efficacy in patients with acute ischemic stroke [2], but it has various limitations including narrow therapeutic window and is contraindicated in patients with history of intracranial hemorrhage. We will describe some of the recent advancements regarding acute reperfusion therapy to salvage brain tissue damage in this article.

REVIEW

In 2015, MR CLEAN trial [3], established the safety and efficacy of intra-arterial treatment administered within 6 hours after the onset of stroke caused by proximal intracranial occlusion of the anterior circulation. This was a multi-centered randomized clinical trial with blinded end-point evaluation done on 500 patients, comparing the efficacy and safety of intra-arterial treatment (either intra-arterial thrombolysis or mechanical thrombectomy or both with usual care (includes intravenous thrombolysis) alone. The results were in absolute favor of intervention group (32.6% vs. 19.1%), with respect to functional outcome (modified Rankin score) at 90 days. This evidence is also supported by few other studies showing significant improvement in the rates of cerebral perfusion because of substantial advancement in endovascular thrombectomy [4]. A meta-analysis of 8 trials involving 2423 patients with acute ischemic stroke, showed higher rates of revascularization and better functional outcomes in the endovascular thrombectomy group compared to the usual...
medical care group, but without much difference in the incidence of symptomatic intracranial hemorrhage or all-cause mortality rate at 90 days [5]. But most of these studies failed to evaluate the long term clinical outcome in the endovascular intervention group patients.

In 2017, this question was answered when MR CLEAN trial investigators published the 2 year follow-up clinical data [6] from their initial study, which showed better functional outcome in endovascular intervention group patients at 2 years similar to that of initial study. In this follow-up study, primary outcome was proven to be better in endovascular treatment than standard treatment, as measured by the distribution of functional outcome on the modified Rankin scale (adjusted common odds ratio, 1.68; 95% confidence interval [CI], 1.15 to 2.45; P = 0.007). Secondary outcome as measured by the mean quality-of-life score using European Quality of Life-5 Dimensions questionnaire, was 0.48 for endovascular treatment group as compared to 0.38 for conventional treatment group (mean difference, 0.10; 95% CI, 0.03 to 0.16; P = 0.006). Mortality rate at 2 years was also lower in endovascular intervention group (26.0%) as compared to the control group (31.0%) (Adjusted hazard ratio, 0.9; 95% CI, 0.6 to 1.2; P = 0.46). Thus the additional follow-up data mirrored the results of the initial MR CLEAN trial, and showed that endovascular thrombectomy group patients had both short term and long term better outcomes compared to conventional treatment group.

The former 2013 American Stroke Association (ASA) guidelines were published prior to results of the positive early window mechanical thrombectomy trials such as MR CLEAN, ESCAPE, EXTEND-I, SWIFT PRIME and REVASCAT. In accordance with the results of these trials, 2018 AHA/ASA guidelines now recommend endovascular thrombectomy as the gold standard treatment for patients with acute ischemic stroke involving the internal carotid artery or proximal segment of middle cerebral artery within 6 hours of onset [7]. The AHA guidelines recommend that mechanical thrombectomy with a stent retriever must be the treatment of choice in stroke patients meeting all the below criteria:

1) Pre-stroke modified Rankin score of 0 to 1
2) Occlusion of the internal carotid artery or proximal (M1) segment of MCA
3) Age ≥ 18 years
4) National Institutes of Health Stroke Scale (NIHSS score) ≥ 6
5) Alberta Stroke Program Early CT Score (ASPECTS) ≥ 6 and
6) Treatment can be started within 6 hours of onset of stroke symptoms.

A meta-analysis of the 5 trials (HERMES [Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials], which included MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), showed that the odds of better functional outcomes of endovascular intervention group decreased as the time from the onset of stroke symptoms to the intervention increased [8]. But two recent trials DAWN [9] and DEFUSE-3 [10] showed positive outcome of delayed or extended window mechanical thrombectomy up to 16-24 hours after the stroke onset in selected patients.

DAWN trial published in late 2017 showed beneficial results of delayed endovascular thrombectomy within 6 to 24 hours from the stroke onset in selected patients with clinical infarct mismatch. Clinical infarct mismatch was defined as mismatch between the volume of the ischemic core on CT perfusion imaging and clinical deficit as measured by National Institutes of Health Stroke Scale (NIHSS) and categorized according to the age as follows:

1) Age ≥ 80 y; NIHSS ≥ 10; Ischemic core < 21 mL
2) Age < 80 y, NIHSS ≥ 10; Ischemic core < 31 mL
3) Age < 80 y, NIHSS ≥ 20; 31≤ Ischemic core<51 mL

The study was started on 209 randomized stroke subjects with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery, who were last known to be well 6 to 24 hours earlier and fulfilled the above criteria for clinical infarct mismatch. But the trial was terminated because of the results of an interim analysis showing clear benefits of thrombectomy over the standard treatment alone. Primary end point at 90 days as measured by the rate of functional independence was 49% in the thrombectomy group compared to 13% in the control group (adjusted difference, 33 percentage points; 95% credible interval, 24 to 44), but no significant difference was noted in the occurrence of intracranial hemorrhage or mortality rate in both groups.

Another major trial in favor of delayed window thrombectomy was DEFUSE-3 published in 2018. This was a multi-centered randomized trial started on 182 acute ischemic stroke patients from 32 centers presenting 6 to 16 hours after they were last known to be well, with a region of tissue on imaging that was ischemic but not yet infarcted and fulfilling the criteria for target mismatch (TMM) as follows:

1) Ischemic core volume (by CT perfusion imaging) < 70 mL
2) Mismatch ratio ≥ 1.8
3) Mismatch volume ≥ 15 mL

Endovascular therapy group had favorable outcome at 90 days as shown by better functional outcomes on modified Rankin scale (odds ratio, 2.77; P < 0.001) and 45% of the patients with functional independence as compared to 17% in the medical treatment only group. Currently these two are the only available studies demonstrating the benefits of extended window thrombectomy, but the major drawback of both the studies waste demonstration of beneficial results in only selected patients who fulfilled the above mentioned eligibility criteria. In accordance with the above results, 2018 AHA/ASA guidelines [7] were updated recommending mechanical thrombectomy in patients with acute ischemic stroke with occlusion of large vessel in anterior circulation, within 6 to 16 hours of last known to be normal and meeting the eligibility criteria of either DAWN or DEFUSE-3 trials and even within 6 to 24 hours if DAWN eligibility criteria were met. Recent guidelines also recommend an urgent CT angiogram.
or Magnetic Resonance (MR) Angiogram for patients who may be candidates for mechanical thrombectomy, but thrombolysis with intravenous t-PA if indicated must not be delayed even in these patients. But AHA/ASA 2018 guidelines [7] have not made any recommendation for the emergency medical services, whether to bypass a closer hospital with the availability of intravenous t-PA therapy for a hospital with thrombectomy facility.

Another recent advance in secondary prevention of stroke is the evidence of role of patent foramen ovale (PFO) closure. Cryptogenic strokes were long known to have an association with patent foramen ovale, suggesting paradoxical emboli through a PFO to be the cause of stroke. But the effectiveness of PFO closure in the prevention of recurring ischemic stroke has always been a topic of unending discussion. Although majority of previous clinical trials failed to prove the benefits of PFO closure over medical therapy, a few of them were slightly in favor of PFO closure [11,12]. A study of pooled data from 2,303 patients from 3 different trials, showed that PFO closure has statistically significant effect on the reduction of recurrent stroke only with adjusted but not with unadjusted analyses [13].

But three recent clinical trials (CLOSE [14], Gore REDUCE [15], and RESPECT-Extended [16] have provided a closure to this long standing debate by providing the evidence that trans-catheter closure of PFO has significant advantage over usual medical therapy in preventing stroke recurrence, particularly in patients with a large right to left shunt and atrial septal aneurysm. CLOSE study [14] was a multi-centered randomized trial which included patients who experienced ischemic stroke within the previous 6 months with no other identifiable cause than a PFO, categorized into three randomized groups. Results showed that the rate of recurrent ischemic stroke was significantly lower among PFO closure group (combined with antiplatelet therapy) compared to medical therapy alone group (hazard ratio, 0.03; 95% confidence interval, 0 to 0.26). But there was a higher rate of atrial fibrillation in the PFO closure group within one month of closure, indicating the procedure to be the most likely cause. Gore Reduce study [15], a multinational randomized trial on patients who had an ischemic stroke due to a PFO with right to left shunt within the previous 180 days also showed the superiority of PFO closure in the prevention of stroke recurrence over medical therapy alone with anti-platelets (hazard ratio, 0.23; 95% confidence interval [CI], 0.09 to 0.62). But PFO closure was associated with device related complications and atrial fibrillation. Another similar study RESPECT- Extended [16], also emphasized the benefits of PFO closure in recurrent stroke prevention compared to medical therapy (hazard ratio with PFO closure vs. medical therapy, 0.55; 95% confidence interval [CI], 0.31 to 0.999) but associated with increased events of venous thromboembolism. A recently published pooled data analysis study of five randomized trials (CLOSURE I, PC Trial, REDUCE, RESPECT, and CLOSE) showed that patients under PFO closure group scored better in the prevention of recurrent ischemic stroke with 2.02% incidence rate of recurrence in the PFO closure compared to 4.4% in the medical therapy group (RR 0.42, 95% CI 0.20, 0.91) [17]. This is followed by the results from another pooled data analysis study of 3627 patients with 3.7-year mean follow-up, showing a constant decline in the recurrence of stroke after PFO closure with an absolute risk reduction of 2.11 [18]. Results from all these recent studies cleared the existing doubts regarding the efficacy of PFO closure in prevention of ischemic stroke recurrence.

Major revelations have also been made in the recent times regarding the role of novel non-vitamin K antagonist oral anticoagulants (NOACs) in stroke prevention, in patients with atrial fibrillation with coexisting valvular heart disease. A substantial proportion of strokes are caused by atrial fibrillation and so is the anticoagulation warranted for their prevention [19]. In the past vitamin K antagonists used to be the only oral anticoagulants approved for this indication. Conclusions drawn from the review of existing research data have established that novel oral anticoagulant medications are as effective as warfarin in terms of prevention of stroke in non valvular atrial fibrillation patients with additional benefits of decreased bleeding risk and other adverse effects [20]. But up until recently there has been a paucity of data available regarding the efficacy of NOACs for the prevention of stroke in patients with atrial fibrillation and valvular heart diseases like mitral stenosis. Recent publication of results from ENGAGE AF-TIMI 48 trial [21] established the efficacy and safety of NOACs (edoxaban) for this purpose. This was a randomized, double blind study in which patients with moderate to high risk atrial fibrillation were treated and followed up for a mean period of 2.8 years. Results showed that edoxaban therapy had similar efficacy compared to warfarin therapy in the prevention of stroke or systemic embolic events in patients with valvular atrial fibrillation (for SSEE, HR: 0.69; 95% CI: 0.44 to 1.07). In addition edoxaban treated patients showed less major bleeding compared to warfarin treated group (HR: 0.74; 95% CI: 0.53 to 1.02). A recent meta-analysis [22] of four randomized controlled trials describing the efficacy and safety of NOACs versus warfarin showed reduced incidence of stroke or systemic embolic events (HR: 0.70; 95% CI, 0.60–0.82) and decreased risk of intracranial hemorrhage in patients with valvular atrial fibrillation. However reduced risk of intracranial hemorrhage was seen with apixaban, edoxaban, and dabigatran but not with rivaroxaban.

CONCLUSIONS

Tremendous advances are made in the field of stroke management in the recent past like the proven efficacy of mechanical thrombectomy in both short and long term clinical outcomes, and also with extended therapeutic time window. Advances are also made pertaining to the efficacy of PFO closure in the prevention of secondary stroke, especially in patients with large right to left shunt or atrial septal aneurysm. Furthermore NOACs can now be considered as a safe alternative to vitamin K antagonist anticoagulants in patients with atrial fibrillation and valvular heart disease.

REFERENCES


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